UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ALLERGAN, INC., **Plaintiff,** **vs.** **UNITED STATES OF AMERICA; UNITED STATES FOOD & DRUG ADMINISTRATION; DR. MARGARET HAMBURG, Commissioner of the United States Food & Drug Administration; and KATHLEEN SEBELIUS, Secretary of the United States Department of Health & Human Services,** **Defendants.**	**CASE NO.: _____**

MEMORANDUM OF LAW IN SUPPORT OF
MOTION FOR PRELIMINARY INJUNCTION

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INTRODUCTION

Plaintiff Allergan, Inc. ("Allergan") distributes Botox®, a prescription drug that is FDA-approved to treat several conditions, including cervical dystonia. Dystonias are involuntary muscle contractions, and Botox®, a purified form of botulinum toxin, is injected into the affected muscles to relax them. Botox® is also frequently used "off-label" by doctors to treat other conditions, including various forms of spasticity. Spasticity also results from involuntary muscle contractions, which Botox® relieves in the same way as when it is used for dystonia. The off-label use of Botox® to treat spasticity is perfectly lawful and so widely medically-accepted that both Medicare and Medicaid reimburse doctors for certain spasticity-related indications.

As with many prescription drugs, however, there have been reports of adverse events, and rare reports of serious adverse events, following the use of Botox® to treat spasticity. Allergan has been distributing Botox® worldwide for over 20 years, and Botox® is approved for one or more forms of spasticity in nearly every major market other than the United States. As Botox®'s manufacturer, Allergan is uniquely positioned to inform physicians about the steps they can take to achieve the benefits of treatment while minimizing risks, including risks of serious adverse events, and thereby improve the quality of patient care. Although Allergan is free to share such medical evidence about on-label uses of Botox®, if it does so in conjunction with an off-label use, Allergan risks criminal sanction for contributing to the debate.

Allergan is chilled from speaking on this important topic by the FDA's regulatory regime, which makes almost any discussion of an off-label use criminal, and by the Government's aggressive prosecution of pharmaceutical companies for speaking about off-label uses of FDA-approved drugs. The Government's position that a manufacturer commits a crime by engaging in any or virtually any speech about off-label uses is derived from several overlapping statutory and regulatory provisions:

- The Food, Drug & Cosmetic Act ("FDCA" or "Act") prohibits a manufacturer from "suggest[ing]" an off-label use of a drug in "labeling," which the FDA has defined to include any tangible materials about that use that are disseminated by the manufacturer, whether or not they accompany the drug. 21 U.S.C. §§ 355(a), 321(p); 21 C.F.R. § 202.1(*l*)(2).

- The Government takes the position that it is unlawful to make even *bona fide* scientific claims about an off-label use in tangible materials about that use that are disseminated by the manufacturer, on the rationale that all speech about an off-label use is by definition "false or misleading." *See* U.S. Sentencing Memo., *United States v. Warner-Lambert Co.* at 8–9, No. 04-10150 (D. Mass. 2004) ("*Warner-Lambert* Sentencing Memo"); 21 U.S.C. § 352(a).

- The FDA has imposed a *per se* ban on "advertisement[s]" for an off-label use of a prescription drug, 21 C.F.R. § 202.1(e)(4)(i)(a), including advertisements directed to health care professionals.

- And FDA regulations prohibit a manufacturer from "express[ing]" an "intent" or merely "know[ing]" or having "notice" that its product "is to be used" off-label. 21 C.F.R. §§ 201.100, 201.128; *see* 21 U.S.C. § 352(f)(1).

The Government's position leaves Allergan no clearly lawful avenue through which to communicate important safety information to physicians.

Each of these statutes and regulations, as applied to Allergan's speech to medical professionals, violates the First Amendment. To suppress Allergan's truthful speech about the lawful use of its lawful product, the Government must prove — at a minimum — that the suppression is no more extensive than necessary to directly further its substantial interests. *Thompson v. Western States Med'l Ctr.*, 535 U.S. 357, 367 (2002). The sweeping prohibitions on off-label speech do not pass muster under this test and, *a fortiori*, fail strict scrutiny. First, the total suppression of Allergan's speech cannot be justified as necessary to protect the public health: Far from seeking to stamp out off-label use, federal law recognizes that off-label uses may be medically supported and sufficiently important to the public health as to justify taxpayer reimbursement. Depriving doctors of truthful information about proper off-label treatment protocol harms, not helps, patients. Second, the Government's position is far more restrictive of

speech than is necessary to further the only interest it has identified for its regime — the creation of an incentive for manufacturers to seek FDA approval for off-label uses. The Government could create an adequate, and potentially more effective, incentive through numerous and obvious less-restrictive means, such as limiting the regime only to uses for which approval is not being sought, mandating clear disclosure that a use is off-label, requiring a manufacturer to seek FDA approval for an off-label use if sales pass a threshold, taxing sales for off-label uses more heavily, or imposing tailored restrictions on *some* off-label marketing practices. The availability of these many less-restrictive alternatives is fatal: "[I]f the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so." *Id.* at 371.

This Court also can remedy the constitutional difficulties with the Government's position without striking down any statutes or regulations as violating the First Amendment. Each plank of the Government's position, as applied to Allergan's truthful speech to physicians, is contrary not only to the First Amendment, but also the Act itself. The Act contains no hint that Congress intended the FDA to have authority to prohibit off-label speech in every forum, at every time, to every audience. Rather, on its face, the Act restricts a manufacturer's truthful speech in one specific forum — "labeling," which Congress limited to the label, container, wrappers, and other materials accompanying the drugs— but does not ban it across the board. 21 U.S.C. §§ 355(a), 321(p), (m), 352(n). Lacking a clear statutory warrant, the FDA has read innocuous statutory provisions as giving it unprecedented and unconstitutional power over manufacturer expression. This is not a reasonable approach to regulation. Congress does not "hide elephants in mouseholes." *Whitman v. Am. Trucking Ass'ns*, 531 U.S. 457, 468 (2001). And because the FDA's sweeping prohibitions of off-label speech give rise to serious constitutional doubt —

indeed, serious constitutional violations — the lack of clear direction from Congress is dispositive. The regulations are invalid as a matter of statutory interpretation.

To be clear, Allergan respects the FDA's regulatory mission and recognizes the centrality of the drug approval process to that mission. The FDA must ensure that marketed drugs are safe and effective, and its ability to do so may be reduced if manufacturers do not seek FDA approval for new uses of approved drugs. Allergan also recognizes that manufacturer speech about prescription drugs must be truthful and non-misleading. Allergan thus has no objection to measured regulation of manufacturer speech that is necessary to further these interests.

Unfortunately, that is not the regime that the FDA has adopted. Instead, lacking clear statutory authorization to suppress speech outside the narrow context of "labeling," the FDA has seized upon statutory provisions that do not directly address these complex and important issues to promulgate regulations that combine to prohibit virtually all, if not all, manufacturer speech about off-label uses. The result is a regime that is utterly out of balance: Off-label use is lawful, commonplace, and necessary to the provision of quality medical care — it is no exaggeration to say that the FDA's current regulatory regime could not function if it did not tolerate significant off-label use — but manufacturers' free speech rights are totally suppressed and the public's interest in the free flow of information is totally disregarded.

Fundamentally, the Government has refused to adopt the kind of clear and tailored regulation that the First Amendment demands. Based on its position that all or virtually all manufacturer speech about off-label uses gives rise to criminal liability, the Government can prosecute virtually any manufacturer, at any time, for the alleged crime of "off-label promotion." The First Amendment does not permit the Government to criminalize a broad category of truthful speech and relegate citizens to trusting in prosecutorial grace. *See Houston v. Hill*, 482 U.S. 451,

465–67 (1987). The Government cannot be allowed to continue the status quo, in which significant off-label use of FDA-approved drugs by doctors is permitted and even encouraged, but the manufacturer that supplies the FDA-approved drugs to those doctors commits a crime by speaking about the off-label use.

The threat of prosecution is currently chilling Allergan's First Amendment right to share truthful medical information with physicians about how to safely use Botox® off-label to achieve a benefit while minimizing risk of serious adverse events. Allergan respectfully requests that this Court enter a preliminary injunction against the enforcement of the FDA's unconstitutional and invalid regulations to protect Allergan's free speech rights — and the public health — from further injury during the pendency of this matter.

BACKGROUND

A. The Statutory Scheme

The Act prohibits the introduction or delivery for introduction into interstate commerce of a "new drug" that has not been approved by the FDA. 21 U.S.C. §§ 331(d), 355(a). To obtain FDA approval to market a "new drug," a manufacturer must submit a detailed application to the FDA, including reports of trials demonstrating the drug's safety and efficacy, as well as proposed labeling for the drug. § 355(b). The FDA evaluates whether the manufacturer has proven that the drug is safe and effective, and it ensures that the labeling is not "false or misleading in any particular." § 355(d); 21 C.F.R. § 601.5 (biologics). The Act generally imposes the same requirements for biologics such as Botox®. *See* 42 U.S.C. § 262(a), (j); *see also id*. § 262(i) (defining "biological product").[1]

[1] Unless otherwise noted, a reference herein to a "drug" also refers to a biologic.

The Act defines a "new drug" to include any drug that "prescribe[s], recommend[s], or suggest[s]" in its "labeling" a use that has not been FDA-approved. 21 U.S.C. § 321(p); *see also Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 632 (1973). The Act defines "labeling" as "written, printed, or graphic matter" (1) upon a drug itself, its immediate or other "containers or wrappers," or (2) "accompanying such article." § 321(m), (k). Materials "accompan[y an] article" of a drug if they are sent from the same origin to the same destination as part of an "integrated . . . transactio[n]" and the two have a "textual relationship." *Kordel v. United States*, 335 U.S. 345, 348–50 (1948). Under these definitions, after the FDA has approved a drug for one use, that "old" drug becomes a "new drug" that cannot be sold if "written, printed, or graphic matter" upon or accompanying the drug's packaging "suggest[s]" that the drug be employed for a new use that the FDA has not approved. § 321(m), (p). The Act by its terms thus prohibits a manufacturer from obtaining FDA approval for one use and then "suggest[ing]" on the "labeling" itself that it be used for an "off-label" use.

The Act also makes it a crime to introduce into interstate commerce a "misbranded" drug. 21 U.S.C. § 331(a), 333(a), 352. A drug is "misbranded" if its "labeling" includes a statement that is "false or misleading in any particular." § 352(a); *see also* § 321(n) (statements and omissions may make a statement false or misleading). A drug is also generally "misbranded" if its labeling lacks "adequate directions for use," § 352(f)(1), though "drug[s] dispensed . . . by prescription" are exempt from this requirement. 21 U.S.C. § 353(b)(2). A drug dispensed by prescription is instead misbranded "if at any time prior to dispensing the label . . . fails to bear, at a minimum, the symbol 'Rx only.'" § 353(b)(4). A prescription drug is also "misbranded" if "advertisements and other descriptive printed matter" for that drug fail to disclose (1) the "established name" of the drug; (2)

its formula; and (3) "such other information in brief summary relating to side effects, contraindications, and effectiveness" as the Secretary shall require by regulation. § 352(n).[2]

Although the Act prohibits a manufacturer from "suggest[ing]" an off-label use in the "labeling" of an FDA-approved drug, "[a] physician may prescribe a legal drug to serve any purpose that he or she deems appropriate, regardless of whether the drug has been approved for that use by the FDA." *Wash. Legal Found. v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000) ("*WLF IV*"). Indeed, the "prescription of drugs for unapproved [off-label] uses is commonplace in modern medical practice and ubiquitous in certain specialties." *Id*. In 2001, approximately 150 million prescriptions — 21% of all prescriptions — were to treat off-label conditions. David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 Archives of Internal Med. 1021, 1021 (2006). In specialties like oncology and pediatrics, the majority of patients receive off-label care. GAO Report, *Implications of Drug Labeling and Off-Label Use* 3 & n.6 (1996). Federal law itself recognizes the importance and legitimacy of off-label use by reimbursing off-label prescriptions for drugs, like Botox®, when the off-label use is "medically accepted." 42 U.S.C. §§ 1396b(i)(10), 1396r-8(k)(2), (k)(6).

As with on-label uses of prescription drugs, the safe off-label use of a drug requires the physician to balance the drug's benefits and risks based on available medical evidence in relation to alternative treatments. Physicians thus "need reliable and up-to-date information concerning off-label uses." *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 56 (D.D.C. 1998) ("*WLF II*"), *vacated as moot on other grounds by WLF IV*. Indeed, physicians' need for information about off-label uses is "particularly acute" because the FDA-approved labeling does not provide such information. *Id*.

[2] The FDA does not, however, have broad authority to regulate misleading advertisements for drugs; that authority belongs instead to the Federal Trade Commission. 15 U.S.C. § 55(a); *Kordel*, 335 U.S. at 351.

B. The Regulatory Regime

While the Act regulates manufacturer speech on a drug's label and its accompanying packaging and requires disclosures in prescription-drug advertisements, it does not otherwise restrict manufacturer speech. The FDA has nonetheless issued regulations that are much broader and more restrictive. Notwithstanding the acute need for medical information about off-label uses, the Government's position is so broad that it appears to prohibit a manufacturer from speaking truthfully to medical professionals about off-label uses of prescription drugs, the therapeutic benefits and limitations offered by an off-label drug, the risks that an off-label use may present, and the steps physicians can take to minimize those risks. Indeed, with the possible exception of actively discouraging off-label uses — something the FDA does not in fact want and the regulatory regime does not support — there is nothing a manufacturer can say about an off-label use without triggering criminal liability under the FDA's regulations.

1. FDA Regulations Prohibit Communication About Off-Label Uses Via Tangible Media

The Act closely regulates manufacturer speech in the specific context of "labeling," but the Act defines that term narrowly to mean "written, printed, or graphic matter" upon the article itself, its "containers or wrappers," or "accompanying such article." 21 U.S.C. § 321(m), (k); *see also Kordel*, 335 U.S. at 348–50. By regulation, however, the FDA has re-defined "labeling" beyond recognition to capture a vastly greater universe of speech:

> "Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the 'Physicians Desk Reference') for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer,

> or distributor, are hereby determined to be labeling . . . ." 21 C.F.R. § 202.1(*l*)(2).

Speech thus is "labeling" if (1) it is fixed in virtually any tangible medium; (2) it is "disseminated by or on behalf" of a manufacturer; and (3) it "contain[s] drug information supplied by the manufacturer." *Id*. Notably, despite the statutory definition, 21 C.F.R. § 202.1(*l*)(2) does not require that materials "accompan[y]" the drug.

The FDA's dramatic expansion of "labeling" correspondingly expands the scope of the prohibition on speech, because the statutory prohibition against "suggest[ing]" that a drug be used off-label applies to "sugges[tions]" made in "labeling." 21 U.S.C. §§ 355(a), 321(p). The FDA's expansion of "labeling" also expands the scope of the rule that a drug is "misbranded" if its "labeling" is "false or misleading in any particular." § 352(a). And that provision creates a far greater First Amendment problem than first appears because the Government has interpreted "false or misleading" to include any "scientific claims about the safety, effectiveness, contraindications, side effects, and the like" where the FDA has not "had the opportunity to evaluate" those claims — even if *bona fide* scientific research establishes that the manufacturer's speech is *true*. *See WLF II*, 13 F. Supp. 2d at 67. Elsewhere, the Government has taken the similar position that any "suggest[ion] that [a] drug is safe and effective" for an off-label use is "false or misleading," irrespective of the scientific support for the suggestion. *Warner-Lambert* Sentencing Memo at 8–9.

2. <u>FDA Regulations Impose a *Per Se* Ban on Off-Label Advertisement</u>

The Act generally permits "advertisements" for prescription drugs, provided that they disclose certain information. 21 U.S.C. § 352(n). FDA regulations, however, flatly prohibit prescription-drug "advertisements," even directed to physicians, that "recommend or suggest any use that is not in the labeling accepted in [that drug's] approved new-drug application." 21 C.F.R.

§ 202.1(e)(4)(i)(a). The FDA has circularly defined "advertisement" in § 352(n) to mean "advertisements" that are (1) printed "in published journals, magazines, other periodicals, and newspapers"; or (2) "broadcast through media such as radio, television, and telephone communication systems." *Id*. This regulation bans all advertisement of off-label uses, including truthful advertisements directed to physicians.

3. FDA Regulations Prohibit a Manufacturer from Communicating About or Having Constructive Knowledge of the Off-Label Use of a Prescription Drug

Under the Act, a drug generally is "misbranded" unless its labeling contains "adequate directions for use." 21 U.S.C. § 352(f)(1). However, the Act exempts drugs dispensed by prescription from the "adequate directions" requirement of § 352(f)(1). 21 U.S.C. § 353(b)(2). The FDA has nullified this broad statutory exemption by a regulation that limits the exemption from the "adequate directions" requirement to prescription drugs with labeling that contains "adequate *information*" for use. 21 C.F.R. § 201.100(c)(1) (emphasis added). "Adequate information" for use, in turn, means adequate directions "*for the purposes for which [the drug] is intended, including all purposes for which it is advertised or represented.*" *Id*. (emphasis added). FDA regulations thus require a prescription drug's "labeling" to contain directions for all "intended uses."

If the "intended uses" for which § 352(f)(1) required manufacturers to provide adequate directions in labeling were defined to match up with the uses for which § 355(a) permitted the manufacturer to provide adequate directions in labeling — namely, the FDA-approved on-label uses — those provisions would operate harmoniously. But the FDA has set §§ 352(f)(1) and 355(a) on a collision course by adopting the broadest possible conception of "intent." The FDA broadly defines a drug's "intended uses" to include not only FDA-approved on-label uses, but also any use "objective[ly] inten[ded]" by the manufacturer. 21 C.F.R. § 201.128. And a

manufacturer's "objective intent" may be shown via its expression in labeling, advertisement, or other "oral or written statements." *Id.* An "objective intent" is also shown if, with the knowledge of the manufacturer, the drug is "offered and used for a purpose for which it is neither labeled nor advertised." *Id.* Most broadly, if a manufacturer merely "*knows,* or has knowledge of facts that would give *notice"* that its drug "is to be used" off-label, it "is required to provide adequate labeling for such a drug which accords with [those] uses." *Id.* (emphasis added).

21 C.F.R. §§ 201.100 and 201.128, along with the misbranding statute to which they are linked, prohibit virtually all manufacturer expression and knowledge about the off-label use of a prescription drug. The manufacturer commits a "springing" misbranding violation whenever its speech reflects its "objective intent" that a drug be used off-label, because the drug's labeling by definition does not contain "adequate directions" for that off-label use. *See* 21 C.F.R. §§ 201.100, 201.128; 21 U.S.C. § 352(f)(1). Although the drug was properly labeled when introduced into commerce, the violation springs into being if the manufacturer speaks about the off-label use in any forum, to any audience, even if the speech is neither "labeling" nor an "advertisement." And the manufacturer cannot avoid this misbranding violation, because changing the "labeling" to add directions for an off-label use is itself unlawful: "suggest[ing]" an off-label use on a drug's "labeling" transforms that drug into a "new drug" that cannot be sold. 21 U.S.C. §§ 321(p), 355(a). Any speech by a manufacturer about an off-label use thus places the manufacturer in a Catch-22: It violates § 355(a) to change the labeling to add adequate directions for that off-label use, but it violates the "intended use" regulations and § 352(f)(1) *not* to change the labeling to add adequate directions for that use.

4. The FDA Has Not Provided Exceptions Permitting Communication of Truthful Medical Evidence or Otherwise Accommodating First Amendment Concerns

The regulatory regime is built on a fundamental dichotomy in the treatment of doctors, whose off-label use of drugs is permitted, and manufacturers, whose speech about off-label uses is broadly suppressed by the FDA regulations just described. Unfortunately, the FDA has refused to limit the legal scope of those regulations by creating regulatory safe harbors to allow non-misleading manufacturer speech about off-label uses. In 2002, the FDA published a Request for Comment on First Amendment Issues. 67 Fed. Reg. 34,942 (May 16, 2002). The FDA received extensive comments but still has taken no action.

The FDA has issued a "Good Reprint Practices" guidance document that purports to open a small sliver of breathing space, but in reality the Guidance underscores the breadth of the Government's legal position and its threat to speech. The Guidance reiterates that an "approved new drug that is marketed for an unapproved use is an unapproved new drug with respect to that use," and a drug "that is marketed for an unapproved use (whether in labeling or not) is misbranded because the labeling of such drug does not include 'adequate directions for use.'"[3]

The Guidance purports to allow manufacturers to disseminate reprints of medical journal articles — ordinarily core scientific speech fully protected by the First Amendment — in certain narrowly confined situations. *Id.* But materials may not be distributed if, for example, they were "written, edited, excerpted, or published specifically for, or at the request of," the manufacturer. And even this narrow passage is not a true safe harbor: "Guidance documents do not establish legally enforceable rights or responsibilities," 21 C.F.R. § 10.115(d)(1).

[3] Good Reprint Practices for Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm ("Good Reprint Practices").

C. Factual Background

Allergan markets Botox®, a prescription biologic that must be injected by health care professionals. Compl. ¶ 51. Botox® is a purified botulinum toxin formulation that has been safely used for decades to treat millions of patients. *Id*. at ¶¶ 53–54.[4] The FDA has approved Botox® to treat several conditions, and Botox® is also frequently used to treat a variety of off-label conditions, including conditions related to spasticity. *Id*. at ¶¶ 51, 55–56. The use of Botox® for spasticity is so broadly medically accepted that both Medicaid and Medicare reimburse doctors who employ Botox® to treat spasticity-related indications. *See id*. at ¶¶ 60–63. Allergan has applied for and is nearing FDA approval for Botox® to treat upper-limb spasticity in adults, and Botox® is also commonly used for lower-limb spasticity in adults and for spasticity in juvenile patients with cerebral palsy. *Id*. at ¶ 56–57. Botox® is approved to treat spasticity in adults or children in more than 60 countries in Europe and worldwide. *Id*. at ¶ 59.

Botulinum toxin, including Botox®, has a therapeutic effect by temporarily reducing the activity of the muscle into which it is injected. As with many pharmaceuticals, there is some risk associated with Botox® treatment, including the risk of serious adverse events associated with possible risk of "distant spread of toxin." *See* Ex. A, Decl. of Dr. Sef Kurstjens ¶ 12. This risk appears to increase when very large doses are used, and the doses typically used to treat spasticity tend to be larger than those for other uses. Compl, ¶ 65. A causal connection to Botox® has not been established, and such adverse events are rare, but, based on its review of available medical information, Allergan believes the risk can be reduced further still by proper dosing, patient selection, and injection technique. *See* Ex. A ¶¶ 31–33; Ex. B, Decl. of Beta Bowen ¶¶ 14–15.

[4] The FDA has also approved Botox® Cosmetic, to temporarily improve the look of moderate to severe frown lines between the eyebrows (glabellar lines). Botox® Cosmetic is not at issue in this litigation.

On April 29, 2009, the FDA ordered every manufacturer of botulinum toxin in the United States, including Allergan, to add a "boxed warning" to the drug's label and package insert to address the risk of potential distant spread of toxin and to implement a Risk Evaluation and Mitigation Strategy ("REMS"), including a Dear Health Care Provider letter and a Medication Guide for patients. *See id*. at ¶¶ 71–72; *see also* 21 U.S.C. § 355-1(2)(A) (FDA may require a REMS only based on "new safety information") . The FDA emphasized, however, that it "d[id] not mean in any way to discourage" the use of botulinum toxin for spasticity, as spasticity is a "significant disabilit[y]" for which botulinum toxins are a "very effective" and "commonly used" treatment.[5] The FDA approved Allergan's REMS and new labeling, including the "boxed warning," on July 31, 2009. Compl. ¶ 72–73. The boxed warning states in general terms that such a risk exists and that it "is probably greatest in children treated for spasticity." *Id*.

D. Allergan's Chilled Speech

The boxed warning and REMS materials identify the risk of potential distant spread of toxin effect, but they do not give physicians using Botox® for spasticity specific guidance about how to further minimize that risk while still obtaining an acceptable therapeutic effect. Ex. A ¶ 30. Based on its review of available data, Allergan believes that this risk may be affected by several factors relating to the physician's treatment choices, including the dose used at a given injection site, the number and location of injection sites, the frequency of treatment, the injection technique used, as well as factors relating to patient selection, such as the severity of the spasticity, the presence of local muscle weakness, the patient's overall medical condition including any pre-existing debility and relevant co-morbidities (additional medical conditions), and the patient's

[5] FDA Media Briefing on Botulinum Toxin Products, Transcript, Apr. 30, 2009 at 12, *available at* http://www.fda.gov/downloads/NewsEvents/Newsroom/MediaTranscripts/UCM169170.pdf ("FDA REMS Announcement").

response to previous treatment. *Id*. at ¶¶ 30–33; Ex. B ¶¶ 12–17. Allergan seeks to proactively provide physicians with this important medical information. Ex. A ¶¶ 34–35; Ex. B ¶¶ 25–40.

Allergan is chilled, however, because communicating such medical information to physicians would expose Allegan to criminal liability. Ex. A ¶ 38; Ex. B ¶ 40. First, any expression in tangible media, such as pamphlets, letters to physicians, and printed slide presentations, Ex. B ¶¶ 34–38, would appear to fall within the FDA's definition of "labeling." 21 C.F.R. § 202.1(*l*)(2). Any "suggest[ion]" in such materials that Botox® be used to treat spasticity would thus expose Allergan to liability for the distribution of an unapproved "new drug." 21 U.S.C. §§ 355(a), 321(p). Second, Allergan fears its proposed communications would render Botox® "misbranded" under 21 U.S.C. § 352(f)(1), because its "labeling" would necessarily lack "adequate directions for [the off-label] use." Although Botox®'s "labeling" already contains adequate directions for every on-label use, speech about the use of Botox® to treat spasticity likely would express Allergan's "intent" under 21 C.F.R. §§ 201.100 and 201.128 that Botox® be used for that purpose. Third, the Government's theory that scientific claims about off-label uses, even if objectively true and non-misleading, are prohibited by 21 U.S.C. § 352(a), would cover Allergan's proposed speech. Finally, Allergan fears that communicating with physicians about off-label uses via printed materials or email, *see* Ex. B ¶ 35, would be deemed unlawful "advertisement." 21 C.F.R. § 202.1(e)(4)(i)(a), (*l*)(1).

JURISDICTION

The Declaratory Judgment Act authorizes a district court to issue declaratory relief in "a case of actual controversy within its jurisdiction." 28 U.S.C. § 2201(a). Allergan plainly raises federal questions. *See* 28 U.S.C. § 1331. And the dispute here is clearly an "actual controversy," because it is "definite and concrete, touching the legal relations of parties having adverse legal

interests" and "real and substantial," "admitting of specific relief through a decree of a conclusive character." *Aetna Life Ins. Co. v. Haworth*, 300 U.S. 227, 240–41 (1937).

"[W]here threatened action by government is concerned," neither Article III nor the Declaratory Judgment Act requires a party to "expose himself to liability before bringing suit to challenge the basis of the threat — for example, the constitutionality of a law threatened to be enforced." *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 128–29 (2007). That is particularly true where, as here, the party seeking declaratory relief does so to avoid a chill on the exercise of its First Amendment rights. *See Seegars v. Gonzales*, 396 F.3d 1248, 1252–54 (D.C. Cir. 2005). A First Amendment challenge is ripe if (1) the challenged law "arguably chills" the plaintiff's First Amendment rights; and (2) there is a "credible threat of prosecution" thereunder, meaning that the plaintiff's "intended behavior is covered by the statute and the law is generally enforced." *Chamber of Commerce* v. *FEC*, 69 F.3d 600, 603 (D.C. Cir. 1995); *Seegars*, 396 F.3d at 1252; *see also Babbitt v. United Farm Workers Nat'l Union*, 442 U.S. 289, 302 (1979) (a threat is "credible" unless the State has "disavowed any intention" of prosecuting and fear is "imaginary or wholly speculative."). This standard is readily satisfied here.

First, the chill is profound, direct, and immediate. Allergan would provide physicians with medical information concerning the use of Botox® to treat spasticity, *see* Ex. B ¶¶ 13–17, 25–38, but the challenged statutes and regulations prohibit manufacturer expression so broadly that they appear to criminalize Allergan's sharing with physicians of truthful medical evidence about this use. Rather than "ris[k] prosecution," Allergan has been forced to "abando[n its] rights" and refrain from speaking on this important matter of public concern. *Id*. at ¶ 39; Ex. A ¶ 36; *MedImmune*, 549 U.S. at 129. Second, the threat of prosecution is also far too real. The Act is much more than "generally" enforced. The Department of Justice has aggressively prosecuted

manufacturers for alleged "off-label promotion." *See* GAO Report, *FDA's Oversight of the Promotion of Drugs for Off-Label Uses* 2–3, 26–28 (2008); *see also, e.g., United States v. Eli Lilly & Co.*, No. 09-020 (E.D. Pa. 2009). Further substantiating the threat, in March 2008, the U.S. Attorney's Office for the Northern District of Georgia subpoenaed Allergan, requesting production of documents relating to Allergan's past sales and marketing practices in connection with Botox®. Compl. ¶ 98.

This action seeks prospective relief to halt the ongoing suppression of Allergan's First Amendment freedoms; it does not address past conduct, such as that at issue in the Georgia investigation.[6] The present chill is most evident with respect to Allergan's inability to speak lawfully in support of the REMS, but the chill is broader and more fundamental. The inconsistency that lies at the heart of the FDA's regulatory regime places Allergan in an untenable position. While on the one hand the FDA encourages off-label uses as an integral part of quality medical care, on the other hand its regulations forbid a manufacturer from selling an approved drug with constructive knowledge that it is to be used off-label. 21 C.F.R. §§ 201.100, 201.128. Allergan can hardly avoid violating this Kafkaesque rule. Off-label use accounts for a substantial percentage of Botox®'s total use, Compl. ¶ 55, and this is likely to continue even if the FDA approves Botox® for adult upper-limb spasticity. Allergan's only choice is to speak as little as possible so that prosecutors, in the exercise of their discretion, hopefully will not decide to prosecute it. The danger is thus largely "one of self-censorship[,] a harm that can be realized even without an actual prosecution." *Virginia v. Am. Booksellers Ass'n*, 484 U.S. 383, 393 (1988). This

[6] The existence of a pending investigation is a reason to exercise jurisdiction here, not to decline it. The Declaratory Judgment Act authorizes relief "whether or not further relief is or could be sought" elsewhere. 28 U.S.C. § 2201. When a threat of a federal prosecution is presently injuring a party by chilling its First Amendment rights, district courts can and will adjudicate a declaratory action to vindicate those rights — even if the party demands that the Court enjoin the pending investigation. *Boggs v. Bowron*, 842 F. Supp. 542, 546–49 (D.D.C. 1993). Allergan is not seeking to enjoin the Georgia investigation; *a fortiori*, jurisdiction is proper here.

Court thus should not be "troubled by the pre-enforcement nature of this suit." *Id.* This declaratory action is a suitable vehicle for vindicating Allergan's rights.

ARGUMENT

I. THE PRELIMINARY INJUNCTION FACTORS OF IRREPARABLE HARM, BALANCE OF THE EQUITIES, AND THE PUBLIC INTEREST FAVOR ALLERGAN

Allergan is entitled to a preliminary injunction because it satisfies every prong of the familiar four-factor test: (1) it is substantially likely to succeed on the merits; (2) it is likely to suffer irreparable harm in the absence of preliminary relief; (3) the balance of equities tips in its favor; and (4) an injunction is in the public interest. *See, e.g.*, *Mills v. District of Columbia*, 571 F.3d 1304, 1308 (D.C. Cir. 2009).

Allergan is likely to succeed on the merits as demonstrated in the balance of this brief. In light of the serious First Amendment rights at stake, Allergan will manifestly suffer irreparable injury without this Court's intervention. The "loss of constitutional freedoms, 'for even minimal periods of time, unquestionably constitutes irreparable injury.'" *Id.* at 1312 (quoting *Elrod v. Burns*, 427 U.S. 347, 373 (1976) (plurality)). Irreparable harm occurs whenever "First Amendment interests are either threatened or in fact being impaired at the time relief is sought." *Nat'l Treas. Emps. Union v. United States*, 927 F.2d 1253, 1254–55 (D.C. Cir. 1991) (Thomas, J.) (quoting *Elrod*, 427 U.S. at 373); *see also Chaplaincy of Full Gospel Churches v. England*, 454 F.3d 290, 300 (D.C. Cir. 2006) (collecting cases).

The balance of equities and the public interest also support preliminary relief where, as here, the movant is likely to succeed on the merits of its First Amendment challenge. "These [two] factors merge when the Government is the opposing party." *Nken v. Holder*, 129 S. Ct. 1749, 1762 (2009). This is because the Government and the public have a strong interest in the enforcement of constitutional consumer-protection laws, but no legitimate interest in enforcing *un*constitutional

laws. The public also has a strong interest in access to truthful commercial speech. *See, e.g.*, *Western States*, 535 U.S. at 366. This interest is particularly strong here, because Allergan seeks to provide physicians with important medical information to help them treat their patients safely and effectively. *See* Ex. B ¶¶ 13–17, 31; Ex. A ¶¶ 30–35.

II. ALLERGAN IS LIKELY TO SUCCEED IN SHOWING THAT THE PROHIBITIONS AGAINST OFF-LABEL SPEECH INFRINGE ITS FIRST AMENDMENT RIGHTS

The effective prohibition on all or virtually all truthful, non-misleading manufacturer speech about a lawful off-label use is not contained in a single, readily-identifiable statutory or regulatory provision. Instead, the prohibition is the net effect of a complex web of statutory and regulatory provisions. But this complexity should not obscure the reality that the resulting regulatory regime bans speech about the lawful use of a lawful product in a manner that is unprecedented, antithetical to the First Amendment, and bears almost no resemblance to the underlying statutory regime. As to each of the key provisions that make up this regulatory web, the Government's position is unconstitutional under the First Amendment and invalid as a statutory matter.

A. The First Amendment Rigorously Protects Allergan's Truthful, Non-Misleading Speech to Medical Professionals About Off-Label Uses

1. The Prohibited Speech Is Core Scientific Speech

The FDCA and the FDA's regulations prohibit Allergan from speaking truthfully to health care professionals about medical issues associated with the off-label use of Botox®. This chilled speech is core scientific speech that triggers strict scrutiny. "[T]he First Amendment protects scientific expression and debate just as it protects political and artistic expression." *Bd. of Trustees of Leland Stanford Junior Univ. v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991). Content-based restrictions on such vital speech are "presumptively invalid" and subject to strict scrutiny. *R.A.V. v. St. Paul*, 505 U.S. 377, 382 (1992).

Although the Supreme Court has accorded lesser, but still rigorous, scrutiny to regulations of "commercial speech," it defines this category narrowly as speech that "does no more than propose a commercial transaction." *Edenfield v. Fane*, 507 U.S. 761, 767 (1993). Allergan's speech does not fit that mold.[7] Allergan's speech would do much "more than propose a commercial transaction": Allergan will inform physicians how to reduce the risk of potential distant spread of toxin and to evaluate the risk-benefit profile of Botox® treatment, *see* Ex. B ¶¶ 13–17, 31; Ex. A ¶¶ 30–35, matters primarily related to the audience's legitimate medical interests as physicians. Allergan's speech would not be directly promotional; it would assume a transaction may take place (the physician's purchase of Botox® to use off-label) and provide medical evidence about how to help the physician do so safely. Speech providing further safety and efficacy information may impact off-label sales (doctors may prefer a product they can use safely to treat a serious debility), but that impact makes the speech no less informative.[8]

At most, Allergan's speech would have some implicit "commercial character" because it relates to a product that Allergan manufactures. *Riley v. Nat'l Fed'n of the Blind, Inc.*, 487 U.S. 781, 796 (1988). But any such character will be "inextricably intertwined" with "informative and perhaps persuasive speech." *Id*. In such a case, a court "cannot parcel out the speech, applying one test to one phrase and another test to another phrase"; instead, a court must apply the test for "fully protected expression." *Id*. So too here.

[7] Allergan submits that "commercial speech" is entitled to full First Amendment protection. *See Western States*, 535 U.S. at 367–68 (five Members of the Court have "expressed doubts" about the *Central Hudson* test).

[8] *WLF II* applied a different test, deeming speech "commercial" that is intended "to arouse a desire to buy or patronize" a specific product and that is disseminated with a profit motive. 13 F. Supp. 2d at 64. Allergan does not intend "to arouse a desire to buy or patronize"; Allergan assumes that physicians may purchase Botox® for off-label use, and Allergan intends to educate those purchasers to help them use its product as safely as possible.

2. At a Minimum, Allergan's Proposed Speech Is Rigorously Protected as Commercial Speech Under *Western States*

At a minimum, Allergan's speech is protected as "commercial speech" under the Supreme Court's recent decision in *Western States*. *See* 535 U.S. at 365; *United States v. Caputo*, 517 F.3d 935, 939 (7th Cir. 2008) ("drugs are not a special case for first amendment analysis"). As the Court reiterated, a restriction of "commercial speech" is constitutional only if the Government proves (a) as a threshold matter that the speech "concerns unlawful activity or is misleading"; or (b) that the restriction (1) furthers a "substantial" governmental interest; (2) that it does so "directly"; and (3) that it does so without being "more extensive than is necessary to serve that interest." *Western States*, 535 U.S. at 365 (quoting *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of N.Y.*, 447 U.S. 566 (1980)). The Government cannot shoulder its burden of proving that the sweeping proscriptions of off-label speech pass muster under this rigorous test.

First, Allergan easily passes the *Western States* threshold requirement because it seeks relief only as to non-misleading speech about the lawful use of its lawful product. Although "[o]ffers to engage in illegal transactions are categorically excluded from First Amendment protection," *United States v. Williams*, 128 S. Ct. 1830, 1841 (2008), it is perfectly lawful for a physician to prescribe Botox® for an off-label use. *E.g.*, *WLF IV*, 202 F.3d at 333. An offer to sell Botox® for use to treat spasticity, therefore, is protected speech. *WLF II*, 13 F. Supp. 2d at 66; *Caputo*, 517 F.3d at 939; *cf. Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 571 (2001) ("[S]o long as the sale and use of tobacco is lawful for adults, the tobacco industry has a protected interest in communicating information about its products. . . ."). Moreover, to be excluded as "misleading," commercial speech must be actually or inherently misleading, not merely "potentially misleading." *Ibanez v. Florida Dep't of Bus. & Prof'l Regulation*, 512 U.S. 136, 146 (1994); *WLF II*, 13 F. Supp. 2d at 66. Despite the Government's asserted position that any scientific claims about an off-

label use are automatically "false or misleading" in violation of § 352(a), the FDA itself has acknowledged that this is not so and that a manufacturer's speech about an off-label use is at most "potentially misleading." *See* 62 Fed. Reg. 64,074, 64,079 (Dec. 3, 1997). And when the Government has been bold enough to argue that off-label speech is inherently misleading because the FDA has not evaluated and approved its content, courts have rebuked the Government in the strongest terms. *See WLF II*, 13 F. Supp. 2d at 67 (rejecting this argument as "exaggerat[ing] FDA's overall place in the universe"); *cf. Pearson v. Shalala*, 164 F.3d 650, 655 (D.C. Cir. 1999) (rejecting similar argument as "nearly frivolous").

Turning to *Western States*' three-factor test for non-misleading speech about a lawful product, the 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. *Western States*, 535 U.S. at 369; *WLF II*, 13 F. Supp. 2d at 71. That interest surely may justify some restriction of a manufacturer's ability to market a drug for an off-label use, and it could potentially even be used to justify a regime in which drugs could be prescribed only for FDA-approved uses. That would be a very different regime from the one we have now, however, in which physicians are permitted and even encouraged to prescribe drugs off-label, but manufacturers are forbidden to speak about off-label uses without regard to whether FDA approval for the use at issue has been sought or, indeed, is imminent.

At issue here is whether the Government's interest in encouraging applications for additional uses can justify the suppression of virtually all off-label speech, including Allergan's non-misleading speech to physicians about reducing the risk of potential distant spread of toxin.

The Government's burden is heavy. To survive this as-applied challenge, the Government must prove "not merely that its regulation[s] will advance its interest[s], but also that [they] will do so 'to a material degree.'" *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 505 (1996) (quoting *Edenfield*, 507 U.S. at 771). "[M]ere speculation or conjecture" is insufficient; the Government "must demonstrate that the harms it recites are real and that its restriction[s] will in fact alleviate them." *Edenfield*, 507 U.S. at 770–71. The Government also must prove that the restrictions on commercial speech are "not more extensive than is necessary to serve" its substantial interests. *Western States*, 535 U.S. at 367 (quoting *Central Hudson*, 477 U.S. at 566). "[I]f the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, *the Government must do so*." *Id*. at 371 (emphasis added). "If the First Amendment means anything, it means that regulating speech must be a last — not first — resort." *Id.* at 373.

The Supreme Court's commercial speech jurisprudence makes it abundantly clear that the Government's interest in protecting the public health cannot justify censorship of truthful commercial speech to physicians about public health. The Government may not "preven[t] the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions. . . ." *Id*. at 374–75; *see also 44 Liquormart*, 517 U.S. at 503. A paternalistic approach to regulating speech is "even more unsupportable than usual" when the Government seeks to "protect" health care professionals from truthful medical information. *WLF II*, 13 F. Supp. 2d at 70. Indeed, any paternalistic justification for limiting off-label speech would founder upon the Government's own recognition that doctors are sophisticated enough to make the sometimes life-or-death decision to prescribe a drug off-label. The First Amendment does not permit the Government to force doctors to make that decision with *less* truthful information.

As applied here, therefore, the FDA's regulations must stand or fall on the Government's interest in protecting the integrity of the new drug approval process. To be constitutional under *Western States*, the Government must prove that the suppression of Allergan's non-misleading speech to physicians is no more extensive than necessary to directly further the Government's interest in ensuring that manufacturers seek FDA approval for new uses of drugs. *See Western States*, 535 U.S. at 365. Each of the key regulatory provisions and all of them collectively manifestly fail to meet this test. *See infra* at Part II.B. Since they cannot satisfy this standard, *a fortiori*, they fail strict scrutiny. *See R.A.V.*, 505 U.S. at 382.[9]

B. Allergan Is Likely To Succeed In Challenging The FDA's Prohibitions of Off-Label Speech As Applied to Allergan's Truthful, Non-Misleading Speech

The FDA's off-label promotion regulations violate the Constitution and cannot be squared with the statutory text. As this suit illustrates, the FDA's ban on speech is both sweeping and indiscriminate. Under the FDA's regulations, Allergan's truthful speech to physicians, informing them about the steps they can take to minimize the risk of a rare but serious adverse event while maintaining therapeutic benefits, is just as unlawful as unilaterally including an unapproved use of a drug on its label or running a direct-to-consumer advertisement falsely touting non-existent medical benefits. Indeed, under the "intended use" regulations, the filing of this lawsuit apparently misbrands Botox® because it demonstrates Allergan's "knowledge" that Botox® "is to be used" off-label to treat spasticity. 21 C.F.R. § 201.128. Such a heavy-handed approach leaves no

[9] In the past, the Government has contended that these prohibitions regulate conduct, not speech, but "the activities at issue in this case are only 'conduct' to the extent that moving one's lips is 'conduct' . . ." *WLF II*, 13 F. Supp. 2d at 59. Allergan fears prosecution under the Act for distributing an unapproved "new drug" or a "misbranded" drug. The content of Allergan's speech is an element of each offense. It is unlawful to distribute an FDA-approved drug if its "labeling" (1) contains a "suggest[ion]" of an off-label use, 21 U.S.C. §§ 331(d), 355(a), 321(p); (2) contains statements that are "false or misleading in any particular," §§ 331(a), 352(a); or (3) does not contain "adequate directions for use," §§ 331(a), 352(f)(1). And the FDA's flat ban on advertisement of off-label uses obviously bans speech. Crimes defined by the content of speech in "labeling" and "advertisement" are plainly content-based. S*ee, e.g.*, *Western States*, 535 U.S. at 367 (applying First Amendment scrutiny to prohibition of drug advertisement based on content).

meaningful channels of communication open and suppresses far more speech than is necessary to achieve the Government's stated objective. Accordingly, the FDA's regulations are unconstitutional as applied here.

The FDA's regulations are also invalid as a matter of statutory interpretation. The Act establishes a scheme that creates incentives for manufacturers to seek FDA approval for new uses of drugs so they can market the new use on the drug's label. When correctly interpreted, the Act restricts only a relatively narrow area of protected off-label speech to achieve that end, *i.e.*, written speech on the label itself or "accompanying" the drug in commerce. *See* 21 U.S.C. § 321(m). The Act provides no warrant — and surely no clear warrant — for the FDA to create a regulatory regime that bans off-label speech across the board. Given the serious First Amendment concerns raised by wholesale suppression of protected speech, the lack of clear direction from Congress is dispositive: The FDA's regulations must be set aside as contrary to the Act. Where there are "serious doubts" as to a statute's constitutionality, a court will construe it to avoid the constitutional problem absent "affirmative intention of Congress clearly expressed" to raise that serious constitutional question. *Edward J. DeBartolo Corp. v. Florida Gulf Coast Bldg. & Const. Trades Council*, 485 U.S. 568, 584 (1988); *AFL-CIO v. FEC*, 333 F.3d 168, 175 (D.C. Cir. 2003) (courts do not accord an agency deference when its regulations create serious constitutional difficulties); *Whitaker v. Thompson*, 353 F.3d 947, 952 (D.C. Cir. 2004) ("the canon of constitutional avoidance can trump *Chevron*").

1. Allergan's Challenge to FDA's "Intended Use" Regulations Is Likely To Succeed

The FDA's broadest prohibition of off-label speech stems from its "intended use" regulations. Under 21 C.F.R. §§ 201.100 and 201.128, a manufacturer's expression of its "intent" (and even its mere notice) that doctors will take the perfectly lawful step of using a drug off-label

misbrands the drug in violation of 21 U.S.C. § 352(f)(1), unless the manufacturer adds adequate directions for that off-label use to the drug's "labeling." But §§ 355(a) and 321(p) make it a crime for a manufacturer to change the drug's "labeling" to comply with the FDA's reading of § 352(f)(1) . Thus, the FDA's "intended use" regulations transform the Act into a free-speech Catch-22. Given the prevalence of off-label use, this regulatory regime means that many pharmaceutical companies operate in ongoing violation of the law, and must self-censor in the hope that the Government's prosecutorial discretion will save them. In light of the weighty First Amendment interests at stake, this situation is constitutionally intolerable.

a. The FDA's "Intended Use" Regulations Suppress Far More Speech Than Is Necessary To Create An Incentive for Manufacturers to Seek FDA Approval

The "intended use" regulations are unconstitutional as applied to Allergan's non-misleading speech because the Government cannot prove that such sweeping censorship is "not more extensive than is necessary" to provide an incentive for manufacturers to seek FDA approval for off-label uses. *See Western States*, 535 U.S. at 367 (quotation omitted). The "intended use" regulations are obviously overbroad. The sweeping ban on off-label speech is ostensibly to "incentivize" applications for FDA approval but, symptomatic of the complete lack of tailoring, the ban continues to apply even if that behavior has already been induced and the manufacturer has already applied for FDA approval. In fact, the "intended use" regulations are so overbroad that they stand as an obstacle to a manufacturer lawfully seeking FDA approval. To apply for FDA approval for a new use, a manufacturer must have notice of the possibility and intend that the drug be used to treat that new use, and it must assemble extensive empirical data about that use, including reports of clinical and pre-clinical trials. *See* 21 U.S.C. § 355(b). On the face of the "intended use" regulations, however, the expression and knowledge inherent in these steps would trigger the Catch-22, as they would demonstrate the manufacturer's "objective intent" that the drug

be used for a new use that is not yet on-label. 21 C.F.R. §§ 201.100, 201.128. The "intended use" regulations are thus so broad that they impede the very behavior they seek to induce.[10]

The Government has "numerous and obvious less-burdensome alternatives" at its disposal that would provide direct and powerful incentives for manufacturers to seek FDA approval, in lieu of the "drastic" means of "wholesale suppression of truthful, non-misleading information." *City of Cincinnati v. Discovery Network, Inc.*, 507 U.S. 410, 417 n.13 (1993); *44 Liquormart*, 517 U.S. at 505. For example, the Government could use "more speech," rather than "enforced silence," and require a manufacturer to disclose in speech about an off-label use that the FDA has *not* found the drug to be safe and effective for that use. *44 Liquormart*, 517 U.S. at 498 (internal quotation marks omitted). Such a disclosure would reduce the efficacy of off-label speech as a tool of product promotion and thus preserve the incentive to seek FDA approval for new uses. The Government could tailor restrictions on off-label speech to become progressively less burdensome as a manufacturer progressed through the FDA approval process, thereby creating a direct incentive to seek FDA approval while suppressing correspondingly less speech. The Government could preserve the integrity of the FDA approval process without regulating speech at all, for example by mandating that manufacturers apply for FDA approval of certain off-label uses, such as uses that pass a threshold of prevalence or sales. Or the Government could tax off-label sales more heavily than on-label sales, thereby creating a powerful financial incentive to get important off-label uses on-label.

The Government also could, so far as the First Amendment is concerned, prohibit all off-label sales and all off-label prescriptions. To be sure, this alternative would require revamping the

[10] Even if the Government would not prosecute a manufacturer for engaging in the very behavior it seeks to incentivize, that would be a product of prosecutorial discretion, not any logical limitation of the Government's theory. With First Amendment values at stake, such an overbroad approach is unjustifiable. The Government cannot ban speech in sweeping terms and ask citizens to trust it to exercise prosecutorial discretion. *See, e.g.*, *Chicago v. Morales*, 527 U.S. 41, 60 (1999).

regulatory system because, without access to drugs through off-label prescriptions, patients would demand access through other channels. Either the FDA would have to speed up its approval process massively or the FDA would have to create a far more robust pathway to access investigational drugs. *See No Regulatory Slack for Tough Supplemental Indications*, PINK SHEET, Sept. 7, 2009, at 21 (quoting FDA official as noting that patients have access to cancer drug off-label while it undergoes strict testing that delays approval for new use). But the Government cannot make off-label use integral to quality medical care and a necessary element of its regulatory regime as we know it, while at the same time prohibiting all manufacturer speech about off-label uses on the ground that doing so provides an incentive to seek FDA approval. Surely there is a more tailored means of providing that incentive than a muzzle.

Indeed, the Act itself, when correctly interpreted, stands as an example of a more tailored approach. Under the Act's "new drug" provision, 21 U.S.C. § 355(a), a manufacturer may not "prescrib[e], recommen[d], or sugges[t]" an off-label use on a drug's "labeling," which the Act defines as "written, printed, or graphic matter" upon a drug, its packaging, or "accompanying such article" in interstate commerce, § 321(m). This statutory rule creates a powerful and direct incentive for manufacturers to seek FDA approval for off-label uses. The materials upon a drug's packaging or sent along with a drug in interstate commerce — its "labeling" — are obviously critical from a marketing perspective. *Cf. TrafFix Devices, Inc. v. Marketing Displays, Inc.*, 532 U.S. 23, 28 (2001) (describing trademark protection for "trade dress," including the packaging of a product). Restricting a manufacturer's speech in the critical forum of "labeling" substantially limits the manufacturer's ability to market a drug to promote off-label sales and thereby preserves the manufacturer's incentive to seek FDA approval for new uses. At the same time, however, the Act's narrow definition of "labeling" ensures that manufacturers' First Amendment rights are not

unduly burdened: Some speech is restricted, but most avenues for truthful speech about off-label uses are unfettered.

The "intended use" regulations replace this more-targeted statutory prohibition with a regime that suppresses completely and indiscriminately all off-label speech. *See* 21 C.F.R. §§ 201.100, 201.128; 202.1(*l*)(2), 202.1(e)(4)(i)(a). As the foregoing discussion shows, there are many less-restrictive alternatives available to the Government. The Government cannot prove that these alternatives, alone or in combination, would not directly advance the Government's asserted interest in preserving the integrity of the FDA's approval process. Under *Western States*, therefore, the FDA's "intended use" regulations are unconstitutional as applied here: "[I]f the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, *the Government must do so*." 535 U.S. at 371 (emphasis added).

The "intended use" regulations also "violat[e] the requirement that a legislature establish minimal guidelines to govern law enforcement." *Morales*, 527 U.S. at 60 (internal quotation marks omitted), and the rule that the Government "cannot vest restraining control over the right to speak . . . in an administrative official where there are no appropriate standards to guide his action." *Kunz v. New York*, 340 U.S. 290, 295 (1951). The "intended use" regulation is likely "violated scores of times daily," *Houston v. Hill*, 482 U.S. 451, 466 (1987), as off-label use is commonplace and mere constructive knowledge that a drug will be used off-label is sufficient to trigger the Catch-22 and subject a manufacturer to prosecution. 21 C.F.R. § 201.128. Yet no regulation purports to cabin the prohibition or limit the Government's exercise of its enforcement discretion. Officials at the DOJ and the FDA thus may prosecute virtually any manufacturer they wish, at any time, for engaging in constitutionally protected expression. "Far from providing the 'breathing space' that First Amendment freedoms need to survive," *Houston*, 482 U.S. at 467, this

regime casts a pall on speech, leading manufacturers to silence themselves to diminish the risk of prosecution. The First Amendment does not permit our Government to operate this way.

b. The FDA's "Intended Use" Regulations Are Contrary to the Act

The FDA's "intended use" regulations fail First Amendment scrutiny, whether under *Western States* or, *a fortiori*, under strict scrutiny. At a bare minimum, though, the regulations give rise to grave constitutional doubt. To be valid as a matter of statutory interpretation, therefore, the "intended use" regulations must be supported by a clear demonstration of congressional intent. *DeBartolo*, 485 U.S. at 584. The Act provides no such clear statement. Section 352(f)(1) states that a drug's "labeling" must bear "adequate directions for use"; it does not specify which "use[s]" are covered. If anything, by stating that the directions must appear on "labeling," § 352(f)(1) strongly suggests that directions need be provided only for the "uses" that are suggested on "labeling" — namely, the FDA-approved on-label uses.

The statutory context strongly supports this reading of § 352(f)(1). Even if the phrase "adequate directions for use" in isolation could be susceptible to the FDA's reading, "a reviewing court should not confine itself to examining a particular statutory provision in isolation." *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 132 (2000). Rather, "the words of a statute must be read in their context and with a view to their place in the overall statutory scheme," fitting, "if possible, all parts [of the statute] into an harmonious whole." *Id*. at 133 (internal quotation marks omitted); *see also W. Va. Univ. Hosps., Inc. v. Casey*, 499 U.S. 83, 101 (1991) (courts should "make sense rather than nonsense out of the *corpus juris*"). If § 352(f)(1) requires labeling to bear directions only for uses suggested in that "labeling," then § 352(f)(1) and § 355(a) operate in harmony: To "sugges[t]" a new use in "labeling," FDA approval must be obtained; when this approval is obtained, the FDA will ensure that the directions are adequate. *See* § 355(a), (b), (d). By contrast, the FDA's "intended use" regulations place § 352(f)(1) in conflict with § 355(a): The

former requires a manufacturer to provide "adequate directions" for an off-label use, but the latter makes doing so a crime. Moreover, the statute must be interpreted to make sense in light of the Government's policies of permitting doctors to prescribe drugs off-label and tolerating substantial off-label use for many drugs. It is simply bizarre to create a scheme in which it is unlawful to speak about a lawful act.

The FDA's regulations also read too much into too little. Section 352(f)(1) regulates the content of a drug's "labeling," and it contains no hint that Congress intended to regulate speech *outside* the context of that term of art. Nonetheless, the FDA has used § 352(f)(1) as the basis to assert sweeping regulatory power over manufacturer expression in every forum, to every audience. This is not a reasonable reading of "adequate directions for use" in § 352(f)(1). "Congress . . . does not alter the fundamental details of a regulatory scheme in vague terms or ancillary provisions — it does not, one might say, hide elephants in mouseholes." *Whitman v. Am. Trucking Ass'ns*, 531 U.S. 457, 468 (2001). If Congress had intended the FDA to have comprehensive power to prohibit truthful, non-misleading manufacturer speech about off-label uses — despite the obvious constitutional concerns that such a regime would raise — Congress would have said so clearly, not covertly. *See also DeBartolo*, 485 U.S. at 584.

c. The "Intended Use" Regulation Conflicts With 21 U.S.C. § 353(b)(2), Which Exempts Prescription Drugs From The Act's Adequate Directions For Use Requirement

The FDA's requirement that prescription drugs bear "adequate information" for "intended uses" also conflicts with 21 U.S.C. § 353(b)(2). Section 353(b)(2) provides that "any drug dispensed by . . . prescription . . . shall be *exempt* from the requirements of section 352 of this title, except paragraphs (a), (i)(2) and (3), (k), and (l), and the packaging requirements of paragraphs (g), (h), and (p)." *Id*. (emphasis added). Paragraph (f), which imposes the "adequate directions" requirement, is absent from this plainly exhaustive list. The statute would be no more clear, but a

bit longer, if it provided that "drugs dispensed by prescription shall be exempt from the requirements of paragraphs (b), (c), (d), (e), (f), (i)(1), (j), (m), (n), (o), (q), (r), (s), (t), (u), (v), (w), and (x), and the non-packaging requirements of paragraphs (g), (h), and (p)." Whether stated in terms of inclusion or exclusion, the result is the same: § 352(f) does not apply to prescription drugs. The Act reinforces that prescription drugs are exempt from the ordinary "adequate directions" requirement by imposing a different requirement specifically for prescription drug labeling: A prescription drug is instead misbranded "if at any time prior to dispensing the label of the drug fails to bear, "at a minimum, the symbol 'Rx only.'" § 353(b)(4).

The FDA's "intended use" regulations are contrary to § 353(b). First, 21 C.F.R. § 201.5 defines "adequate directions" to mean directions adequate for a "layman," a standard that by statute prescription drugs cannot satisfy. *Compare* § 201.5(a) *with* 21 U.S.C. § 353(b)(1) (defining prescription drugs as drugs that cannot be used safely by a layman). A different FDA regulation then provides that prescription drugs are exempt from the Act's "adequate *direction*s for use" requirement only if their labeling contains, *inter alia*, "adequate *information*" for use. 21 C.F.R. § 201.100(c)(1) (emphasis added). Under the FDA's regulations, therefore, a prescription drug need not and cannot comply with the "adequate directions" requirement, but it is exempt from this requirement only if its labeling bears "adequate information" for use. This makes no sense.

The FDA has defended this strange regime by adding an additional layer of complexity — namely, by arguing that the § 353(b)(2) exemption arises only at the time when a prescription drug is dispensed and, that prior to dispensing, its labeling must bear "adequate directions for use." *E.g., United States v. Evers*, 643 F.3d 1043, 1050–52 (5th Cir. 1981) (accepting this argument). But the FDA's regulations do not regulate *when* a drug's labeling must bear adequate directions; they simultaneously provide that a prescription drug's labeling can *never* bear "adequate

directions" for use, 21 C.F.R. § 201.5(a), and that it must *always* bear "adequate information" for use, 21 C.F.R. § 201.100(c)(1). In all events, because the FDA's "intended use" regulations provoke grave constitutional doubt, the FDA's interpretation of § 353(b)(2) must be supported by clear congressional intent. *DeBartolo*, 485 U.S. at 584. It is not, and accordingly it must be set aside.

2. Allergan's Challenge to The FDA's Re-Definition of "Labeling" Is Likely to Succeed

The Act expressly grants the FDA authority to regulate the content of a drug's "labeling," *e.g.*, 21 U.S.C. §§ 352(a), 352(f)(1), 355(a), 321(p), which it defines narrowly as "written, printed, or graphic matter" upon a drug, its "container[s] or wrappers," or "accompanying such article," § 321(m). Allergan proposes to disseminate informational materials generally to health care professionals; these materials would not be sent along with any particular article of Botox® in connection with its sale. *See* Ex. B ¶¶ 25, 33–38. These materials thus would not be "labeling" under the Act. *See Kordel*, 335 U.S. at 348–50. The FDA has re-defined "labeling," however, to extend far beyond its statutory moorings. To the FDA, materials are "labeling" if they are tangible, disseminated by the manufacturer, and contain manufacturer-supplied drug information. 21 C.F.R. § 202.1(*l*)(2). Crucially, materials may be "labeling" even if they do not "accompan[y]" a drug in any meaningful sense. The application of the FDA's expanded definition of "labeling" to proscribe Allergan's speech is contrary to § 321(m) and exacerbates the First Amendment difficulties with the rest of the FDA's interrelated off-label-use regulations.

a. The FDA's Definition of "Labeling" Suppresses Far More Speech Than Is Necessary To Create An Incentive for Manufacturers to Seek FDA Approval

The FDA's expansion of "labeling" to include virtually any drug materials disseminated by a manufacturer radically restricts a manufacturer's freedom to speak about lawful off-label uses of its products, because the term "labeling" defines the scope of the Act's prohibitions. First, under

the Government's interpretation of "false or misleading" in § 352(a), it is unlawful for a manufacturer to make scientific claims about an off-label use in "labeling." *See WLF II*, 13 F. Supp. 2d at 67. Second, a "suggest[ion]" in "labeling" that a drug be used off-label transforms an "old" drug into a "new drug" that cannot be sold. §§ 355(a), 321(p). To make matters worse, the FDA has not defined "sugges[t]." This word is broad and vague in ordinary speech. *E.g.*, WEBSTER'S NEW INT'L DICTIONARY 2521 (2d ed. 1954) ("To put (something) into one's mind"; "to call or bring to mind by way of a mental process"); OXFORD ENGLISH DICTIONARY 118 (2d ed. 1989) ("To cause to be present to the mind as an object of thought."). The uncertain meaning of "suggests" magnifies the First Amendment problem, as manufacturers will avoid disseminating any materials discussing of off-label uses, rather than risk violating § 355(a) by "bring[ing] to a [physician's] mind" the lawful off-label use of the drug. *See Keyishian v. Bd. of Regents*, 385 U.S. 589, 603–04 (1967). The FDA's re-definition of "labeling" and its failure to define "suggests," in statutory context, thus combine to deter virtually all tangible manufacturer expression about off-label use — just as they have deterred Allergan's communication of important medical evidence to an audience of physicians.

The Government's interest in encouraging manufacturers to seek FDA approval for new uses of drugs cannot justify such sweeping suppression of protected speech. As set forth above, the Government could further that interest through numerous less-restrictive means, such as by mandating disclosure of the lack of FDA approval, requiring manufacturers to seek FDA approval for off-label uses that become common, taxing off-label sales more heavily, developing more tailored regulations of speech, *see supra* at 27–29, or simply applying the statute and its more modest conception of labeling set forth in § 321(m), *see infra*. In light of these myriad less-restrictive alternatives, the Government cannot prove that the FDA's expansive re-definition of

"labeling" is "not more restrictive than is necessary." *Western States*, 535 U.S. at 365 (quoting *Central Hudson*, 477 U.S. at 566).

b. The FDA's Re-Definition of "Labeling" Is Contrary to the Act's Definition of "Labeling"

At a minimum, the FDA's re-definition of "labeling" creates grave constitutional doubt by greatly restricting a manufacturer's freedom to speak about a lawful use of a lawful product. To be valid, 21 C.F.R. § 202.1(*l*)(2) must be supported by a clear indication of Congress's intent for "labeling" to encompass the broad universe of protected speech that the FDA seeks to regulate. *DeBartolo*, 485 U.S. at 575. Congress has given no such clear indication. Congress defined "labeling" as "written, printed, or graphic matter" upon a drug itself, its immediate or other "containers or wrappers," or "accompanying such article." 21 U.S.C. § 321(m), (k). The verb "accompany" means "[t]o go with as a companion or associate; to go along with." WEBSTER'S NEW INT'L DICTIONARY, *supra*, at 16; *see also* 1 OXFORD ENGLISH DICTIONARY, *supra*, at 60 ("accompanying" means "[a]cting as a companion; going along with; attending; attached; appended"). Congress thus did not clearly express an intent to encompass materials that are not sent along with an article of a drug in connection with its sale; such materials do not "accompany" a drug, as that word is ordinarily understood.

The statutory context further confirms that Congress intended "accompanying" in its ordinary sense, not in some abstract metaphysical sense. Words "are generally known by the company they keep." *Logan v. United States*, 128 S. Ct. 475, 482 (2007). In the Act, "accompanying such article" appears along with "written, printed, or graphic matter" upon a drug itself, its "immediate container," and upon "any of its containers or wrappers," § 321(m), (k), all terms with a plainly tangible meanings. Yet the FDA has imparted an intangible meaning to

"accompanying," reading it to mean materials that "contai[n]" drug information. 21 C.F.R. § 202.1(*l*)(2). This reading of "accompanying" parts company with the rest of § 321(m).

The FDA's interpretation of "accompanying" also violates the rule that, if possible, a statute should be read as a harmonious whole to make sense, not nonsense, out of the statute. *Brown & Williamson*, 529 U.S. at 133; *Casey*, 499 U.S. at 101. Under the FDCA, the prohibited act is the introduction into interstate commerce of an article of a "misbranded" or unapproved "new drug." 21 U.S.C. §§ 331(a), (d), 355(a). The violation is thus tied to the introduction of a physical drug into commerce. Interpreting "accompanying" to reach materials that are not distributed along with a particular physical article, 21 C.F.R. § 202.1(*l*)(2), gives rise to confusion and produces irrational results: Either there is no crime at all, because no particular "misbranded" or "new" drug can be identified as having been introduced into commerce accompanied by the offending "labeling," or *all* distribution of the drug is a crime — no matter the proportion of off-label uses. This anomaly disappears, however, if "labeling" is given its ordinary meaning to refer only to materials sent along with a particular shipment of a drug in connection with its sale: Each illicit shipment would be readily identified.

A page of history further confirms the error of the FDA's reading of "accompanying." When Congress defined "labeling" in 1938, the then-prevailing understanding was that Congress's Commerce Clause power extended only to the "original package" of items shipped in commerce. *E.g., Vance v. W. A. Vandercook Co.*,170 U.S. 438, 444–45 (1898). And the Supreme Court had held that Congress's power to regulate an original package of drugs extended just far enough to reach materials that are "*accompan[ying] the article in the package*." *7 Cases of Eckman's Alterative v. United States*, 239 U.S. 510, 517 (1916) (emphasis added). Congress's choice of language in § 321(m) thus was no accident; in drafting § 321(m), Congress incorporated *7 Cases'*

operative language nearly verbatim. It is thus unthinkable that Congress intended for the definition of "labeling" to extend federal control over materials disseminated without connection to a particular shipment of a drug: The Congress responsible for the language would have viewed doing so as blatantly unconstitutional.

Lacking support in the Act's text, context, structure, or history, the FDA relies solely on isolated language in *Kordel* to support its reading of "accompanying." *See* 62 Fed. Reg. 64,074, 64,076 (Dec. 3, 1997). But *Kordel* supports Allergan's measured reading of "accompanying," not the FDA's inflated conception of it. The question in *Kordel* was whether a manufacturer can evade the "labeling" definition by the simple expedient of sending the drug and the written materials in separate packages. Not surprisingly, the Court answered that question in the negative, but it limited its holding to the facts of the case. The Court held that written materials "accompany" a drug, despite being sent in physically separate shipments, provided that they are (1) sent from the same place; (2) to the same place; (3) as part of an "integrated . . . transactio[n]"; and (4) they "supplement or explain" the use of the drug, thereby having a "textual relationship" to it. 335 U.S. at 348–50. The FDA, however, has taken just one of the four factors supporting the Court's decision — the "textual relationship" — and treated it as if it were sufficient alone. *See* 62 Fed. Reg. at 64,076 (*Kordel* establishes that if "material supplements, explains, or is otherwise textually related to a product, it is deemed to accompany the product"). Nothing in *Kordel* justifies the FDA's sweeping rule.

Regardless, even if the FDA's effort to expand *Kordel* beyond all recognition were a minimally permissible interpretation of ambiguity in § 321(m), the canon of constitutional avoidance would preclude application of this expansive definition here. *Founding Church of Scientology v. United States*, 409 F.2d 1146 (D.C. Cir. 1969), is instructive. In *Founding Church*,

the Church was prosecuted for misbranding the "e-Meter," a device central to its religious practice, by making "false or misleading" statements about its medical benefits in religious literature the Church distributed separately. *See id*. at 1151–53, 1158–59. A conviction for making "false or misleading" religious claims would pose a serious Free Exercise Clause problem. *See id*. at 1156–57. Accordingly, rather than construing "accompanying" broadly to encompass the literature, the Court construed it narrowly to avoid the constitutional doubt. *See id*. at 1159. This Court should do the same here. Because construing "accompanying" expansively to encompass generally-disseminated materials would produce a serious First Amendment problem by greatly restricting manufacturers' ability to speak truthfully about the lawful off-label use of their products, this Court should follow *Founding Church* and read "accompanying" reasonably to avoid the problem.[11]

3. Allergan's Challenge to the Government's Interpretation of "False or Misleading" Is Likely to Succeed

The Act deems a drug "misbranded" if its "labeling" is "false or misleading in any particular." 21 U.S.C. § 352(a). The Government takes the position that § 352(a) prohibits any scientific claims about off-label uses that the FDA has not reviewed and approved — even statements that accurately describe *bona fide* scientific research. *See WLF II*, 13 F. Supp. 2d at 67; *Warner-Lambert* Sentencing Memo at 8–9. This interpretation does violence not only to the English language, but also to the First Amendment.

It is one thing for the Government to ban false or misleading commercial speech, but quite another to ban speech merely because its content is not Government-approved. The First

[11] *Founding Church* involved the Free Exercise Clause, not the Free Speech Clause, but that is because at the time it was decided, "commercial speech" was understood to lack any Free Speech Clause protection. *See Valentine v. Chrestensen*, 316 U.S. 52, 54 (1942). The Court now recognizes that the First Amendment robustly protects commercial speech. *E.g., Western States*, 535 U.S. at 366–67. *Kordel* likewise was decided even before the Court recognized First Amendment protection for commercial speech and therefore provides no support for the constitutionality of 21 C.F.R. § 202.1(*l*)(2). On the constitutionality of § 202.l(*l*)(2), *Western States* is the apposite precedent, not *Kordel*.

Amendment permits the former, but was adopted precisely to prevent the latter. *See, e.g.*, *Patterson v. Colorado*, 205 U.S. 454, 462 (1907). The Government's interpretation of § 352(a) also runs directly counter to the First Amendment principle that the public health is hampered — not materially furthered — by the suppression of truthful, non-misleading speech about prescription drugs. *See Western States*, 535 U.S. at 374–76. To the extent that a manufacturer's scientific claims about its product are potentially misleading because the audience must take into account the manufacturer's self-interest in the product, *see* 62 Fed. Reg. at 64,079, any potential to mislead — which is unlikely to be lost on doctors in any event — can be cured through myriad less intrusive means, such as simply requiring a manufacturer to disclose its self-interest. *See also supra* at 27–29. In short, there can be no justification for prohibiting speech that is not actually misleading under the guise that it is "false or misleading."

The Government's interpretation of § 352(a) is self-evidently contrary to its plain language. The Act prohibits labeling claims that are "false or misleading in any particular." It does not purport to prohibit statements that are *not* misleading. Indeed, a House Report explained that "Congress *may not*, by a simple and unqualified prohibition against misleading representation, penalize the making of a representation of therapeutic effect regarding the truth of which expert opinion differs." H.R. Rep. No. 73-2139, at 7 (1938), *reprinted in* 6 Legis. History of the Federal FDCA and Its Amendments 300, 306 (1979). When the Government argued the contrary in *WLF*, this Court correctly observed that in appointing itself the exclusive and final arbiter of whether an assertion is misleading, the FDA "exaggerated [its] overall place in the universe." *WLF II*, 13 F. Supp. 2d at 67; *cf. Pearson*, 164 F.3d at 655 (rejecting similar argument as "nearly frivolous"). At the very least, § 352(a) surely does not prohibit non-misleading speech *unambiguously*. Given the

patent unconstitutionality of the Government's reading of § 352(a), the lack of clear statutory support is sufficient to foreclose it.[12]

4. Allergan's Challenge to the FDA's *Per Se* Ban on Off-Label "Advertisement" Is Likely to Succeed

Western States leaves no doubt that application of the FDA's flat ban on off-label prescription-drug advertisement in 21 C.F.R. § 202.1(e)(4)(i)(a) to Allergan's proposed speech also would be unlawful. As in *Western States*, the FDA's regulation is a *per se* ban on a form of commercial advertisement for a lawful product or service. 535 U.S. at 368. As in *Western States*, the Government must defend its *per se* ban as necessary to promote the integrity of the new-drug approval process. *Id*. Having made the decision to permit doctors to prescribe drugs for off-label uses, the Government cannot require prescription decisions to occur in a no-speech zone where the entity with the greatest incentive to speak is silenced for fear that its speech will unduly sway doctors. Such paternalism has been rejected with regard to far less sophisticated audiences. *See id.* at 374–76. As in *Western States*, the Government could create incentives for manufacturers to seek FDA approval without taking the "drastic" means of the "wholesale suppression of truthful, non-misleading information." *Id*.; *44 Liquormart*, 517 U.S. at 505. In addition to the many less-restrictive approaches discussed above, *see supra* at 27–29, the FDA could require manufacturers to disclose in any off-label advertisement the fact that the use being advertised is not FDA-approved. Such disclosures would undermine the efficacy of advertisements as a tool for driving sales, and thus manufacturers would retain the incentive to seek FDA approval for off-label uses. "The fact that all of these alternatives could advance the Government's asserted interests in a

[12] The Government's reading of § 352(a) also violates the rule of lenity. *See United States v. Granderson*, 511 U.S. 39, 54 (1994). Having not set forth its utterly countertextual reading of § 352(a) in formal regulations, the Government cannot prosecute a manufacturer for violating it. *See United States v. Farinella*, 558 F.3d 695, 699 (7th Cir. 2009) (it is unconstitutional "to convict a person of a crime because he violated some bureaucrat's secret understanding of the law").

manner less intrusive to First Amendment rights indicate[s] that the law [is] more extensive than necessary," and therefore unconstitutional. *Western States*, 535 U.S. at 371–72 (internal quotation marks and alterations omitted).

To be sure, the Government's interests in protecting public health and preserving the new-drug approval process may justify some restrictions on off-label advertisement. But the FDA prohibits *all* off-label advertisement. The ban applies whether the advertisement is misleading or truthful; and although health care professionals understand the distinction between on-label and off-label uses, understand a manufacturer's profit motive, and can use their professional expertise to critically evaluate manufacturers' claims, the ban applies equally to *direct-to-physician* and *direct-to-consumer* advertisements. *See* 21 C.F.R. § 202.1(e)(4)(i)(a). The FDA has also not defined "advertisement." Like the word "suggested" in 21 U.S.C. § 321(p), advertisement" is ambiguous and reasonably understood to encompass a vast array of speech. *Compare* WEBSTER'S NEW INT'L DICTIONARY, *supra*, at 39 ("to give notice to; to inform; to notify"), *with id*. ("to call public attention to, esp. by emphasizing desirable qualities in order to arouse a desire to purchase"). The uncertain scope of the FDA's prohibition magnifies the chilling effect, as manufacturers will engage in even less speech to avoid potential liability. *See Keyishian*, 385 U.S. at 603–04. Although targeted and well-defined restrictions on direct-to-consumer advertisement could potentially withstand constitutional scrutiny, the FDA's undifferentiated ban cannot.

Yet again, the FDA's indiscriminate approach to banning off-label speech is also contrary to the Act. Under 21 U.S.C. § 352(n), prescription-drug advertisements are *lawful* provided that they disclose the drug's "established name," its formula, and "such other information in brief summary relating to side effects, contraindications, and effectiveness" as the Secretary shall require. Rather than ban advertisements, the Act permits them with appropriate disclosures.

Section 352(n) further reinforces that more speech — not censorship — is the proper course by providing that, "except in extraordinary circumstances, no regulation . . . shall require prior approval by the Secretary of the content of any advertisement." *Id.*

The FDA has turned § 352(n)'s disclosure scheme on its head. Rather than setting forth the "brief summary" information that an off-label advertisement must disclose, the FDA has chosen the route of "enforced silence." *44 Liquormart*, 517 U.S. at 498. The FDA also effectively contradicts the Act's express command against "requir[ing] prior approval by the Secretary of the content of [an] advertisement," by permanently withholding approval where an advertisement's content relates to an off-label use. In short, § 202.1(e)(4)(i)(a) would not be a reasonable interpretation of § 352(n) even under *Chevron*. And given the serious constitutional doubt that arises from the FDA's flat ban on truthful advertisement of off-label uses to physicians — and the fact that the constitutional problem would disappear under the disclosure regime mandated by the Act itself — no statutory ambiguity could support the FDA's *per se* ban.

C. The FDA's Prohibitions of Off-Label Speech Are Unconstitutional As Applied to Allergan's Speech Under the Unique Circumstances of This Case

For the reasons set forth above, the FDA's prohibitions against off-label speech are far too broad to be constitutionally applied to suppress Allergan's non-misleading speech about the lawful use of its lawful product. At the very least, however, these prohibitions cannot be constitutionally applied in the unique circumstances of this case, where (1) Allergan is already in the process of seeking FDA approval for the use of Botox® to treat adult upper-limb spasticity; (2) the use of Botox® to treat spasticity is widely medically accepted; or (3) in the new "boxed warning" and in connection with the REMS for Botox®, the FDA has required Allergan to speak about the use of Botox® for spasticity. Under these circumstances, any interest that the Government otherwise might have in suppressing Allergan's speech falls away.

First, the Government's only asserted interest in suppressing off-label speech is its interest in ensuring that manufacturers seek FDA approval for new uses of drugs. *See United States v. Caronia*, 576 F. Supp. 2d 385, 398 (E.D.N.Y. 2008); *WLF II*, 13 F. Supp. 2d at 70–71; *see also Western States*, 535 U.S. at 369. Allergan is in the final stages of the FDA approval process for the use of Botox® to treat upper-limb spasticity in adults. Compl. ¶¶ 57–58. Whatever the weight of the Government's interest in other settings, when a manufacturer is actively seeking approval for a particular use, that interest cannot justify the wholesale suppression of the manufacturer's off-label speech. Indeed, Allergan has already spent years and millions of dollars in conducting clinical studies and preparing the application to the FDA. There is no reason to impose a draconian penalty — the total suppression of Allergan's speech, and the resulting lack of information for physicians — to ensure that Allergan will continue to pursue the drug approval process.

Second, the prohibitions on off-label speech cannot be sustained as applied to an off-label use that is already widely accepted in the medical community. When the off-label use of a drug becomes sufficiently prevalent, it becomes virtually impossible for a manufacturer not to have "knowledge of facts that would give [it] notice" that its drug will be used off-label. 21 C.F.R. § 201.128. Botox®'s use for spasticity is so well established that, since 1998, at least one statutorily-recognized medical compendium has listed Botox® for a spasticity-related indication. Compl. ¶ 61. Because of these listings, Medicaid is required by statute to reimburse prescriptions for Botox® to treat these off-label indications. *See* 42 U.S.C. §§ 1396b(i)(10), 1396r-8(k)(2)-(3), 1396r-8(k)(6), 1396r-8(g)(1)(B)(i). Such compendium listings plainly give a manufacturer "notice" that its drug will be used off-label. *See* 21 C.F.R. §§ 201.100, 201.128. At the same time, such compendium listings reflect wide medical support for that use, which belies any notion that everything the manufacturer could say about that use will be "false or misleading" in violation of §

352(a). And where a drug is being widely used off-label, it is all the more important that the manufacturer be free to communicate truthful information about that use, rather than silenced by a two-faced legal regime that encourages widespread off-label use but requires the manufacturer to pretend that the off-label use is not occurring and remain silent in an effort to avoid liability. It would be nothing short of perverse to impose criminal liability on a manufacturer for speaking truthfully about an off-label use that is widely recognized.

Third, the prohibitions on off-label speech cannot be sustained as applied to an off-label use about which the Government is requiring the manufacturer to speak. The FDA recently required Allergan to alter Botox®'s package insert to mention safety risks associated with the off-label use of Botox® to treat spasticity, including especially its use to treat children with cerebral palsy. Compl. ¶¶ 71–74. The FDA also required Allergan to develop documents for distribution to patients and health care professionals describing these risks. *Id*. The FDA's actions reflect the reality, as discussed above, that the use of Botox® for spasticity is widespread and medically supported. The FDA's actions were intended to make this use of Botox® safer, not to stamp it out. *Id*. at ¶ 75; *see* FDA REMS Announcement at 12 (the FDA "d[id] not mean in any way to discourage" the use of Botox® for spasticity). Allergan's proposed speech would communicate additional, more detailed safety information and thus would further the interest that the Government itself has identified. Where the FDA has recognized the need for truthful speech by a manufacturer about an off-label use, it can serve no legitimate interest to suppress additional truthful speech by the manufacturer about that use.

CONCLUSION

The Government's complicated regulatory web leaves Allergan with no lawful avenue to provide truthful and non-misleading information about a lawful use of its product. To justify the suppression of Allergan's truthful speech, the Government must prove, at a minimum, that the

suppression is not more extensive than necessary to directly further its substantial interests. *Western States*, 535 U.S. at 367, 373. Allergan recognizes the Government's substantial interest in providing incentives for drug manufacturers to seek FDA approval for additional uses, and that interest could justify some measured and clear restrictions on a manufacturer's ability to speak about off-label uses of prescription drugs. Such a measured and clear approach would be a welcome change, however, from the current regime of indiscriminate suppression. The Government has made no meaningful effort to tailor its position to further its interests while leaving room for protected speech, nor has it attempted to prove that the staggering breadth of its sweeping restrictions is necessary. "If the First Amendment means anything, it means that regulating speech must be a last — not first — resort. Yet here it seems to have been the first strategy the Government thought to try." *Id*. at 373. The Government's regulatory regime thus violates the First Amendment. And because that regime finds no warrant in the Act itself, the Government's position also fails as a matter of statutory interpretation. For the foregoing reasons, Allergan respectfully requests that the Court preliminarily enjoin the defendants from enforcing the challenged statutes and regulations against it based on its truthful, non-misleading speech about the off-label use of Botox® until a final resolution of this matter.

Respectfully submitted,

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October 1, 2009

CERTIFICATE OF SERVICE

I hereby certify that I have this day caused true and correct copies of the foregoing to be served via mail or personal service upon:

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This 1st day of October, 2009.

/s/
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