**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

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| **ALLERGAN, INC.,**<br><br>**Plaintiff,**<br><br>**vs.**<br><br>**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,**<br><br>**Defendants.** | **CASE NO.: _____** |

**COMPLAINT**

Plaintiff Allergan, Inc. ("Allergan") makes this Complaint for declaratory judgment and injunctive relief against Defendants the United States of America, the United States Food & Drug Administration, Dr. Margaret Hamburg, and Kathleen Sebelius, stating as follows:

## I. THE PARTIES

1. Allergan is a Delaware corporation with its principal place of business at 2525 Dupont Drive, Irvine, California 92612. Allergan manufactures pharmaceutical and biological products, including onabotulinumtoxinA (formerly known by the non-proprietary name botulinum toxin type A), which is marketed for prescription, physician-administered use as Botox®.

2. Defendant the United States Food & Drug Administration ("FDA") is a federal agency of the United States, within the United States Department of Health & Human Services ("HHS"). The FDA is responsible for approving, disapproving, and otherwise regulating food,

drugs, medical devices, and biologics under the Food, Drug, & Cosmetic Act (the "Act"). The FDA's headquarters are in Silver Spring, Maryland.

3. Defendant Dr. Margaret Hamburg is sued in her official capacity as the Commissioner of Food and Drugs, the most senior official at the FDA. As Commissioner, Dr. Hamburg is directly responsible for execution and administration of the Act.

4. Defendant Kathleen Sebelius is sued in her official capacity as the Secretary of HHS, which in turn is the parent of the FDA. Secretary Sebelius is Commissioner Hamburg's immediate superior, and as such Secretary Sebelius is responsible for the execution and administration of the Act.

## II. JURISDICTION AND VENUE

5. This action seeks declaratory relief under the Federal Declaratory Judgment Act, 28 U.S.C. § 2201.

6. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. § 1331 because all causes arise under the Constitution and laws of the United States.

7. Venue is proper in this judicial district pursuant to 28 U.S.C. § 1391(e).

8. There is currently an actual, justiciable controversy between the parties considering the constitutionality and meaning of the statutes and FDA regulations that the Government uses to ban and punish a pharmaceutical manufacturer's speech.

9. Declaratory relief will resolve this controversy and eliminate the chill that such statutes and regulations currently have on Allergan's First Amendment rights.

10. A preliminary injunction against the Defendants, preventing them from enforcing the challenged statutes and regulations, will shield Allergan's First Amendment rights from ongoing harm while this litigation is pending.

11. A permanent injunction against the Defendants, preventing them from enforcing the challenged statutes and regulations, will protect Allergan's rights prospectively after the final resolution of this matter.

## III. FACTUAL ALLEGATIONS

### A. The Statutory Scheme.

12. The Food, Drug, & Cosmetic Act ("Act") prohibits the introduction or delivery for introduction into interstate commerce of any new drug or biologic that has not been approved by the FDA. 21 U.S.C. §§ 331(d), 355(a); 42 U.S.C. § 262(a). The Act also prohibits the introduction or delivery for introduction into interstate commerce of any drug or biologic that is "misbranded." 21 U.S.C. §§ 331(a), 352; 42 U.S.C. § 262(j). The Act authorizes United States District Courts to restrain violations of the Act's "new drug" or "misbranding" requirements. 21 U.S.C. § 332. Violation of the Act's "new drug" or "misbranding" requirements is also a criminal offense. 21 U.S.C. § 333(a); 42 U.S.C. § 262(f).

13. To obtain FDA approval for a "new drug" or new biologic, a pharmaceutical manufacturer must submit a detailed application to the FDA. The new drug application ("NDA") includes, *inter alia*, detailed reports of pre-clinical and clinical trials demonstrating safety and efficacy and proposed labeling for the drug or biologic. 21 U.S.C. § 355(b); 42 U.S.C. § 262(a); 21 C.F.R. § 601.2. The FDA then evaluates whether the drug is safe and effective (or the biologic is safe, pure, and potent) under the conditions "prescribed, recommended, or suggested" in the proposed labeling, and ensures that the labeling is not "false or misleading in any particular." 21 U.S.C. § 355(d); 42 U.S.C. § 262(a); 21 C.F.R. § 601.2.

14. If the FDA approves a drug or biologic application, the approval extends only to the conditions indicated on the FDA-reviewed "labeling." If the manufacturer subsequently

alters the "labeling" to "prescribe[e], recommen[d], or sugges[t]" a new use for that drug, then the FDA deems that drug a "new drug," 21 U.S.C. § 321(p), and the manufacturer must apply for and obtain FDA approval for that new use. 21 U.S.C. § 355(a); 42 U.S.C. § 262(a).

15. The Act defines a "label" to mean "a display of written, printed, or graphic matter upon the immediate container of any article." 21 U.S.C. § 321(k). The Act defines "labeling" to mean "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). 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).

16. The Act's prohibition against the introduction into interstate commerce of a "misbranded" drug also regulates the content of a manufacturer's speech in a drug's "labeling." A drug is "misbranded," *inter alia*, if the manufacturer alters the FDA-approved labeling to include a statement that is "false or misleading in any particular." 21 U.S.C. § 352(a). A statement may be false or misleading because it is affirmatively misleading or because of material omissions. 21 U.S.C. § 321(n). A drug is generally "misbranded" if its labeling lacks "adequate directions for use," 21 U.S.C. § 352(f)(1), but the Act exempts "drug[s] dispensed by . . . prescription" 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.'" 21 U.S.C. § 353(b)(4).

17. The Act also deems a prescription drug "misbranded" unless "all advertisements and other descriptive printed matter" issued by the manufacturer with respect to that drug 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 shall be required in regulations issued by the Secretary. 21 U.S.C. § 352(n).

18. Although the Act prohibits a manufacturer from introducing into interstate commerce a drug if its labeling "prescribe[s], recommend[s], or suggest[s]" that the drug be used for a use that the FDA has not approved, 21 U.S.C. §§ 355(a), 321(p), the Act does not limit or interfere with the authority of a health care professional to prescribe or administer any legal drug or biologic to a patient to treat any condition or disease in any manner.

19. Health care professionals may lawfully prescribe or use an FDA-approved drug both for any uses suggested on the labeling itself, *i.e.*, "on-label uses," and in ways that are not prescribed, recommended, or suggested on the FDA-approved labeling, *i.e.*, "off-label uses."

20. Off-label use of prescription drugs is common, and in some medical specialties it accounts for a majority of prescriptions.

21. Many off-label uses have become the standard of medical care.

22. The FDA has expressly recognized the freedom that health care professionals enjoy to use and prescribe approved drugs off-label: "[O]nce a [drug] product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens of patient populations that are not included in approved labeling." 59 Fed. Reg. 59,820, 59,821–22 (Nov. 18, 1994) (internal quotation marks omitted) (alterations in original).

23. On its face, the Act permits a pharmaceutical manufacturer to speak freely to health care professionals about an off-label use of a prescription drug, provided that (1) the manufacturer does not alter the drug's "labeling" so as to (a) "prescrib[e], recommen[d], or sugges[t]" that drug for the off-label use; (b) render the labeling "false or misleading in any particular"; or (c) deprive the labeling of "adequate directions for use" (if § 352(f)(1) applies at

all to prescription drugs); and provided (2) that any "advertisement" for that prescription drug discloses the information required under 21 U.S.C. § 352(n).

**B. The Regulatory Regime.**

24. The FDA, however, has promulgated a series of overlapping and interlocking regulations that combine to render unlawful virtually all manufacturer communication, through any avenue, to any audience, about the lawful off-label use of a prescription drug. These regulations may prohibit a manufacturer from providing information about the safe and effective use of FDA-approved drugs for off-label indications and even prohibit a manufacturer from informing medical professionals who already use a drug off-label how to minimize the risk of rare but serious adverse events. The FDA's regulations violate manufacturers' First Amendment rights while also impairing public health and safety.

25. By regulation, the FDA has radically expanded the scope of materials deemed "labeling." As noted, the Act defines "labeling" to encompass "written, printed, or graphic matter" found upon the article itself, its "containers or wrappers," or "accompanying such article." 21 U.S.C. § 321(k), (m). This is a relatively narrow category of manufacturer expression. In 21 C.F.R. § 202.1(*l*)(2), however, the FDA redefined "labeling" to mean any "[b]rochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug 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." The FDA has thus redefined "labeling" to encompass any tangible materials distributed by the manufacturer that contain manufacturer-

supplied drug information, irrespective of whether those materials "accompan[y an] article" of a drug as 21 U.S.C. § 321(m) requires.

26. Due to the FDA's redefinition of "labeling," it is unlawful for a manufacturer to disseminate tangible materials containing manufacturer-supplied drug information if those materials "sugges[t]" that a drug be used off-label, as it is unlawful to make such a "suggest[ion]" in "labeling" absent FDA approval. *See* 21 U.S.C. §§ 321(p), 355(a). The FDA has not defined "suggest" to provide any guidance to manufacturers as to what, if any, expression in labeling about an off-label use would be lawful.

27. Due to the FDA's redefinition of "labeling," it is also unlawful for a manufacturer to disseminate tangible materials containing manufacturer-supplied drug information, if those materials contain any statement that is "false or misleading in any particular." 21 U.S.C. § 352(a).

28. Although the Government may regulate speech that is actually or inherently false or misleading consistent with the First Amendment, *Ibanez v. Florida Dep't of Bus. & Prof'l Regulation*, 512 U.S. 136, 142, 146 (1994), the Government has interpreted § 352(a) to prohibit not just speech that is actually false or misleading, but also to reach protected speech that is neither actually nor inherently false or misleading.

29. The Government has interpreted § 352(a) to prohibit the inclusion in labeling of any "scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs" where the FDA has not "had the opportunity to evaluate" those claims — even when *bona fide* scientific research establishes that the manufacturer's scientific claims are true. *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998), *vacated as moot on other grounds sub. nom. Wash. Legal Found. v. Henney*, 202 F.3d

331, 333 (D.C. Cir. 2000). Similarly, in criminal prosecutions, the Government has interpreted § 352(a) to be violated by the mere "suggest[ion] that [a] drug is safe and effective for uses which have not been approved by the FDA" — irrespective of the scientific support for such a suggestion. U.S. Sentencing Memorandum at 8–9, *United States v. Warner-Lambert Co.*, No. 04-10150 (D. Mass. 2004).

30. The FDA's expansive definition of "labeling" and the Government's counter-textual reading of § 352(a) substantially impair a manufacturer's ability to communicate truthful and important information to health care professionals to reduce the risk of potentially serious adverse events arising from an off-label use of a prescription drug. For example, a statement acknowledging that many doctors have found a drug useful for an off-label use, and then addressing the appropriate dosage for that use in light of a risk of serious adverse events, would appear to run afoul of the Government's interpretation of § 352(a).

31. By regulation, the FDA has also prohibited a manufacturer from communicating truthful off-label safety information to medical professionals via direct-to-physician "advertisement." Although the Act generally permits "advertisements" for prescription drugs, provided only that the advertisements disclose certain information, 21 U.S.C. § 352(n), FDA regulations provide that "[a]n 'advertisement' for a prescription drug "shall not 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). Direct-to-physician advertisements suggesting off-label uses are thus flatly unlawful, irrespective of the nature or quantity of the manufacturer's informational disclosures about that use. *Id.*

32. The FDA's expansive definition of "labeling" and its outright prohibition on "advertisement" combine to leave little, if any, space in which a manufacturer may lawfully

communicate truthful and important information to health care professionals about an off-label use of a prescription drug.

33. By regulation, the FDA has eliminated any last sliver of arguable breathing room by rendering unlawful apparently any manufacturer communication about an off-label use of a prescription drug. The Act generally deems a drug "misbranded" if its labeling lacks "adequate directions for use." 21 U.S.C. § 352(f)(1). But the Act exempts "drug[s] dispensed by . . . prescription" from this requirement. 21 U.S.C. § 353(b)(2).

34. In conflict with 21 U.S.C. § 353(b)(2)'s exemption for prescription drugs, an FDA regulation nonetheless provides that a prescription drug is exempt from the requirement that its labeling bear "adequate *directions* for use" only if its labeling bears "adequate *information* for its use." 21 C.F.R. § 201.100(c)(1) (emphasis added).

35. FDA regulations further define "adequate information" for a prescription drug's use to mean directions under which medical professionals "can use the drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.100(c)(1). Under the FDA's regulations, a drug's "intended uses" are not limited to the uses listed in its FDA-approved "labeling." Instead, a drug's intended uses encompass "all purposes for which it is advertised or represented." *Id*. Because a drug's FDA-approved labeling by definition includes only directions for on-label uses, if a manufacturer "advertise[s] or represent[s]" a prescription drug for an off-label use, the drug is automatically and necessarily misbranded.

36. FDA regulations further expand the scope of this prohibition by defining a drug's "intended uses" to encompass any use "objective[ly] inten[ded]" by the manufacturer. 21 C.F.R. § 201.128. According to the "intended use" regulation, a manufacturer's "objective intent" may be shown via manufacturer expression in any forum, be it in labeling, advertisement, or in any

other "oral or written statements." *Id*.; *see also id*. (objective intent is 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"). Most broadly, if a manufacturer merely "*knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with*" those uses. *Id*. (emphasis added). FDA regulations thus require that a prescription drug bear adequate directions for any "intended use," with "intended use" defined to include every use that the manufacturer intends or of which the manufacturer has knowledge or notice.

37. Under the "intended use" regulations of 21 C.F.R. §§ 201.100 and 201.128, any affirmative manufacturer communication about an off-label use — no matter where or how the communication is made, who the audience is, how truthful the information is, or how copiously the manufacturer discloses the lack of FDA approval for the use — would arguably demonstrate the manufacturer's "intent" to sell the drug for that off-label use under the FDA's broad and counter-intuitive conception of "intent." Any such communication would demonstrate that the manufacturer knew or should have known that the drug is used off-label. See 21 C.F.R. § 201.128. Under 21 C.F.R. §§ 201.100 and 201.128, therefore, a manufacturer that speaks about an off-label use thus must provide "adequate directions" for that off-label use in the drug's "labeling."

38. The manufacturer cannot, however, lawfully alter the "labeling" of a drug to provide "adequate directions" for an off-label use. Such a modification to a drug's FDA-approved "labeling" would transform the drug into a "new drug" that cannot be sold. 21 U.S.C. §§ 321(p), 355(a).

39. The confluence of the "intended use" regulations and the "new drug" statute effectively places a manufacturer's truthful speech regarding off-label uses under a prior restraint. This restraint is only lifted when, if at all, the FDA approves the off-label use.

40. FDA approval takes years, costs millions of dollars, and is an uncertain endeavor, as the FDA may refuse the application for approval. Even if the manufacturer seeks FDA approval, off-label uses may become widespread and medically supported while the manufacturer awaits the FDA's decision.

41. In the interim period after a manufacturer communicates, or gains "knowledge of facts that would give him notice," that a drug is used to treat an off-label condition, but before the FDA approves the drug to treat that use, a manufacturer is caught in a Catch-22: changing the drug's labeling to add directions for that off-label use violates § 355(a)'s "new drug" rule, but *not* changing the labeling to add directions for that use will violate § 352(f)(1)'s rule against "misbranding." The manufacturer cannot avoid violating at least one criminal provision, and it may well violate both provisions. If the manufacturer does not add adequate directions for use (and so squarely violates § 352(f)(1)), but its "labeling" as broadly construed by the Government still "suggest[s]" an off-label use, then it violates § 355(a) as well. And if the manufacturer does provide directions for the off-label use (and so squarely violates § 355(a)), but the FDA deems those directions inadequate, then the manufacturer violates § 352(f)(1) as well. At a minimum, though, a manufacturer's communication about (or even mere knowledge of) the off-label use of a prescription drug renders *per se* unlawful what otherwise is a lawful sale of a lawful product to be used in a lawful manner.

42. Under the Government's interpretation of these statutes and regulations, when a drug's off-label uses become significant, or when an off-label use presents a risk to public health

that the manufacturer could mitigate by providing truthful information about that off-label use, the manufacturer may not speak about (or, indeed, have knowledge of) that use. No amount of disclosure by the manufacturer would render such truthful speech lawful.

43. The Acting United States Attorney for the District of Massachusetts recently explained the breadth of this theory, in relation to a criminal prosecution that produced a $2.3 billion settlement: "Any indication not on the label is off-label, and selling an approved drug intending that it be used for an off-label use is a violation of the law." Michael Loucks, Justice Dep't Press Conference, Health Care Fraud Settlement with Pfizer (Sept. 2, 2009).

44. The FDA has promulgated no regulations that would ameliorate the substantial chill that the Government's interpretation of these statutes and its regulations has placed on manufacturers' truthful, non-misleading speech to medical professionals about off-label uses of prescription drugs.

45. Rather, the FDA itself has asserted that "[a]n approved new drug that is marketed for an unapproved use is an unapproved new drug with respect to that use," and that "[a]n approved 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.'" 74 Fed. Reg. 1694 (Jan. 13, 2009); 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").

46. Although the FDA has issued a "Good Reprint Practices" guidance document, this document does not reduce the substantial chill the FDA's regulations impose on manufacturers' off-label speech. The Guidance states that a manufacturer may distribute reprints of certain

articles in medical journals or reference publications. *Id*. The Guidance does not apply to distribution of an article that was "written, edited, excerpted, or published specifically for, or at the request of," a manufacturer or that was "edited or significantly influenced" by a manufacturer "or any individuals having a financial relationship with the manufacturer." *Id*. More fundamentally, even within the very limited window of speech considered "Good Practice" under the Guidance, the manufacturer faces the risk of prosecution because "Guidance documents do not establish legally enforceable rights or responsibilities." 21 C.F.R. § 10.115(d)(1). Indeed, the Guidance itself states that it does not "operate to bind FDA or the public," let alone prosecutors at the Department of Justice.

47. Introduction of a "misbranded" drug or an unapproved "new drug" into interstate commerce is generally a misdemeanor, although the offense becomes a felony if it is committed "with the intent to defraud or mislead" or after a prior conviction has become final. 21 U.S.C. § 333(a).

48. Conviction under the Act also may carry serious collateral consequences. Under 42 U.S.C. § 1320a-7(b), the Secretary may exclude from participation in any federal health care program an individual or entity that has been convicted of a criminal offense "relating to fraud, theft, embezzlement, breach of fiduciary responsibility, or other financial misconduct" "in connection with the delivery of a health care item or service or with respect to any act or omission" in a government-operated health care program. If the conviction is for a felony offense in connection with the delivery of a health care item or service, exclusion is mandatory. 42 U.S.C. § 1320a-7(a)(3). To the extent a "new drug" or "misbranding" violation arising from off-label speech falls within the scope of § 1320a-7, a conviction therefore carries a risk of total exclusion from federal reimbursement.

49. The Government has aggressively prosecuted pharmaceutical manufacturers for "off-label promotion," *i.e.*, the purported crime of speaking about an off-label use of an FDA-approved prescription drug. See GAO Report, FDA's Oversight of the Promotion of Drugs for Off-Label Uses at 26–27 (2008), available at http://www.gao.gov/cgi-bin/getrpt?GAO-08-835 ("DOJ Oversight Report"); *see also, e.g.*, *United States* v. *Eli Lilly & Co.*, No. 09-020 (E.D. Pa. 2009); *United States* v. *Eli Lilly & Co.*, No. 05-01884 (S.D. Ind. 2005); *United States* v. *Warner-Lambert Co.*, No. 04-10150 (D. Mass. 2004). In addition to criminal liability, these enforcement actions may involve civil remedies such as disgorgement and civil restitution for alleged violations of the Act. *See* 21 U.S.C. § 332(a); Complaint for Permanent Injunction, *United States* v. *Eli Lilly & Co.*, No. 05-01884 (S.D. Ind. 2005).

50. Faced with prosecution for alleged "off-label promotion," manufacturers have settled the claims against them at substantial cost. *See, e.g.*, DOJ Oversight Report at 2–3, 27 (reporting settlements for $430 million and more than $500 million). For example, Eli Lilly & Co. recently settled charges of "off-label promotion" of Zyprexa for more than $1.4 billion. FDA News, Eli Lilly & Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa, Jan 15, 2009, *available at* http://www.usdoj.gov/opa/pr/2009/January/09-civ-038.html.

**C. Allergan's Products and their Uses.**

51. Among other products, Allergan produces and markets onabotulinumtoxinA (formerly known by the non-proprietary name botulinum toxin type A) for injection by health care professionals under the name Botox®. The FDA has approved Botox® to treat strabismus (crossed eyes), blepharospasm (spasm of the eyelids) associated with dystonia, cervical dystonia (involuntary neck muscle contractions), and severe primary axillary hyperhidrosis (excess underarm sweating) that is inadequately managed by topical agents. Dystonias are involuntary

muscle contractions, and Botox® is injected into the affected muscles to relieve them. Botox® was first approved in the United States in 1989.

52. The FDA has also approved Allergan's distribution of Botox® Cosmetic (onabotulinumtoxinA), a prescription drug injected by a physician 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.

53. Botox® is a purified protein formulation that is administered through an injection by a physician. The effect of Botox® lasts from approximately one to six months, depending on the individual patient, dose, site of injection, and other circumstances of the particular use.

54. Botox® is currently approved for more than 20 indications in approximately 80 countries. Allergan monitors and reports every available adverse event report received following treatment with Botox® anywhere in the world.

55. Although many health care professionals frequently use Botox® to treat on-label conditions, health care professionals use Botox® even more often to treat off-label conditions.

56. Health care professionals frequently use Botox® off-label to treat various conditions associated with spasticity, such as post-stroke spasticity in adults and lower-limb spasticity in pediatric patients with cerebral palsy ("juvenile cerebral palsy" or "JCP"). Like dystonia, spasticity results from involuntary muscle contractions, which Botox® relieves in the same way as when it is used for dystonia.

57. In August 2008, Allergan submitted a supplemental Biologics License Application (sBLA), seeking approval for the use of Botox® to treat adults who suffer from upper-limb spasticity after stroke. Allergan received a "complete response letter" from the FDA on May 26, 2009. Although Allergan requested approval only for treatment of adult upper-limb

spasticity experienced after stroke, the FDA's letter proposed approving Botox® to treat all adult upper-limb spasticity regardless of cause.

58. The FDA's letter acknowledges that Allergan's sBLA supports the efficacy and safety of Botox® for the treatment of upper-limb spasticity, but requests that Allergan provide additional details about certain clinical trials. The FDA further requested that Allergan conduct a post-approval study to test Botox® in the treatment of upper-limb spasticity in pediatric patients ages 2 to 17. Allergan submitted this requested information to the FDA on September 29, 2009.

59. Botox® is approved to treat spasticity in adults or children in more than 60 countries, including Canada, Germany, Norway, Sweden, the United Kingdom, Australia, and Japan.

60. Although the FDA has not yet approved Botox® to treat any spasticity disorders, the use of Botox® to treat spasticity is sufficiently common that it is a medically accepted standard of care: Health care professionals frequently use Botox® to treat spasticity; statutorily recognized compendia cite botulinum toxin type A use for spasticity-related indications, and Medicaid is statutorily required to reimburse prescriptions for Botox® to treat these compendia-listed spasticity indications; Medicare reimburses for the use of Botox® to treat certain spasticity-related indications; the FDA has openly acknowledged the widespread use of Botox® to treat spasticity; and Botox® is widely approved to treat spasticity in other countries.

61. For each year since 1998, there has been support in one or more statutorily recognized medical compendia for use of botulinum toxin type A to treat a spasticity-related indication. For the last six years of its existence (2002–2007), the United States Pharmacopeia compendium listed botulinum toxin type A for at least one spasticity-related indication. The

Drugdex compendium has also consistently listed botulinum toxin type A for use for at least one spasticity-related indication.

62. Because of these compendia listings, the federal Government reimburses Botox prescriptions to treat spasticity. Medicaid generally reimburses for "covered outpatient drugs" used for a "medically accepted indication." *See* 42 U.S.C. §§ 1396b(i)(10), 1396r-8(k)(2)-(3). In defining "medically accepted indication," the Medicaid statute refers to uses that are supported by citations in several listed compendia. *See* 42 U.S.C. §§ 1396r-8(k)(6), 1396r-8(g)(1)(B)(i). If a compendium lists a drug for a particular condition, Medicaid must reimburse prescriptions for that condition.

63. The Medicare statute prohibits reimbursement for expenses that are not "reasonable and necessary for the diagnosis or treatment of illness or injury." 42 U.S.C. § 1395y(a)(1)(A). For an off-label use to satisfy the "reasonable and necessary" requirement, Medicare contractors must determine the use to be "medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice." *Medicare Benefit Policy Manual*, Ch. 15, § 50.4.2, *available at* http://www.cms.hhs.gov/Manuals/downloads/bp102c15.pdf. All or virtually all Medicare contractors thus reimburse for the use of Botox® to treat spasticity-related indications.

**D. Adverse Events Associated with Botox for Spasticity and the FDA's Response**

64. The FDA has evaluated records of adverse event reports submitted to the agency via the Adverse Event Reporting System over the time that all botulinum toxin products have been on the global market. In response to FDA's request, Allergan submitted more than 1,000 pages of clinical data, including pediatric safety data, for the FDA's review. The FDA also requested and reviewed data from drug sponsors that manufacture different a formulation of botulinum toxin Type A and a formulation of botulinum toxin Type B.

65. On February 8, 2008, the FDA issued an Early Communication based on its review of the data for all botulinum toxin products. The Early Communication stated that the Agency had "received reports of systemic adverse reactions including respiratory compromise and death following the use of botulinum toxins types A and B for both FDA-approved and unapproved uses. The reactions reported are suggestive of botulism, which occurs when botulinum toxin spreads in the body beyond the site where it was injected. The most serious cases had outcomes that included hospitalization and death, and occurred mostly in children treated for cerebral palsy-associated limb spasticity." The FDA's press release accompanying the Early Communication stated that, "based on the FDA's ongoing safety review, the agency said the reactions may be related to overdosing. There is no evidence that these reactions are related to any defect in the products." "The most severe adverse effects were found in children treated for spasticity in their limbs associated with cerebral palsy."

66. Following the FDA's identification of the risk of potential distant spread of botulinum toxin effects, the FDA concluded that the labeling for all botulinum toxin products, including Botox®, required updated warnings regarding the potential for spread of toxin effect beyond the site of local injection, including the potential for dysphagia (difficulty swallowing) and breathing difficulties. The FDA concluded that the risk of such serious adverse effects is probably greatest in children treated for spasticity.

67. On February 29, 2008, Allergan submitted a proposed modification to the Botox® package insert and a proposed "Dear Doctor" letter to the FDA for review and comment based on the reported cases of possible distant spread of toxin. The draft package insert and letter stated: "In clinical trials for pediatric cerebral palsy, doses greater than 8 U/kg [units per kilogram] have not been adequately studied."

68. Eight units per kilogram body weight is comparatively lower than dose recommendations developed in certain physician-organizational treatment guidelines and retrospective chart reviews supporting safe use of Botox®.

69. On March 4, 2008, the FDA responded, instructing Allergan to remove the statement that "in clinical trials for pediatric cerebral palsy, doses greater than 8 U/kg have not been adequately studied." The FDA stated that, "as written, this implies that doses less than or equal to 8 U/kg have been adequately studied in clinical trials for pediatric cerebral palsy; however, this is not an approved use in the United States."

70. Consistent with the FDA's March 4 instruction to delete the warning that doses greater than 8 U/kg have not been adequately studied, on March 18, 2008, Allergan submitted a revised draft package insert to the FDA that did not include that statement. The pediatric use section of the existing package insert was left unchanged, however, stating that "safety and effectiveness in children below the age of 12 have not been established for blepharospasm or strabismus, or below the age of 16 for cervical dystonia or 18 for hyperhidrosis."

71. On April 29, 2009, Allergan received a formal requirement from the FDA that Allergan implement safety label changes to Botox® and that it implement a Risk Evaluation and Mitigation Strategy ("REMS"), including a Medication Guide for patients. *See* 21 U.S.C. 355-1(2)(A) (the FDA may require a REMS when justified by "new safety information").

72. In the April 29, 2009 letter, the FDA proposed a new "boxed warning" stating: "Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved

uses, including spasticity in children and adults, and in approved indications, cases of spread of effect have occurred at doses comparable to those used to treat cervical dystonia and at lower doses."

73. On July 31, 2009, the FDA approved the REMS, including the new boxed warning. The final FDA-approved boxed warning was identical to the warning that FDA had proposed in its April 29, 2009 letter. The FDA also approved Allergan's Dear Health Care Provider letter and Medication Guide in a form nearly identical to that originally proposed by FDA.

74. The REMS requires Allergan to communicate regarding the risk reflected in the boxed warning and to ensure that the safety message is understood and acted upon so that Allergan can report back to the FDA to show whether the benefits of the drug outweigh the risks. The approved letter and guide contain certain information related to the risk to pediatric cerebral palsy patients of Botox® treatment, but the materials do not contain more detailed information related to an evaluation of pre-existing co-morbidities (additional relevant medical conditions) such as dysphagia or aspiration pneumonia, or more detailed information relevant to other factors such as dose, site of injection, or frequency of dosing.

75. Although the FDA has taken steps to warn physicians in general terms about the risk of potential distant spread of toxin associated with use to treat spasticity, the FDA also has recognized the validity of this treatment. In a press conference on April 30, 2009, announcing changes to the labeling of Botox® and other botulinum toxin drugs, the Acting Deputy Director for the FDA's Office of Drug Evaluation, Dr. Ellis Unger, recognized that use of botulinum toxin products, including Botox®, to treat spasticity "is becoming more common." FDA News, Transcript, FDA Media Briefing on Botulinum Toxin Products, Apr. 30, 2009 at 17, *available at*

http://www.fda.gov/downloads/NewsEvents/Newsroom/MediaTranscripts/UCM169170.pdf. The FDA further strongly suggested that Botox® was a safe and effective treatment for spasticity: "[T]hese are patients who have . . . significant disabilities because of spasticity, and these [botulinum toxin] products offer a . . . very effective means to relieve a very important problem and they're commonly used. And we do not mean in any way to discourage that kind of use." *Id.* at 11.

**E. Allergan's Proposed Speech.**

76. The FDA has required Allergan to warn health care professionals about a rare but serious safety risk potentially associated with the use of Botox® to treat spasticity. The FDA-approved boxed warning, the FDA-approved Dear Health Care Provider letter, and the FDA-drafted Medication Guide provide general warnings but do not provide additional, specific guidance to physicians as what steps they can take, if they use Botox® for spasticity, to achieve the desired effect while reducing the risk of adverse events and improving the overall risk-benefit profile. In particular, the FDA-approved communications do not provide detailed information concerning factors such as dose at an injection site, the number of injection sites, frequency of administration, injection technique, or the patient's overall medical condition, such as any pre-existing debility, relevant co-morbidities, and the patient's response to previous treatment,.

77. To supplement this general warning with additional information to help health care professionals balance appropriately the relevant risks and benefits of Botox® treatment, Allergan would like to communicate with health care professionals to convey to them the medical information that Allergan possesses.

78. Allergan does not seek to engage in direct-to-consumer communications about the off-label use of Botox®.

79. In all the communications outlined below, Allergan would disclose that Botox® is not approved by the FDA for the treatment of spasticity and that the FDA has not approved the specific information that Allergan is sharing with these physician audiences.

80. Allergan would inform health care professionals about the significant clinical safety data Allergan has gathered through its monitoring of adverse events and clinical trials relating to the dosing of Botox for spasticity in children two years or older. The exact dosage and number of injection sites should be tailored to the patient's needs based on the size, number, and location of the muscles involved as well as the severity of the spasticity, presence of local muscle weakness, and the patient's response to previous treatment.

81. Allergan would inform physicians that the full effect of an injection of Botox® may not be apparent until a significant period of time after the injection. Allergan's clinical studies and clinicians' experience indicate that treatment of spasticity with Botox® does not lead to clinical improvement immediately; usually clinical improvement occurs in the first two weeks after injection. However, benefits may continue to accrue for several weeks after injection, and the therapeutic effect of the injection diminishes only gradually. A subsequent treatment at a given site should normally be administered only after the therapeutic effect of a previous injection has diminished, typically not more frequently than every three months.

82. Allergan would inform physicians about patient selection, especially within JCP patients. The severity of overall debility in JCP varies significantly in sub-populations. For instance, treatment considerations and the overall risk-benefit assessment for a hemiplegic patient (whose spasticity is limited to one side of the body) may vary significantly from those of a quadriplegic patient (with generalized spasticity involving all four limbs, often with neck and sometimes facial/swallowing/respiratory involvement). Further, some patients may be in stable

overall health with few co-morbidities, while others may suffer from significant co-morbidities that could be relevant to a decision to use Botox®. The existence and severity of certain co-morbidities may bear on the appropriate dose, number or location of treatment sites, pre- and post-treatment management, and consideration of whether botulinum toxin treatment is appropriate for the patient.

83. Allergan would pursue a wide-ranging communication plan to ensure that the relevant physician audiences receive the important information that Allergan possesses.

84. Allergan would instruct Company medical and scientific representatives to visit treating physicians across the United States who treat spasticity in pediatric cerebral palsy patients in order to provide information as described above.

85. Allergan would draft and distribute printed and electronic communications for treating physicians relating to treatment of spasticity in pediatric patients with cerebral palsy in order to provide information as described above.

86. Allergan would make formal presentations to physicians at meetings of professional societies, such as the 38th Annual Meeting of the Child Neurology Society on October 14, 2009 in Louisville, Kentucky, and the American Academy of Physical Medicine and Rehabilitation in Austin, Texas on October 22, 2009. Allergan would make presentations at these conventions and host meetings for smaller groups of treating physicians at these conventions. Allergan's presentations and meetings would present clinical safety risk data relating to dosing, total dose exposure, frequency of dosing, injection technique, and the importance of consideration of the patient's presentation and underlying co-morbidities.

87. Allergan would design and implement content for academic lecture forums such as continuing medical education, grand rounds, and injection training programs regarding the use

of Botox® for treatment of spasticity, including spasticity associated with JCP. These programs would focus on providing information to physicians likely to treat spasticity, with a particular focus on treatment of JCP. Allergan would develop specific slide presentations regarding the assessment of dosing and underlying debility based on information collected and synthesized by Allergan. Allergan would emphasize the importance of dosing, total dose exposure, frequency of dosing, proper and safe injection technique, and the importance of consideration of the patient's presentation and underlying co-morbidities.

88. Allergan fears, however, that its planned truthful, non-misleading scientific speech to physicians about the use of Botox® to treat spasticity would lead to criminal prosecution and severe civil penalties. The Government's interpretation of the statutes and FDA regulations set forth above comprehensively prohibits a manufacturer from speaking truthfully to health care professionals about how to improve the risk-benefit profile associated with off-label uses of prescription drugs.

89. Allergan does not propose to alter any "written, printed, or graphic matter" found upon Botox® itself, its "containers or wrappers," or "accompanying such article" in interstate commerce. §§ 321(m), (k). Allergan's speech thus would not constitute "labeling" as defined in the Act. *See Kordel*, 335 U.S. at 348–50.

90. Nonetheless, if Allergan were to engage in the speech it proposes, as outlined above, much of its speech would fall within the FDA's expansive definition of "labeling." 21 C.F.R. §202.1(*l*)(2). The FDA thus would deem Botox® "misbranded" if, in such expression, Allergan made any scientific claims that the FDA had not previously approved, on the theory that unapproved speech is inherently "false or misleading."

91. In addition, Allergan fears that its expression of true medical information would be deemed by the Government to be a "suggest[ion]" that Botox® be used to treat spasticity, and thus expression of such information also would give rise to a substantial risk that Allergan would be prosecuted for distributing an unapproved "new drug." 21 U.S.C. § 321(p).

92. To the extent that forms of Allergan's proposed speech would constitute "advertisement," Allergan's truthful and non-misleading speech would violate 21 C.F.R. § 202.1(e)(4)(i)(a).

93. Any of Allergan's proposed communications, whether or not in the forms of "labeling" or "advertisement," would render Botox "misbranded" under the Government's interpretation of the statutes and regulations discussed above, including the FDA's "intended use" regulations. Allergan cannot speak to physicians about the use of Botox® to treat spasticity without Allergan being on "notice" that those doctors may use Botox® to treat spasticity. Indeed, to the extent that truthful safety information would lead physicians to believe that the risk associated with off-label uses of Botox® is relatively low, Allergan's speech may encourage such uses. Under 21 C.F.R. §§ 201.100 and 201.128, the proposed speech would be sufficient to show "intent," and intent is sufficient to render unlawful an otherwise lawful sale of Botox® to a physician who may lawfully prescribe Botox® off-label.

94. Even by filing this complaint and thereby exercising its First Amendment right to petition the Government, Allergan fears that it will run afoul of the FDA's regulatory regime by demonstrating its knowledge that Botox® is sold to physicians who use it to treat spasticity and other off-label conditions. On the Government's view, Allergan's possession of this knowledge — and its choice to defend its constitutional rights — violates 21 C.F.R. § 201.128 on its face.

95. The Government has substantiated the threat to Allergan through its aggressive prosecution of constitutionally protected manufacturer speech under the theory that such speech constitutes unlawful "off-label promotion": "Any indication not on the label is off-label, and selling an approved drug intending that it be used for an off-label use is a violation of the law." Michael Loucks, Justice Dep't Press Conference, Health Care Fraud Settlement with Pfizer (Sept. 2, 2009).

96. To avoid prosecution and civil penalty for exercising its First Amendment rights, Allergan has refrained from engaging in truthful scientific speech on a matter of medical concern.

97. Allergan's allegations in this Complaint are justiciable.

98. Allergan's fear of prosecution for its planned truthful, non-misleading speech about off-label uses of Botox® is substantiated by the Government's aggressive prosecution of pharmaceutical manufacturers for "off-label promotion" as described above, and also by the fact that Allergan currently is the subject of a Department of Justice investigation in the Northern District of Georgia that concerns past sales and marketing practices in connection with Botox®.

## COUNT I

### The FDA's Definition of "Labeling" in 21 C.F.R. § 202.1(*l*)(2) is Unconstitutional or Invalid As Applied To Allergan's Proposed Speech

99. Allergan incorporates and realleges Paragraphs 1–98 as if fully set forth herein.

100. The First Amendment protects Allergan's truthful, non-misleading speech about off-label uses of Botox®.

101. The Act prohibits a manufacturer of an FDA-approved drug from introducing a drug into interstate commerce if the manufacturer has "prescribed, recommended, or suggested" a new off-label use for that drug in its "labeling." 21 U.S.C. §§ 331(d), 355(a), 321(p). The Act

defines "labeling" to encompass only "written, printed, or graphic matter" found upon a drug itself, its "containers or wrappers," or "accompanying such article." §§ 321(m), (k).

102. The FDA, however, has defined "labeling" far more broadly, to encompass all tangible materials distributed by the manufacturer that contain manufacturer-supplied drug information. 21 C.F.R. § 202.1(*l*)(2). The FDA deems these materials "labeling" irrespective of whether those materials "accompan[y an] article" of a drug, as 21 U.S.C. § 321(m) requires.

103. 21 C.F.R. § 202.1(*l*)(2) vastly increases the amount of a manufacturer's protected expression that is deemed "labeling." Because the Act's "new drug" and "misbranding" prohibitions are keyed to "labeling," 21 C.F.R. § 202.1(*l*)(2) correspondingly increases the amount of a manufacturer's protected expression that is prohibited under the Act.

104. Allergan does not propose to alter any "written, printed, or graphic matter" found upon Botox® itself, its "containers or wrappers," or "accompanying such article" in interstate commerce. §§ 321(m), (k). Allergan's speech thus would not constitute "labeling" under § 321(m), but it may constitute "labeling" under 21 C.F.R. § 202.1(*l*)(2).

105. As-applied to prohibit Allergan's proposed truthful speech, 21 C.F.R. § 202.1(*l*)(2) violates the First Amendment.

106. 21 C.F.R. § 202.1(*l*)(2) is also invalid because it is inconsistent with 21 U.S.C. § 321(m). At the very least, 21 C.F.R. § 202.1(*l*)(2) is an unreasonable interpretation of any ambiguity in § 321(m), in particular because the FDA's definition suppresses a vast array of constitutionally protected expression and thus gives rise to grave constitutional doubt.

107. Allergan has no adequate remedy at law.

108. Allergan thus seeks the entry of a judgment declaring that 21 C.F.R. § 202.1(*l*)(2) is unconstitutional as applied to prohibit a manufacturer's truthful and non-misleading speech

about off-label uses, or that it is invalid because it conflicts with or is an unreasonable interpretation of 21 U.S.C. § 321(m).

## COUNT II

### 21 U.S.C. § 352(a)'s Prohibition on Labeling that is "False or Misleading in Any Particular" Is Unconstitutional As Applied To, or Does Not Encompass, Speech About Off-Label Uses That Is Actually Truthful And Non-Misleading

109. Allergan incorporates and realleges Paragraphs 1–108 as if fully set forth herein.

110. The First Amendment protects Allergan's truthful, non-misleading speech about off-label uses of Botox®.

111. The Act prohibits a manufacturer from introducing a drug into interstate commerce if its "labeling" is "false or misleading in any particular." 21 U.S.C. §§ 331(a), 352(a).

112. The Government has prosecuted manufacturers on the ground that any manufacturer speech about an off-label use, even if not actually false or misleading, is nonetheless "false or misleading" under 21 U.S.C. § 352(a) because the manufacturer's speech has not been approved by the FDA.

113. This interpretation of § 352(a) renders unlawful a manufacturer's protected expression, and thereby unconstitutionally infringes Allergan's free speech rights protected under the First Amendment.

114. This interpretation of § 352(a) is also contrary to the plain text of § 352(a) itself, which prohibits only statements in labeling that are actually "false or misleading in [a] particular." At the very least, this interpretation is an unreasonable interpretation of § 352(a), in particular because it suppresses a vast array of constitutionally protected expression and thus gives rise to grave constitutional doubt.

115. Allergan has no adequate remedy at law.

116. Allergan thus seeks the entry of a judgment declaring that 21 U.S.C. § 352(a) is unconstitutional as applied to a manufacturer's truthful and non-misleading speech about off-label uses in "labeling," or that § 352(a) does not prohibit a manufacturer's truthful and non-misleading speech about off-label uses in "labeling."

## COUNT III

### The FDA's Prohibition of any "Advertisement" for an Off-Label Use in 21 C.F.R. § 202.1(e)(4)(i)(a) is Unconstitutional or Invalid

117. Allergan incorporates and realleges Paragraphs 1–116 as if fully set forth herein.

118. The First Amendment protects Allergan's truthful, non-misleading speech about off-label uses of Botox®, even when made in the context of commercial advertisement. *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002).

119. The Act prohibits the introduction of "misbranded" drugs into interstate commerce. 21 U.S.C. § 331(a). The Act deems a prescription drug "misbranded" if an "advertisement" issued by the manufacturer with respect to that drug fails to disclose the "established name" of the drug, its formula, and "such other information in brief summary relating to side effects, contraindications, and effectiveness" as shall be required in regulations issued by the Secretary. 21 U.S.C. § 352(n).

120. FDA regulations provide, however, that a prescription drug is "misbranded" if any "advertisement" for it "recommend[s] or suggest[s] 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). A direct-to-physician advertisement that "suggest[s]" an off-label use is thus per se unlawful, irrespective of the nature or quantity of the manufacturer's disclosures to physicians about that drug, that use, or about any other potentially relevant information. *Id.*

121. 21 C.F.R. § 202.1(e)(4)(i)(a) flatly prohibits Allergan from engaging in protected expression, and thereby is facially unconstitutional and unconstitutional as applied to Allergan's proposed truthful and non-misleading speech.

122. 21 C.F.R. § 202.1(e)(4)(i)(a) is also inconsistent with Congress's command in 21 U.S.C. § 352(n) that advertisements for prescription drugs are permissible provided that adequate disclosure is made. At the very least, 21 C.F.R. § 202.1(e)(4)(i)(a) is an unreasonable interpretation of § 352(n), in particular because its blanket prohibition on "advertisement[s]" of off-label uses gives rise to grave constitutional doubt.

123. Allergan has no adequate remedy at law.

124. Allergan thus seeks the entry of a judgment declaring that 21 C.F.R. § 202.1(e)(4)(i)(a) is facially unconstitutional, that it is unconstitutional as applied to a manufacturer's truthful and non-misleading "advertisement[s]" to physicians, or that it is an invalid interpretation of 21 U.S.C. § 352(n).

## COUNT IV

### The FDA's "Intended Use" Regulations Are Unconstitutional As Applied To Truthful and Non-Misleading Off-Label Speech or They Are Invalid

125. Allergan incorporates and realleges Paragraphs 1–124 as if fully set forth herein.

126. The First Amendment protects Allergan's truthful, non-misleading speech about off-label uses of Botox®.

127. The Act prohibits the introduction of misbranded drugs into interstate commerce. 21 U.S.C. § 331(a). The Act deems a drug "misbranded" if its "labeling" lacks "adequate directions for use." 21 U.S.C. § 352(f)(1).

128. The Act, however, exempts drugs dispensed by prescription from most of the misbranding provisions of § 352, including the requirement that labeling bear "adequate

directions for use." 21 U.S.C. § 353(b)(2). Instead, such a drug is misbranded if its label lacks the symbol "Rx Only." 21 U.S.C. § 353(b)(4).

129. The FDA has promulgated a regulation interpreting the Act's express exemption of prescription drugs from a requirement that their "labeling" bear "adequate directions for use." 21 C.F.R. § 201.100. According to the FDA, the statutory exemption applies only if a prescription drug's "labeling" bears "adequate information for its use." 21 C.F.R. § 201.100(c)(1).

130. 21 C.F.R. § 201.100 is invalid because it conflicts with 21 U.S.C. § 353(b)(2)'s express exemption of prescription drugs from 21 U.S.C. § 352(f)(1)'s "adequate directions for use" requirement.

131. 21 C.F.R. § 201.100 further defines "adequate information" for a prescription drug's use to mean directions under which medical professionals "can use the drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.100(c)(1). A manufacturer is prohibited, however, by the "new drug" provisions of 21 U.S.C. §§ 321(p) and 355(a) from altering a drug's "labeling" to provide what could in fact be "adequate information for [a drug's] use" for an off-label use. With respect to off-label uses, therefore, 21 C.F.R. § 201.100(c)(1) purports to require a manufacturer to do what 21 U.S.C. §§ 321(p) and 355(a) forbid. As a result, if a manufacturer has an "intent" that a drug be used off-label, then by definition under § 201.100(c)(1) that drug is "misbranded."

132. The FDA has further defined "intended uses" in 21 C.F.R. § 201.128 to include any use "objective[ly] inten[ded]" by a manufacturer. The manufacturer's "objective intent" may be shown by its expression, whether in "labeling," "advertisement," or any other "oral or written statements." *Id.* And the manufacturer is deemed to "intend" all uses of which it

"knows, or has knowledge of facts that would give [it] notice." *Id*. Accordingly, all that is required to trigger 21 C.F.R. § 201.128's requirement to provide "adequate directions" or "adequate information" in "labeling" – a requirement that the manufacturer is prohibited by 21 U.S.C. §§ 321(p) and 355(a) from meeting for off-label uses – is the manufacturer's expression about or even its knowledge or notice of an off-label use for its product. Because a violation of 21 C.F.R. § 201.128 is a violation of 21 U.S.C. § 331(a)'s misbranding prohibition, the manufacturer commits a crime if it engages in any expression outside the drug's "labeling" – however truthful, and in whatever form – about an off-label use. 21 C.F.R. § 201.128 thus infringes a manufacturer's First Amendment rights in most of its applications and is both facially unconstitutional and unconstitutional as applied to a manufacturer's speech made outside the drug's "labeling."

133. 21 C.F.R. §§ 201.100 and 201.128 are also invalid as a matter of statutory interpretation to the extent they reach beyond the scope of a drug's "labeling," as that term is defined in the Act. At the very least, 21 C.F.R. §§ 201.100 and 201.128 are unreasonable interpretations of 21 U.S.C. § 352(f)(1), in particular because they give rise to grave constitutional doubt.

134. Allergan has no adequate remedy at law.

135. Allergan thus seeks the entry of a judgment declaring that:

a. 21 C.F.R. § 201.100 is invalid because it is contrary to 21 U.S.C. § 353(b)(2), and

b. 21 C.F.R. § 201.100(c)(1) is unconstitutional as applied to a manufacturer's speech about off-label uses made outside of a drug's "labeling," as that term is defined in 21 U.S.C. § 352(m), and

c. 21 C.F.R. § 201.128 is facially unconstitutional or unconstitutional as applied to a manufacturer's speech about off-label uses made outside of a drug's "labeling," as that term is defined in 21 U.S.C. § 352(m), and

d. 21 C.F.R. §§ 201.100 and 201.128 are invalid as applied to a manufacturer's speech about off-label uses made outside of a drug's "labeling," as that term is defined in 21 U.S.C. § 352(m).

## COUNT V

### The Challenged Statutes and Regulations Are Unconstitutional As Applied To Allergan's Proposed Truthful, Non-Misleading Speech About a Use for which Allergan is Seeking FDA Approval

136. Allergan incorporates and realleges Paragraphs 1–135 as if fully set forth herein.

137. Allergan is currently seeking FDA approval for Botox® to treat upper-limb spasticity in adults, regardless of the cause.

138. For the reasons stated above, the First Amendment broadly protects Allergan's truthful, non-misleading speech about off-label uses of Botox®. At the very least, the First Amendment protects Allergan's truthful, non-misleading speech about off-label uses of Botox® for which it is seeking FDA approval.

139. To restrict pure speech based on its content, the Government must narrowly tailor that restriction to further a compelling governmental interest. *Simon & Schuster, Inc.* v. *Members of N.Y. State Crime Victims Bd.*, 502 U.S. 105, 118-19 (1991). To restrict the content of commercial speech, the Government must have, at a minimum, a substantial governmental interest and the restriction must directly advance that interest without being "more extensive than is necessary to serve that interest." *Western States*, 535 U.S. at 365 (quoting *Central Hudson*, 447 U.S. at 566).

140. The Government has sought to justify the sweeping restrictions on manufacturers' speech challenged herein based on its interest in ensuring that manufacturers seek FDA approval for new uses. *Id*. at 369. Regardless of the validity of that interest in other settings, when a manufacturer has already sought FDA approval for a particular use — as Allergan has with upper-limb spasticity — that governmental interest is not directly furthered by the sweeping prohibitions on a manufacturer's speech concerning that use. Similarly, such sweeping prohibitions are more extensive than necessary when a manufacturer has already sought approval for a particular use.

141. The restrictions on a manufacturer's speech about off-label uses are thus unconstitutional as applied to Allergan's truthful, non-misleading speech about off-label uses of Botox® for which it is seeking FDA approval.

142. Allergan has no adequate remedy at law.

143. Allergan thus seeks the entry of a judgment declaring unconstitutional 21 C.F.R. §§ 201.100, 201.128, 202.1(e)(4)(i)(a), 202.1(l)(2), and 21 U.S.C. § 352(a), as applied to Allergan's truthful, non-misleading speech about off-label uses of Botox® for which it is seeking FDA approval.

## COUNT VI

### The Challenged Statutes and Regulations Are Unconstitutional As Applied To Allergan's Proposed Truthful, Non-Misleading Speech About an Off-Label Use that is Widely Accepted

144. Allergan incorporates and realleges Paragraphs 1–143 as if fully set forth herein.

145. More often than not, Botox® is used to treat off-label conditions, and use for spasticity accounts for most of the off-label use.

146. Statutorily recognized medical compendia contain citations supporting botulinum toxin type A use for the treatment of spasticity-related conditions. Medicaid is required by

statute to reimburse prescriptions for Botox® to treat these listed spasticity-related conditions. *See* 42 U.S.C. §§ 1396b(i)(10), 1396r-8(k)(2)-(3), 1396r-8(k)(6), 1396r-8(g)(1)(B)(i).

147. All Medicare contractors also reimburse for the use of Botox® to treat spasticity-related indications. The Medicare statute prohibits reimbursement for expenses that are not "reasonable and necessary for the diagnosis or treatment of illness or injury." 42 U.S.C. § 1395y(a)(1)(A). For an off-label use to satisfy the "reasonable and necessary" requirement, Medicare contractors must determine the use to be "medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice." *Medicare Benefit Policy Manual*, Ch. 15, § 50.4.2, *available at* http://www.cms.hhs.gov/Manuals/downloads/bp102c15.pdf.

148. For the reasons stated above, the First Amendment broadly protects Allergan's truthful, non-misleading speech about off-label uses of Botox®. At the very least, the First Amendment protects Allergan's truthful, non-misleading speech about off-label uses of Botox® that are so widespread and medically supported that they are recognized in medical compendia and the Government's own reimbursement decisions.

149. When off-label uses of a drug are common, it is all the more important for the manufacturer to speak freely about those uses to ensure that health care professionals are fully informed with respect to safety and efficacy. And when the Government has specifically recognized the validity of an off-label use in its public statements and with its reimbursement decisions, it is even clearer that the Government lacks a valid interest in suppressing manufacturers' speech about that use. Accordingly, the application of 21 C.F.R. §§ 202.1(l)(2), 201.100, and 201.128 and 21 U.S.C. § 352(a) to Allergan's proposed truthful, non-misleading

speech about off-label uses of Botox® that are recognized in medical compendia and the Government's reimbursement decisions infringes Allergan's rights under the First Amendment.

150. Allergan has no adequate remedy at law.

151. Allergan thus seeks the entry of a judgment declaring unconstitutional 21 C.F.R. §§ 201.100, 201.128, 202.1(e)(4)(i)(a), 202.1(l)(2), as applied to Allergan's planned truthful, non-misleading speech regarding off-label uses of Botox® that are recognized in medical compendia and the Government's reimbursement decisions.

## COUNT VII

### The Challenged Statutes and Regulations Are Unconstitutional As Applied To Allergan's Proposed Truthful, Non-Misleading Speech About Off-Label Uses About Which the FDA Has Required Allergan to Speak

152. Allergan incorporates and realleges Paragraphs 1–151 as if fully set forth herein.

153. Beginning with the FDA's letter of April 29, 2009 to Allergan stating that a REMS was required for Botox®, the FDA has required Allergan to take a series of steps to speak about safety risks associated with the off-label use of Botox® to treat spasticity. Most significantly, the FDA ordered Allergan to add a boxed warning to the approved Botox® label describing the risk of potential distant spread of toxin, including the statement that this risk is "probably greatest" in JCP treatment. The FDA also required Allergan to develop documents for distribution to patients and health care professionals describing this risk.

154. For the reasons stated above, the First Amendment broadly protects Allergan's truthful, non-misleading speech about off-label uses. At the very least, though, the First Amendment protects Allergan's truthful, non-misleading speech about off-label uses about which the FDA has required Allergan to speak.

155. Having forced Allergan to speak about certain off-label uses on the Botox® label and through other documents that Allergan must distribute to health care providers and patients, the Government can hardly claim a legitimate interest in suppressing Allergan's truthful, non-misleading speech about those off-label uses.

156. The Government position is that manufacturers must submit their proposed speech to the FDA, while all non-pre-approved speech violates the FDA's regulatory regime. This imposes an effective prior restraint and a licensing system, both of which the First Amendment generally forbids. *Forsyth Cty. v. Nationalist Movement*, 505 U.S. 123, 130 (1992).

157. Allergan thus seeks the entry of a judgment declaring unconstitutional 21 C.F.R. §§ 201.100, 201.128, 202.1(e)(4)(i)(a), 202.1(l)(2), as applied to Allergan's planned truthful, non-misleading speech regarding off-label uses of Botox® about which the FDA has required Allergan to speak.

## COUNT VIII

### 21 U.S.C. § 332(a) Does Not Authorize Monetary Relief

158. Allergan incorporates and realleges Paragraphs 1–157 as if fully set forth herein.

159. The First Amendment protects Allergan's truthful, non-misleading speech about off-label uses of Botox®.

160. The Government has taken the position that "off-label promotion" is both a criminal offense and that it gives rise to a civil cause of action under the Act for disgorgement or other backward-looking monetary relief. This position is contrary to the plain text of the statute, which allows the government to seek only forward-looking remedies. 21 U.S.C. § 332(a) (granting district courts jurisdiction to "restrain violations of section 331"); *cf. United States* v. *Philip Morris USA, Inc.*, 396 F.3d 1190 (D.C. Cir. 2005) (holding that identical language in RICO did not make a disgorgement remedy available).

161. The threat of enforcement action seeking retrospective monetary relief based on truthful, non-misleading speech further chills Allergan's protected speech about off-label uses of Botox®. Limiting the remedies available for violations of the Act under 21 U.S.C. § 332(a) to prospective injunctions — as required by § 332(a) itself — would lessen this chill by eliminating the possibility that the Government could recover retrospective damages based on Allergan's exercise of its First Amendment rights.

162. The Government's role as regulator of speech should not be skewed by the incentives created by the recovery of retrospective monetary penalties absent a clear congressional direction to that effect.

163. Allergan has no adequate remedy at law.

164. Allergan thus seeks the entry of a judgment declaring that 21 U.S.C. § 332(a) does not authorize monetary relief for a violation of the "misbranding" or "new drug" provisions of 21 U.S.C. § 331.

## PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully requests that this Court:

A. Declare that 21 C.F.R. § 202.1(*l*)(2) is unconstitutional as applied to prohibit a manufacturer's truthful and non-misleading speech about off-label uses, or that it is invalid because it conflicts with or is an unreasonable interpretation of 21 U.S.C. § 321(m).

B. Declare that 21 U.S.C. § 352(a) is unconstitutional as applied to a manufacturer's truthful and non-misleading speech about off-label uses in "labeling," or that § 352(a) does not prohibit a manufacturer's truthful and non-misleading speech about off-label uses in "labeling."

C. Declare that 21 C.F.R. § 202.1(e)(4)(i)(a) is facially unconstitutional, that it is unconstitutional as applied to a manufacturer's truthful and non-misleading "advertisement[s]" to physicians, or that it conflicts with or is an unreasonable interpretation of 21 U.S.C. § 352(n).

D. Declare that:

i. 21 C.F.R. § 201.100 is invalid because it is contrary to 21 U.S.C. § 353(b)(2), and

ii. 21 C.F.R. § 201.100(c)(1) is unconstitutional as applied to a manufacturer's speech about off-label uses made outside of a drug's "labeling," as that term is defined in 21 U.S.C. § 352(m), and

iii. 21 C.F.R. § 201.128 is facially unconstitutional or unconstitutional as applied to a manufacturer's speech about off-label uses made outside of a drug's "labeling," as that term is defined in 21 U.S.C. § 352(m), and

iv. 21 C.F.R. §§ 201.100 and 201.128 are invalid as applied to a manufacturer's speech about off-label uses made outside of a drug's "labeling," as that term is defined in 21 U.S.C. § 352(m).

E. Declare that 21 C.F.R. §§ 202.1(e)(4)(i)(a), 202.1(l)(2), 201.100, and 201.128 and 21 U.S.C. § 352(a) are unconstitutional as applied to Allergan's truthful, non-misleading speech about off-label uses of Botox® for which it is seeking FDA approval.

F. Declare that 21 C.F.R. §§ 202.1(e)(4)(i)(a), 202.1(l)(2), 201.100, and 201.128 and 21 U.S.C. § 352(a) are unconstitutional as applied to Allergan's planned truthful,

non-misleading speech regarding off-label uses of Botox® that are recognized in medical compendia and the Government's reimbursement decisions.

G. Declare that 21 C.F.R. §§ 202.1(e)(4)(i)(a), 202.1(l)(2), 201.100, and 201.128 and 21 U.S.C. § 352(a) are unconstitutional as applied to Allergan's planned truthful, non-misleading speech regarding off-label uses of Botox® about which the FDA has required Allergan to speak.

H. Declare that 21 U.S.C. § 332(a) does not authorize monetary relief for a violation of the "misbranding" or "new drug" provisions of 21 U.S.C. § 331.

I. Enter a preliminary injunction enjoining Defendants from taking any action, during the pendency of this litigation, to enforce the aforementioned provisions against Allergan based on Allergan's proposed truthful and non-misleading speech, and thus to protect Allergan's First Amendment rights from ongoing harm while this litigation is pending.

J. Enter a permanent injunction enjoining Defendants from taking any action to enforce the aforementioned provisions against Allergan based on Allergan's proposed truthful and non-misleading speech.

K. Award such other and further relief that the Court deems equitable and just.

Respectfully submitted,

/s/

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