UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ALLERGAN, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civil Action No. 09-1879 (JDB)
	)	
UNITED STATES OF AMERICA, *et. al*.,	)	
	)	
Defendants.	)	
	)	

DEFENDANTS' MEMORANDUM OF POINTS AND AUTHORITIES
IN SUPPORT OF MOTION TO DISMISS OR FOR SUMMARY JUDGMENT

Allergan, Inc., the producer and distributor of Botox, seeks permanent injunctive relief against the United States Food and Drug Administration ("FDA"). Allergan alleges that the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") and FDA regulations unconstitutionally restrict a drug sponsor's speech regarding unapproved uses of an approved product in violation the First Amendment. Narrowly, this case involves plaintiff's alleged concern that FDA may take enforcement action with respect to plaintiff's communications regarding unapproved uses for its approved drug product Botox. Broadly, the complaint is a sweeping assault on FDA's authority, established by Congress in 1962, to require manufacturers to show that a drug is both safe and effective for each of its uses before the manufacturer promotes the product for such use.

Allergan is not entitled to any relief. This case is not ripe because there is no actual application of the challenged statute and regulations to provide the context in which to evaluate their constitutionality. Thus, this case should be dismissed for lack of jurisdiction. Even if justiciable, Allergan cannot establish that it is entitled to judgment on the merits. The drug approval system established by the FDCA and FDA regulations is fully consistent with the Constitution and leaves ample room for Allergan to disseminate truthful, non-promotional information about dangers associated with unapproved uses of Botox. Any interest Allergan may have in curtailing FDA authority over drug approval cannot outweigh the paramount interests of the public and the government in ensuring the safety and effectiveness of approved drugs. The Court should deny the motion for a permanent injunction and dismiss the complaint or enter judgment for the government.

I. Regulatory Background

A. The Approval Process for New Drugs and Biological Products

1. The linchpin of drug regulation under the FDCA is the requirement that all "new drugs" obtain approval from FDA before they may be distributed in interstate commerce. 21 U.S.C.

§§ 331(d), 355(a). The FDCA's definition of "drug" includes any article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals," and any article other than food "intended to affect the structure or any function of the body of man or other animals." *Id.* § 321(g)(1)(B)-©. A "new drug" is any drug that is "not generally recognized, among [qualified] experts . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . ." *Id.* § 321(p).

To obtain FDA approval for a new drug, a manufacturer must submit a new drug application ("NDA") that "demonstrate[s] that its product is safe and effective for each of its intended uses." *Wash. Legal Found.* v. *Henney*, 202 F.3d 331, 332 (D.C. Cir. 2000) (*WLF*); 21 U.S.C. § 355(a). FDA reviews the manufacturer's data regarding the effectiveness of new drugs under the substantial evidence standard. See *Weinberger* v. *Hynson, Westcott and Dunning*, 412 U.S. 609, 613-14 (1973). This "rigorous" standard requires well-controlled scientific data and cannot be satisfied by impressions or beliefs of physicians, reports lacking in details, or personal testimonials. *See id.* at 618-19, 630; *Edison Pharm. Co., Inc.* v. *FDA*, 600 F.2d 831, 842-43 (D.C. Cir. 1979); 21 C.F.R. § 314.50(d)(5)(describing the requirements for clinical data). It is one of the cornerstones of evidence-based medicine in the United States.

The Public Health Service Act ("PHSA") establishes a nearly identical approval process for biological products. See 42 U.S.C. § 262(i) (defining "biological products"). The PHSA prohibits the interstate distribution of a biological product without FDA approval. *Id.* § 262(a). A sponsor seeks FDA approval by submitting a biologics license application ("BLA"). 42 U.S.C. § 262(a). To obtain approval, the sponsor must demonstrate, *inter alia*, that the product is "safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i)(I). FDA approves a biological product for a particular use only when there is sufficient evidence, consisting of appropriate laboratory tests or controlled clinical

data, to show that the product will be safe and effective for that use when administered in the manner approved. *See* 42 U.S.C. § 262(a)(2)(A); 21 C.F.R. §§ 600.3(s), 601.2(d). The standards for approval of biological products are construed similarly to the standards for approval of new drugs.[1]

Many biological products, such as Botox, also meet the definition of "drug" under the FDCA. Because the standards for approval of biological products and drugs are comparable, biological products with approved BLAs are not required to file separate NDAs, but in all other relevant respects, they are subject to the drug requirements of the FDCA. 42 U.S.C. § 262(j).

2. Before 1962, drug manufacturers ordinarily were not required to demonstrate that drugs were effective for their intended uses and, accordingly, manufacturers rarely carried out testing to establish effectiveness. Instead, they promoted drugs for uses for which evidence was lacking, or for which the drugs were known to be ineffective; promoted drugs with serious side effects to treat minor conditions, even when possible benefits were outweighed by the risks; and promoted ineffective drugs for serious conditions for which other, effective treatments were available. See Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 Food & Drug L.J. 299, 300-306 (2003) (summarizing evidence before Congress regarding pervasiveness of unsubstantiated claims by drug manufacturers and resulting harms). In theory, manufacturers making false or misleading claims were subject to enforcement proceedings after the product had been distributed. But in practice, such *ex post* remedies were wholly inadequate to deter unsubstantiated and misleading claims and protect the public health. See *id.* at 303, 310-311. As the Secretary of Health, Education, and Welfare told

[1] *See* Food and Drug Administration Modernization Act of 1997 ("FDAMA"), Pub. L. No. 105-115, § 123(f), 111 Stat. 2296, 2324 (1997) (codified at 21 U.S.C. § 355 note) (instructing FDA to "minimize differences in the review and approval" of drug and biological products); *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998, at 2-4, *available at* http://www.fda.gov/ohrms/dockets/98fr/971OOgdl.pdf ("Effectiveness Guidance").

Congress, "[i]t is intolerable to permit the marketing of worthless products under the rules of a cat-and-mouse-game where a manufacturer can fool the public until the [FDA] finally catches up with him." *The Drug Industry Antitrust Act of 1962: Hearings before the Antitrust Subcomm. of the Comm. on the Judiciary*, 87th Cong., 2d Sess. 173 (1962) (statement of HEW Secretary Ribicoff).

Congress sought to end these abuses by enacting the Drug Amendments of 1962. See Pub. L. No. 87-781, 76 Stat. 780 (1962) ("Kefauver-Harris Amendments"). Among other things, these amendments added the requirement that manufacturers demonstrate that their products are effective, as well as safe, for their intended uses *before* they could be distributed. 21 U.S.C. § 355(a), (d). They also revised the FDCA's "new drug" definition to provide that a drug is a new drug if it is not generally recognized as "safe and effective" for its intended uses. *Id.* § 321(p).

Congress added effectiveness to the Act's definition of "new drug" to prevent manufacturers from obtaining approval of a drug for one use, then marketing the drug for unapproved uses, also referred to as off-label uses. See S. Rep. No. 87-1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, 2901-2903 (statement of Senators Kefauver, Carroll, Dodd, Hart & Long, explaining reasons for changing definition of "new drug"). As Senator Kefauver explained, "[t]he considerations which would warrant examination and approval of the initial claim would be just as appropriate and compelling for successive claims". If a manufacturer were not required to demonstrate safety and effectiveness for new intended uses, "[t]he expectation would be that the initial claims would tend to be quite limited"; once the drug was approved for one use, "[t]hereafter 'the sky would be the limit' and extreme claims of any kind could be made . . . ." *Id.*[2] Because a drug is a "new drug" if

[2] After the passage of the Kefauver-Harris Amendments, FDA retained the National Academy of Sciences to evaluate the effectiveness of the 16,500 claims made on behalf of the 4,000 drugs marketed under NDAs in 1962. Seventy percent of these claims were found not to be supported by substantial evidence of effectiveness, and only 434 drugs were found effective for all their claimed uses. *Hynson*, 412 U.S. at 621.

it is not generally recognized as safe and effective for each intended use, a new intended use renders an approved drug a "new drug" with respect to the new use, and the manufacturer cannot distribute the drug in interstate commerce for that use without first obtaining FDA's approval of an application that demonstrates the drug's safety and effectiveness for the new use. See *WLF*, 202 F.3d at 332-33 ("it is unlawful for a manufacturer to introduce a drug into interstate commerce with an intent that it be used for an off-label purpose").

FDA determines that a drug is or is not safe for each particular use and for the conditions relating to that use, e.g., dosage, site of administration, contra-indications, and warnings. This assessment requires a use-specific balancing of risks against benefits. See *United States* v. *Rutherford*, 442 U.S. 544, 555 (1979) ("Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk. Thus, the Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use"); *Rhone-Poulenc, Inc.* v. *FDA*, 636 F. 2d 750, 752 (D.C. Cir. 1980). Many drugs have potentially significant adverse side effects, and therefore may be deemed safe only with respect to particular uses that involve significant countervailing benefits. For example, a particular drug might be found sufficiently "safe" to be approved for the treatment of schizophrenia, but might not found "safe" for the treatment of insomnia. See Declaration of Robert Temple, M.D. ("Temple Decl.") ¶ 6. Moreover, even "[a]n otherwise harmless drug can be dangerous to any patient if it does not produce its purported therapeutic effect." *Rutherford*, 442 U.S. at 556. Thus, a finding by FDA that a drug is safe for one use does not indicate that the drug is safe for an unapproved use.

B. Regulation of Drug Labeling and Prescription Drug Advertising

1. The FDCA vests FDA with authority over drug labels and labeling. The Act defines "label" as "a display of written, printed, or graphic matter upon the immediate container of any

article." 21 U.S.C. § 321(k). "Labeling" is defined to include "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." *Id.* § 321(m). See also 21 C.F.R. § 202.1(*l*)(2) (examples of material that may constitute labeling for prescription drugs).

FDA distinguishes between two types of labeling: "FDA-approved labeling" and promotional labeling.[3] FDA-approved labeling is the labeling submitted to FDA as part of the NDA for inclusion in or within the package from which the drug is dispensed. See 21 U.S.C. § 355(b)(1)(F); *Disease Awareness Guidance* at 2. Promotional labeling refers to any labeling other than FDA-approved labeling. *Id.*

FDA-approved labeling is reviewed and approved by FDA as part of the process for approving an NDA under 21 U.S.C. § 355. Once an NDA has been approved, changes in FDA-approved labeling must be submitted to FDA for review and approval. See 21 C.F.R. § 314.70(b)(2)(v), (c)(6)(iii); see also *id.* § 601.12(f)(1)-(2) (same rules for biological products). In contrast, promotional labeling does *not* require FDA approval. Instead, the manufacturer is merely required to provide FDA with specimens of promotional labeling "at the time of initial dissemination." 21 C.F.R. § 314.81(b)(3)(i); see also id. § 314.70(a)(4).

All drug labeling is subject to the misbranding provisions of the FDCA, which makes it unlawful to misbrand drugs and to distribute misbranded drugs. 21 U.S.C. §§ 331(a), (b), ©, (g), (k), 352. A drug is considered misbranded if, *inter alia*, its labeling is "false or misleading in any particular." *Id.* § 352(a). A drug is also misbranded if its labeling does not contain adequate directions for use. *Id.* § 352(f)(1).

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[3] See *Guidance for Industry: "Help-Seeking" and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms* at 2 (Jan. 2004), available at http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM070068.pdf (*Disease Awareness Guidance*) (summarizing distinction).

Adequate directions for use are "directions under which the layman can use a drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.5; see, e.g., *United States* v. *Articles of Drug*, 625 F.2d 665, 673 (5th Cir. 1980) (sustaining validity of § 201.5 and holding that "a drug's labeling must contain adequate directions for a consumer to engage in self-medication"). Because prescription drugs, by definition, are "not safe for use except under the supervision of a practitioner licensed by law to administer such drug" (21 U.S.C. § 353(b)(1)(A)), labeling cannot render a prescription drug safe for use by laymen. See *id.* at 673. FDA has exercised its authority under 21 U.S.C. § 352(f) to excuse prescription drug manufacturers from their obligation to provide adequate directions for use by laymen on the condition, *inter alia*, that the labeling provide adequate directions for use by practitioners. See 21 C.F.R. § 201.100(c)(1).

2. The FDCA also vests FDA with jurisdiction over prescription drug advertising. Like promotional labeling, advertisements for prescription drugs generally are not subject to FDA approval. See 21 U.S.C. § 352(n) ("except in extraordinary circumstances, no regulation issued under this paragraph shall require prior approval by [FDA] of the content of any advertisement"); see also 21 C.F.R. § 314.81(b)(3)(i). However, advertisements for prescription drugs must comply with the misbranding provisions of the Act. See 21 U.S.C. § 352(n); 21 C.F.R. § 202.1.

A prescription drug is misbranded if its advertising omits, *inter alia*, "such . . . information in brief summary relating to side effects, contraindications, and effectiveness as shall be required in [FDA] regulations . . . ." 21 U.S.C. § 352(n)(3). The requirements for prescription drug advertising are set forth in 21 C.F.R. § 202.1. As a general matter, FDA requires prescription drug advertisements to provide adequate information regarding drug safety and effectiveness and prohibits false or misleading advertising. In addition, advertisements for prescription drugs may not "recommend or suggest" the drug for unapproved uses. *Id.* § 202.1(e)(4)(i)(a).

C. Promotion of Approved Drugs for Unapproved Uses

It is unlawful for a manufacturer to introduce a drug into interstate commerce for an intended use lacking FDA approval. *WLF*, 202 F.3d at 332.[4] But the manufacturer is not obligated to seek approval for unapproved uses that are not intended. Thus, the applicability of the NDA requirement turns on whether particular unapproved uses are intended uses. Intended use also plays an important role in the Act's misbranding provisions, because the obligation to provide adequate directions for use extends to all uses (and only those uses) that are intended. See 21 U.S.C. § 352(f)(1); 21 C.F.R. §§ 201.5, 201.100(c)(1).

In determining a product's intended use, FDA is not limited to examining the product label. Instead, "it is well established that the 'intended use' of a product, within the meaning of the Act, is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source." *Action on Smoking and Health* v. *Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980). Consistent with this settled understanding, FDA's regulations provide that intended use "refer[s] to the objective intent of the persons legally responsible for the labeling of drugs," and "is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article." 21 C.F.R. § 201.128. The manufacturer's objective intent "may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives." *Id.*[5]

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[4] When an intended use is embodied in a drug's labeling, the new drug approval requirement in 21 U.S.C. § 355 is triggered directly by the "new drug" definition, which encompasses all drugs not generally recognized as safe and effective "for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. § 321(p). When the intended use is reflected elsewhere, such as in drug advertising or other promotional activities, the NDA requirement is triggered indirectly, via the FDCA's misbranding provision, 21 U.S.C. § 352. As noted, the misbranding provision requires drug labeling to contain, *inter alia*, adequate directions for all intended uses. *Id.* § 352(f)(1). Thus, a manufacturer cannot promote a use through its advertising or other forms of promotion and simultaneously comply with the misbranding provision without an NDA approval for the use under 21 U.S.C. § 355.

[5] Courts have recognized that intended use may be shown by non-speech evidence that has included, for example,

Thus, a manufacturer's promotion of an unapproved use in a drug's promotional materials is powerful evidence – though by no means the only relevant evidence – that a use is an intended use. If so, the manufacturer cannot market the drug for that use without first obtaining FDA approval, and must include adequate directions for the use in the drug's labeling to avoid misbranding under § 352(f)(1). A drug's labeling may not state or imply that an unapproved use has been approved by FDA, for doing so would render the labeling false or misleading and therefore misbranded under § 352(a).

It is critical to understand, however, that not all speech or actions by a manufacturer regarding an unapproved use is taken by FDA to be evidence of intended use. See Temple Decl. ¶¶ 9-12. In determining whether a particular statement by a manufacturer regarding an unapproved use is evidence of intended use, FDA has traditionally sought to distinguish between promotional and non-promotional activity. *See* Notice, 65 Fed. Reg. 14286, 14287 (Mar. 16, 2000). Thus, for example, FDA has provided manufacturers with guidance regarding the distribution of medical articles discussing unapproved uses of approved drugs to healthcare professionals.[6] The Reprint Guidance provides recommendations for manufacturers relating to the selection of the texts and their manner and context of distribution, which are cumulatively designed to encourage unbiased and non-promotional dissemination of truthful and non-misleading information. If a manufacturer follows

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product formulation and method of intake, actual use of the product by consumers and medical practitioners, and circumstances of sale. *See, e.g., United States v. Ten Cartons, More or Less, of an Article ... Ener-B Vitamin B-12*, 72 F.3d 285, 287 (2d Cir.1995); *United States v. An Article of Device ... Toftness Radiation Detector*, 731 F.2d 1253, 1257-58 (7th Cir.1984) *United States v. Travia*, 180 F. Supp. 2d 115, 119 (D.D.C. 2001); *Am. Health Prods. Co. v. Hayes*, 574 F. Supp. 1498, 1508 (S.D.N.Y.1983).

[6] See *Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (available at http://www.fda.gov/oc/op/goodreprint.html) (*Reprint Guidance*). See also *Guidance for Industry: Industry-Supported Scientific and Educational Activities* (November 1997) (available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125602.pdf).

the recommendations, "FDA does not intend to consider the distribution of such medical and scientific information . . . as establishing intent that the product be used for an unapproved new use." *Reprint Guidance* at 4.

Thus, the bare fact that a manufacturer has disseminated some information about an unapproved use will not necessarily be taken as proof of intended use. In particular, a manufacturer may communicate information regarding an unapproved use to inform practitioners of risks associated with the use and improve the safety of the drug, as long as it does not promote the unapproved use. See Temple Decl. ¶¶ 9-12. Absent promotion, the dissemination of safety information relating to an unapproved use would not establish that the use is an intended use, and therefore would not trigger either the new drug approval process or the misbranding provisions of the FDCA. *Id.* A manufacturer contemplating the distribution of such information need not submit it to FDA for approval (unless the manufacturer wishes to modify FDA-approved labeling, as distinct from promotional labeling), but the manufacturer may choose to seek FDA's guidance on a voluntary basis. *Id.*

II. Factual Background

The essential facts relevant to this motion are undisputed. FDA first approved Allergan's BLA for Botox (botulinum toxin type A) in 1989. Defendants' Statement of Material Facts ("Statement") ¶ 1. At that time, FDA approved Botox to treat strabismus (crossed eyes) and blepharospasm (abnormal involuntary eyelid muscle contractions) associated with dystonia. *Id.* Since that time, FDA has approved Allergan's supplemental BLAs ("sBLAs") for Botox to treat cervical dystonia (involuntary neck muscle contractions) in adults, to decrease the severity of abnormal head position and neck pain associated with cervical dystonia, and to treat severe primary axillary hyperhidrosis (excess sweating) that is inadequately managed with topical agents. *Id.* ¶ 2.

More recently, FDA determined that botulinum toxin ("BTX") products raise safety concerns that necessitated specific safety-related actions by the manufacturers of BTX products. In November 2007, FDA notified Allergan that it had received reports regarding cases of botulism, an illness caused by the toxins produced by the botulinum bacteria, which are contained in BTX products. *Id.* ¶ 4. Botulism is a serious neuroparalytic illness that can lead to respiratory failure and death. *Id.* FDA requested data from Allergan, for FDA review, regarding cases of botulism or other systemic adverse events related to distant spread of toxin effects. *Id.*

In February 2008, FDA issued an Early Communication about an Ongoing Safety Review of Botox and Botox Cosmetic (Botulinum toxin Type A) and Myobloc (Botulinum toxin Type B), to describe emerging safety information under FDA review. *Id.* ¶ 5. FDA explained that it had received reports of systemic adverse reactions including respiratory compromise and death from the use of BTX products for both approved and unapproved uses. FDA further explained that the most serious cases "occurred mostly in children treated for cerebral palsy-associated limb spasticity," which is an unapproved use. *Id.*

In April 2009, FDA issued a supplement request letter to Allergan describing required safety labeling changes (including a boxed warning) for all BTX products, postmarketing requirements and postmarketing commitments, and a Risk Evaluation and Mitigation Strategy ("REMS"). *Id.* ¶ 7. In July 2009, FDA approved Allergan's new safety labeling changes, Medication Guide, and REMS for Botox. *Id.*

The unapproved uses discussed in Allergan's complaint relate to spasticity. In the early 1990s, Allergan began investigating the use of Botox to treat spasticity from multiple origins, e.g., spasticity associated with ambulatory cerebral palsy, cerebral vascular accidents, and traumatic brain injury. *Id.* ¶ 3. Allergan submitted in August 2008 an sBLA for the use of Botox to treat upper limb

spasticity in post-stroke adult patients ("spasticity sBLA"). *Id.* ¶ 6. In May 2009, FDA issued a "complete response letter" to Allergan regarding this sBLA. *Id.* ¶ 8. In that letter, the agency identified deficiencies in the application that prevented approval at that time: the source data documentation was insufficient to verify its integrity; the indication should not be limited to post-stroke upper-limb spasticity in adults, but to upper-limb spasticity of any etiology; and FDA denied Allergan's pediatric waiver request and requested a revised proposed pediatric plan. *Id.* On September 29, 2009, Allergan filed a "resubmission" to address the deficiencies identified by FDA. *Id.* ¶ 9. The goal date for FDA's action on the resubmission is April 1, 2010. *Id.* ¶ 10.[7]

ARGUMENT

Because Allergan's complaint concerns an administrative matter pending before the agency, and there is no context – an actual application of the challenged statute and regulations – in which to evaluate their constitutionality, this case is not ripe, and should be dismissed for lack of jurisdiction. Fed.R.Civ.P. 12(b)(1). If the Court reaches the merits, Allergan has failed to meet the stringent standards for a preliminary or permanent injunction, see *Winter v. NRDC, Inc.*, 129 S. Ct. 365, 386-87, 381 (2009), and this Court should dismiss the complaint or enter summary judgment for defendants. Fed.R.Civ.P. 12(b)(6) and 56.[8]

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[7] With respect to the treatment of ambulatory cerebral palsy, Allergan had requested in May 2003 that its investigational new drug application for that indication be placed on inactive status, but Allergan and FDA have had more recent exchanges regarding safety information and possible further studies for this indication. Temple Decl. ¶ 27. Although there are disputed issues between the parties regarding the details and characterization of some of the recent communications between Allergan and FDA, as reflected in the declarations before the Court, none of these disputes is material to the government's motion. To the extent that further examination of these issues becomes necessary, or upon the Court's request, the agency would provide the written communications to the Court.

[8] We address in detail below why Allergan is not entitled to judgment on the merits of its claims. With respect to the non-merits equitable factors governing injunctive relief, Allergan has failed to establish irreparable injury. Even in First Amendment cases, a finding of irreparable injury is not automatic; a plaintiff must establish a causal link between the allegedly unconstitutional rule or regulation and the alleged injury, and an actual chilling effect on protected speech. *Chaplaincy of Full Gospel Churches v. England*, 454 F.3d 290, 301 (D.C. Cir. 2006). Further, to the extent the complaint seeks relief on grounds other than constitutional violations, Allergan has not asserted any injury, much less irreparable injury. As for the impact of injunctive relief on the government and the public, Allergan admits that "the

I. ALLERGAN'S CLAIMS ARE NOT RIPE FOR REVIEW

The ripeness doctrine is designed "to prevent the courts, through avoidance of premature adjudication, from entangling themselves in abstract disagreements over administrative policies, and also to protect the agencies from judicial interference until an administrative decision has been formalized and its effects felt in a concrete way by the challenging parties." *Nat'l Park Hospitality Ass'n v. Dep't of Interior*, 538 U.S. 803, 807-08 (2003) (quoting *Abbott Laboratories* v. *Gardner*, 387 U.S. 136, 148-149(1967)). See also *Devia v. NRC*, 492 F.3d 421, 424-25 (D.C. Cir. 2007) ("[I]f a plaintiff's claim, though predominantly legal in character, depends on future events that may never come to pass, or that may not occur in the form forecasted, then the claim is unripe"); *Pfizer v. Shalala*, 182 F.3d 975, 978 (D.C. Cir. 1999) ("A claim is not ripe for adjudication if its rests upon contingent future events that may not occur as anticipated, or indeed may not occur at all.")(citing *Texas v. United States*, 523 U.S. 296, 300 (1998)).

Even in the First Amendment context, where the ripeness requirement is sometimes relaxed, a plaintiff must still "demonstrate a live dispute involving the actual or threatened application of [a statute or policy] to bar particular speech." *Renne v. Geary*, 501 U.S. 312, 320 (1991); *see, e.g., Pearson v. Leavitt*, No. 05-1937, 189 Fed. Appx. 161; 2006 U.S. App. LEXIS 15858 (4th Cir. 2006) (First Amendment challenge to FDA's authority over dietary supplements dismissed on ripeness grounds); *Marchi v. Bd. of Coop. Educ. Servs*., 173 F.3d 469, 478-79 (2d Cir. 1999) (even under the relaxed ripeness standard of the First Amendment, claims were not ripe where the claims were "all

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Government and the public have a strong interest in the enforcement of constitutional consumer-protection laws." PI Mem. at 18-19. The fundamental purpose of the drug approval system, including the requirement that manufacturers present evidence showing the safety and effectiveness of each use, is to protect the public. It is well established that "[t]he high purpose of the [FDCA is] to protect consumers who under present conditions are largely unable to protect themselves in this field." *Kordel v. United States*, 335 U.S. 345, 349 (1948). The public and government interests are best served by upholding FDA's authority to regulate the approval of drugs and biological products for each use.

highly fact-specific and, as of yet, hypothetical" and where the plaintiff could not establish a credible fear of enforcement); *Nutritional Health Alliance v. Shalala*, 144 F.3d 220, 225-27 (2d Cir. 1998) (facial challenge to provisions of FDCA and FDA regulations as imposing an unconstitutional ban on certain categories of speech was not ripe for review).

Allergan's complaint does not ask this Court to address the status of any past speech by Allergan regarding unapproved uses of Botox. Instead, the complaint contends that the FDCA and the FDA's regulations are invalid as applied to allegedly truthful and non-misleading speech that Allergan wishes to make in the future. More specifically, the complaint is directed at two kinds of proposed speech: (1) assertedly truthful warnings and safety information relating to the use of Botox to treat certain spasticities, including spasticities relating to juvenile cerebral palsy, and (2) promotional speech relating to the uses that are the subject of Allergan's pending sBLA.[9]

To the extent that Allergan is seeking review regarding the status of its proposed non-promotional safety and warning communications, Allergan's claims are premature because they turn on future factual contingencies whose outcome cannot presently be known.[10] Allergan's claims do not raise purely legal questions that can be resolved in a factual vacuum. The Supreme Court has explained that, even in the context of a facial overbreadth challenge on First Amendment grounds,

> the better course might have been to address in the first instance the constitutionality of [the statute] as applied in [a factual] context . . . . "It is not the usual judicial

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[9] In describing the categories of speech in which it would like to engage, Allergan is not explicitly clear whether it intends to include the uses that are the subject of the pending sBLA. See Compl. ¶¶ 80-82, 88. However, Count V challenges the constitutionality of the Act and regulations as applied to speech regarding unapproved uses during the pendency of a supplemental NDA or BLA.

[10] Ripeness turns upon two primary considerations: (1) "the fitness of the issues for judicial decision" and (2) "the hardship to the parties of withholding court consideration," *Abbott Laboratories*, 387 U.S. at 149; *accord Toilet Goods Ass'n v. Gardner*, 387 U.S. 158, 162 (1967). The first prong of the inquiry -- whether Allergan's claims are fit for judicial resolution – in turn has two components: (a) whether the claims raise purely legal questions, and (b) whether the decisions being challenged constitute final agency action. *Toilet Goods Ass'n*, 387 U.S. at 163-64; *Abbott Laboratories*, 387 U.S. at 149.

> practice, . . . nor do we consider it generally desirable, to proceed to an overbreadth issue unnecessarily -- that is, before it is determined that the statute would be valid as applied . . . ."

Renne, 501 U.S. at 324. *See also Cement Kiln Recycling Coal. v. EPA*, 493 F.3d 207, 216 & n.5 (D.C. Cir. 2007) (case unripe where agency's practical application would be important). As explained below, the Act and regulations provide substantial room for the dissemination of truthful, non-promotional warning information regarding health risks associated with unapproved uses. Insofar as Allergan's proposed warnings prove to be truthful and non-promotional, the Act and the regulations are no impediment. But whether Allergan's speech *will* be truthful and non-promotional cannot be determined at this point, when Allergan has yet to speak and has not set forth the precise statements that it wishes to make. Courts have rightly declined to pass on the constitutionality of the Act and regulations as applied to allegedly truthful claims until the claims have crystallized into specific statements. *See, e.g., Nutritional Health Alliance*, 144 F.3d at 226 (determining whether speech is misleading under the *Central Hudson* analysis would be too speculative and abstract without specific claims to evaluate.)

To the extent that Allergan is seeking review of prospective promotional speech relating to the unapproved uses in its sBLA, Allergan's claims are likewise premature, but for a different reason: there also has been no adverse final agency action. Final agency action "mark[s] the consummation of the agency's decisionmaking process" and is "one by which rights or obligations have been determined, or from which legal consequences will flow." *Bennett v. Spear*, 520 U.S. 154, 156 (1997); *see also Franklin v. Massachusetts*, 505 U.S. 788, 797 (1992) ("The core question is whether the agency has completed its decisionmaking process, and whether the result of that process is one that will directly affect the parties."). FDA expects to issue a decision on the spasticity BLA by April 2010; depending on the decision, Allergan's claims with respect to covered

indications may become moot in whole or in substantial part. In another challenge involving a pending BLA, the court found that "[b]ecause the . . . BLA administrative process is ongoing, [and] the FDA may ultimately approve the application, which would render Plaintiff's claims moot[,] . . . th[e finality] element [necessary] for judicial decision is not met. Consequently, even though Plaintiff raised one purely legal issue, that issue is not fit for judicial decision." *CareToLive v. von Eschenbach*, 525 F. Supp. 2d 938, 947 (S.D. Ohio 2007), *aff'd*, 290 Fed. Appx. 887 (6th Cir. 2008), *cert. denied*, 129 S. Ct. 921 (2009).

Allergan has also failed to show that it will suffer a substantial hardship in maintaining the status quo until FDA issues a final decision on the sBLA. As the *CareToLive* court found:

> Plaintiff faces no greater hardship from waiting for a final agency decision before bringing suit than the patients who might potentially benefit from many other biologics or drugs intended to treat life-threatening conditions that are under review by the FDA at any given time. . . . Indeed, Congress balanced such hardships against the risks and dangers of using unsafe and ineffective drugs when it set the statutory standards for approval of drugs and biologies. *See, e.g., United States v. Rutherford*, 442 U.S. 544, 552-53 & n.9 . . . (1979).

525 F. Supp. 2d at 947-48. *See also Nutritional Health Alliance*, 144 F.3d at 227 (delay in waiting for agency decision was not sufficient to establish hardship prong of ripeness analysis).

II. The FDCA's Longstanding Statutory Provisions and FDA's Longstanding Regulations Relating to Promotion of Drugs for Unapproved Uses Are Valid on Their Face and as Applied

This suit is a frontal assault on the framework for new drug approval that Congress created in 1962. If successful, it would roll back the regulatory clock a half century to the years before the Kefauver-Harris Amendments. Allergan's complaint asks this Court to review a regulatory world in which FDA's approval of a drug for one use would free the manufacturer to promote the drug for other, unapproved uses without seeking FDA approval for such other uses and without conducting adequate clinical trials to determine whether the drug is safe and effective for the unapproved uses.

If the drug proves to be ineffective or unsafe for the new use, the government's only recourse would be the after-the-fact remedies, such as enforcement actions for misbranding, that Congress found to be wholly wanting in 1962. If successful, Allergan's complaint would force the courts -- rather than FDA -- to be the frontline scientific decision-maker and bulwark between the consumers and manufacturers who seek to market unproven medical products. While the judicial machinery for such *ex post* remedies ground on, the manufacturer could continue to promote the drug for unsafe or ineffective uses, placing the public health in ongoing jeopardy.

The extent to which this Court is being asked to dismantle the established system of drug regulation is obvious from Allergan's First Amendment claims, which collectively assert that the First Amendment protects all "truthful, non-misleading speech" about unapproved uses of drugs even when the speech is purely to promote unapproved use. See, *e.g.*, Compl. ¶ 118. What may be less obvious is that Allergan's non-constitutional claims would lead to the same result.

For example, Count IV of Allergan's complaint challenges the validity of 21 C.F.R. § 201.100(c)(1), which that requires prescription drug labeling to include adequate directions for a drug's intended uses. This regulation has been in effect for nearly fifty years (see 25 Fed. Reg. 12593 (Dec. 9, 1960)), yet Allergan now asserts that the regulation conflicts with the Act. Compl. ¶¶ 127-130. Eliminating that requirement would enable prescription drug manufacturers to circumvent FDA's approval requirement, 21 U.S.C. § 355, by promoting unapproved uses in their advertising while leaving their labeling silent with respect to such uses.

As explained above, when a drug's intended use is reflected in advertising rather than in labeling, the requirement for approval for a new drug follows from the manufacturer's obligation to include adequate directions for use in its labeling: the manufacturer must include adequate directions for use in the labeling to avoid misbranding, and new uses reflected in labeling make the drug a "new

drug" with respect to that use, and require submission of an NDA. Without the challenged regulation, no matter how aggressively a manufacturer used its advertising to promote an unapproved use of a prescription drug, nothing would require the manufacturer to include directions for that use in its labeling. And by keeping the intended use out of the labeling itself, the drug would evade "new drug" status – and attendant NDA filing – despite the manufacturer's active promotion of the unapproved use. Thus, if Allergan can free itself and other prescription drug manufacturers from having to comply with 21 C.F.R. § 201.100(c)(1), it will have gone a long way toward returning to the "sky's the limit" era of drug promotion that prevailed before Congress sought to eliminate those very abuses by enacting the Kefauver-Harris Amendments.

Although Allergan is facially challenging the constitutionality of the FDCA's provisions and regulations relating to unapproved uses, the company also challenges their constitutionality as applied in this case. See Compl. ¶¶ 136-57 (Counts V-VII). In particular, Allergan takes issue with the application of the Act and regulations to its proposed efforts to alert physicians about the risks associated with the unapproved use of Botox to treat various forms of spasticity, including spasticity relating to juvenile cerebral palsy. In Allergan's view, the Act and regulations make it unlawful for a manufacturer to engage in truthful and non-misleading speech regarding unapproved uses, even if the manufacturer professes to be motivated solely by the desire to protect the public.

As we show below, this Laocoön-like portrait, in which Allergan is being strangled by laws and regulations that prevent it from warning the public of serious health risks, is profoundly wrong. It rests on basic mischaracterizations of what the law prohibits and what it permits. The Act and regulations leave ample room for Allergan to disseminate truthful, non-promotional information about dangers associated with unapproved uses of Botox, above and beyond the information that FDA has already directed Allergan to provide. Thus, the issue in this case is not whether to permit

Allergan to provide physicians with scientifically supported safety information about unapproved uses. Neither the Act, the regulations, nor FDA prohibit Allergan from doing so. See Temple Decl. ¶¶ 8-12.

A. The Challenged Statutory Provisions and Regulations Are Constitutional and Otherwise Valid on Their Face (Counts I-IV)

1. When a drug manufacturer engages in speech that promotes an unapproved use for an approved drug, the primary role of the speech in the operation of the FDCA is an evidentiary one. That evidentiary role is entirely consistent with the First Amendment and with the Act itself.

Implementation of the FDCA's approval and misbranding provisions turns in significant respects on a product's intended use or uses. The intended use of the product determines whether the product is a "drug" in the first instance; whether the drug is a "new drug" with respect to a particular use, and must, therefore, be approved by FDA before it may be distributed for that use; and whether the drug's labeling contains adequate directions for use. See 21 U.S.C. §§ 321(g)(1)(B)-©, 321(p), 352(f)(1), 355(a); 21 C.F.R. §§ 201.5, 201.100(c)(1).

When a manufacturer engages in speech such as advertising or promotional labeling that expressly or implicitly promotes a particular use, FDA treats such speech as evidence that the use is intended. See 21 C.F.R. 201.128; Temple Decl. ¶ 10. FDA also takes into account all other circumstances surrounding the distribution of the drug. See 21 C.F.R. § 201.128 (intended use "is determined by [responsible] persons' expressions *or may be shown by the circumstances surrounding the distribution of the article*") (emphasis added). If a manufacturer's speech demonstrates, either by itself or in conjunction with the other "circumstances surrounding the distribution of the drug," that an unapproved use is an intended use, the manufacturer may not distribute the drug for that use without filing and obtaining approval of a supplemental NDA that

contains the relevant supporting scientific data and labeling that includes adequate directions for the use in the drug's labeling.

Nothing in the First Amendment prohibits the government from using a person's speech as evidence to establish intended use. The Supreme Court and the D.C. Circuit have both held that using speech as evidence of intent is constitutionally unobjectionable, even when that determination triggers regulatory or criminal consequences. The D.C. Circuit has done so in the context of the FDCA.

In *Wisconsin* v. *Mitchell*, 508 U.S. 476 (1993), the Supreme Court sustained the constitutionality of a state criminal statute against battery that provided for the five-year enhancement of a defendant's sentence based on his racially discriminatory motivation in carrying out the battery. *Id.* at 480-81. The defendant argued, *inter alia*, that the statute violated his right to free speech because his speech was used to prove that he acted with the requisite intent. *Id.* at 488-89. Although the speech evidence enhanced defendant's incarceration by two years, the Court unanimously rejected that argument, holding squarely that "[t]he First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent." *Id.* at 489.

In *Whitaker* v. *Thompson*, 353 F.3d 947 (D.C. Cir. 2004), the D.C. Circuit relied on *Mitchell* to dispose of a similar First Amendment argument under the FDCA. FDA had determined that a particular dietary supplement could not be marketed without FDA approval because the manufacturer's proposed claims showed that the product was intended to treat a disease and therefore was a drug. *Id.* at 948-49. The manufacturer argued, *inter alia*, that its claims were protected commercial speech. The D.C. Circuit rejected that argument on the ground that FDA was using the claims as evidence of the product's intended use. See 353 F.3d at 953. Citing *Mitchell*, the court

held that "th[e] use of speech to infer intent, which in turn renders an otherwise permissible act unlawful, is constitutionally valid," and hence "it is constitutionally permissible for the FDA to use speech [by the manufacturer] . . . to infer intent for purposes of determining that [the manufacturer's] proposed sale * * * would constitute the forbidden sale of an unapproved drug." *Id.* See also *United States* v. *Article of Drug Designated B-Complex Cholinos Capsules*, 362 F.2d 923, 927 (3d Cir. 1966).

Although Allergan's Complaint does not explicitly assert that it is unconstitutional for FDA to rely on a manufacturer's speech as evidence to establish an intended use, Allergan nevertheless claims in Count IV that FDA's intended-use regulation, 21 C.F.R. § 201.128, violates the First Amendment. Compl. ¶ 132. That claim rests on a basic mischaracterization of the regulation.

Allergan construes § 201.128 to treat *any* statement by a manufacturer about an unapproved use to be evidence of intended use, even if the statement does not directly or indirectly promote that use. But the regulation says nothing of the sort. It provides that intended use "may" be shown "by labeling claims, advertising matter, or oral or written statements by such persons or their representatives." The regulation nowhere suggests that every "oral or written statement" by a manufacturer regarding an unapproved use, regardless of its specific content or tenor or the context in which the statement is made, must or ever will be treated as evidence of an intended use, nor does the regulation suggest that any such statement is sufficient to establish intended use. Indeed, FDA does not – as Allergan claims – regard the non-promotional dissemination of all safety or warning information to be evidence of intended use. Temple Decl. ¶ 10.

Allergan also suggests that § 201.128 treats an unapproved use by physicians as an intended use whenever a manufacturer knows of the use, even if the manufacturer does not promote the use and there is no other evidence that it intends such use. Compl. ¶ 132. Again, Allergan misreads the

regulation. Nothing in the regulation obligates FDA to treat known uses as intended uses. Rather, the regulation leaves FDA with discretion *not* to equate the two. See *Sigma-Tau Pharms., Inc.* v. *Schwetz*, 288 F.3d 141, 146-48 (4th Cir. 2002) (rejecting argument that § 201.128 obligates FDA to treat common and foreseeable uses of generic drug as intended uses). In practice, FDA usually does not treat an unapproved use as an intended use solely because the manufacturer knows that the unapproved use is taking place. Temple Decl. ¶ 10. And tellingly, in this case, FDA has never suggested to Allergan that mere knowledge of unapproved uses of Botox, without more, obligates the company to file a supplemental BLA or renders its existing labeling unlawful because it does not include adequate directions for such uses. Thus, Allergan is wrong when it suggests that it "commits a crime if it engages in any expression [regarding an unapproved use] outside the drug's 'labeling'," or if it merely has "knowledge or notice of an off-label use." Compl. ¶ 132.

Allergan also argues that § 201.128 is invalid "as a matter of statutory interpretation" to the extent that it looks beyond a drug's labeling to determine intended use. Compl. ¶ 133. The suggestion that labeling is the only permissible source of evidence regarding intended use is baseless. As a matter of common sense, advertising and other promotional activities for the drug provide compelling relevant evidence of a product's intended use; were the rule otherwise, drug labeling would be rendered virtually useless. Manufacturers would be free to make their most unsupported and lucrative claims through the "back door" in advertising, while leaving the labeling silent about such claims and forcing physicians to search websites and journals for critical prescribing information.

Beyond all that, as a legal matter, it has long been settled that FDA may look to any relevant source for evidence of intended use, specifically including advertising. See, *e.g.*, *Action on Smoking and Health*, 655 F.2d at 239 ("it is well established that the 'intended use' of a product, within the

meaning of the Act, is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source"); *United States* v. *Storage Spaces Designated Nos. "8" and "49*," 777 F.2d 1363, 1366 (9th Cir. 1985) (intended use "may be derived or inferred from labeling, promotional material, advertising, or any other relevant source"); see also *WLF*, 202 F.2d at 336 (if manufacturer distributes medical and scientific publications regarding unapproved uses or supports continuing medical education programs regarding such uses in ways that fall outside statutory and regulatory safe harbors, "the FDA retains the prerogative to use both types of arguably promotional conduct as *evidence* in a misbranding or 'intended use' enforcement action") (emphasis in original). To hold otherwise would mean, for example, that the manufacturer of a drug approved for epileptic seizures could run full-page ads or television commercials promoting the drug for use in treating anxiety, a disorder with different etiology, symptoms, and standard of care, yet the manufacturer would not have to seek FDA approval for the unapproved use, would not have to conduct clinical trials to substantiate the advertising claims, and would be under no obligation to provide adequate directions to assure the drug to be safe and effective for such indication. Nothing in the Act even remotely suggests such a result, much less requires it.

Finally, Allergan makes the remarkable suggestion (PI Mem. 30-31) that § 352(f)(1), which requires labeling to contain "adequate directions for use," requires directions only for uses that are contained in a drug's labeling, and does not require that the directions also address intended uses that are promoted in advertising and elsewhere. FDA first interpreted § 352(f)(1) to require adequate directions for advertised uses in 1938, as part of its original regulations implementing the then newly-enacted FDCA. See 3 Fed. Reg. 3167 (Dec. 28, 1938) (labeling must include "directions for use in all conditions for which such drug or device is prescribed, recommended, or suggested in its labeling, *or in its advertising disseminated or sponsored by or on behalf of its manufacturer or*

packer . . .") (emphasis added). It has been settled law for the intervening 70 years that § 352(f)(1) requires labeling to contain adequate directions for all intended uses, including advertised uses, not merely the uses reflected in the labeling. See, *e.g.*, *V.E. Irons, Inc.* v. *United States*, 244 F.2d 34, 44 (1st Cir. 1957) (in sustaining criminal conviction for misbranding under § 352(f), "we are free to look to all relevant sources in order of [sic, to] ascertain what is the 'intended use' of a drug, and are not merely confined to the labels on the drug or the 'labeling'"). Congress has amended the Act countless times since then, and has amended § 352(f) itself, without ever disturbing this uniform administrative and judicial interpretation. A holding that § 352(f)(1) applies only to uses contained in a drug's labeling would upset an interpretation that has been maintained by the agency, sustained by the courts, and accepted by Congress for more than seven decades, and would eviscerate the Act's new drug and misbranding provisions in the process.

2. The FDCA's misbranding provisions require prescription drug advertisements to contain "a true statement" of "such . . . information in brief summary relating to side effects, contraindications, and effectiveness" as FDA may require by regulation. 21 U.S.C. § 352(n). FDA has exercised this authority by issuing 21 C.F.R. § 202.1, which details the rules for the content of prescription drug advertisements. Among other things, the regulation provides that advertisements for prescription drugs approved since 1962 "shall not recommend or suggest" unapproved uses. 21 C.F.R. § 202.1(e)(4)(i)(a). Allergan claims that this provision conflicts with § 352(n) and that it violates the First Amendment. Compl. ¶¶ 117-24. Both claims are incorrect.

Contrary to Allergan's suggestion, § 202.1(e)(4)(i)(a) is entirely consistent with § 352(n). By its terms, § 352(n) grants FDA general authority to designate the "information . . . relating to side effects, contraindications, and effectiveness" that is to be included in a manufacturer's "true statement." Information "relating to . . . effectiveness" necessarily includes information about

effectiveness for unapproved uses, and FDA is free and, indeed, wise to limit advertisements to claims of effectiveness that have been substantiated through the new drug approval process. Nothing on the face of § 352(n) supports Allergan's suggestion that FDA lacks legal authority to exclude material on unapproved uses from prescription drug advertisements. See also 21 U.S.C. § 371(a) (general authority "to promulgate regulations for the efficient enforcement of this Act").

Unsurprisingly, the challenged regulation likewise readily passes muster under the First Amendment standards that govern commercial speech. *Central Hudson Gas & Elec. Corp.* v. *Pub. Serv. Comm'n*, 447 U.S. 557 (1980) makes clear that "commercial speech enjoys First Amendment protection only if it concerns a lawful activity and is not misleading." *Whitaker*, 353 F.3d at 952; see *Central Hudson*, 447 U.S. at 563. Moreover, even if the speech in question concerns a lawful activity and is not false or misleading, the government may impose restrictions that advance a "substantial" government interest and are no "more extensive than is necessary to serve that interest." *Id.* at 566. This standard does not require the government to employ "the least restrictive means" of regulation or to achieve a perfect fit between means and ends. *Bd. of Trustees* v. *Fox*, 492 U.S. 469, 480 (1989). Instead, it is sufficient that the government achieve a "reasonable" fit by adopting regulations "'in proportion to the interest served.'" *Id.* (quoting *In re R.M.J.*, 455 U.S. 191, 203 (1982)). The requirement of narrow tailoring is satisfied "so long as the . . . regulation promotes a substantial government interest that would be achieved less effectively absent the regulation." *United States* v. *Albertini*, 472 U.S. 675, 689 (1985). "[A] regulation limiting commercial speech can, in fact, be more extensive than is necessary to serve the government's interest as long as it is not unreasonably so." *City of Cincinnati* v. *Discovery Network*, 507 U.S. 410, 434 (1993).

Here, the limitation on advertising that promotes unapproved uses of prescription drugs presents no First Amendment problem under *Central Hudson* because the advertising is designed

to promote a transaction – the distribution of a drug for an unapproved use – that is itself unlawful. As explained above, "it is unlawful for a manufacturer to introduce a drug into interstate commerce with an intent that it be used for an off-label purpose." *WLF*, 202 F.3d at 332-33. It is also unlawful for manufacturer to do an act, e.g., promote a drug for an unapproved use that causes the drug to be misbranded "while it is held for sale after shipment in interstate commerce." 21 U.S.C. § 331(k). The Supreme Court has made clear, both in *Central Hudson* and in later cases, that commercial speech concerning unlawful activity receives no First Amendment protection. See *44 Liquormart, Inc.* v. *Rhode Island*, 517 U.S. 484, 497 n.7 (1996) (plurality opinion) ("the First Amendment does not protect commercial speech about unlawful activities"); *Fla. Bar* v. *Went For It, Inc.*, 515 U.S. 618, 623-24 (1995) ("the government may freely regulate commercial speech that concerns unlawful activity"); *Zauderer* v. *Office of Disciplinary Counsel of Supreme Court of Ohio*, 471 U.S. 626, 638 (1985) ("the States and the Federal Government are free to prevent the dissemination of commercial speech . . . that proposes an illegal transaction"); *Bolger* v. *Youngs Drug Prods. Corp.*, 463 U.S. 60, 69 (1983) ("the State may also prohibit commercial speech related to illegal behavior"); *Central Hudson*, 447 U.S. at 563-64 ("[t]he government may ban . . . commercial speech related to illegal activity"). That is precisely what is at issue here. And as the D.C. Circuit explained in *Whitaker*, even when a manufacturer's speech provides the evidence of intended use that triggers the statutory prohibition on distribution of the drug for unapproved uses, evidentiary reliance on the speech does not remove the case from the principle that commercial speech relating to unlawful activity is constitutionally unprotected. See *Whitaker*, 353 F.3d at 953.

Moreover, even if Allergan's challenge to § 202.1(e)(4)(i)(a) were not barred under the first prong of *Central Hudson*, the regulation's prohibition against prescription drug advertising that recommends or suggests unapproved uses would readily satisfy the remaining elements of the

Central Hudson test. The regulation directly advances the compelling governmental interest in drug safety and public health, and by means "in proportion to the interest served." *Fox*, 492 U.S. at 480.

The new drug approval system created by Congress in 1962 was designed to curb distribution of unsafe and ineffective drugs in the market, by requiring manufacturers to investigate and substantiate the safety and effectiveness of drugs for each intended use *before* offering the drugs for sale to the public, and by shielding patients and physicians from false or misleading claims. Among other things, the statutory scheme is designed to discourage manufacturers from seeking approval for one use (perhaps a quite narrow one), then promoting the drug for other uses for which it may be neither effective nor safe. The prohibition in § 202.1(e)(4)(i)(a) against advertising unapproved uses for prescription drugs directly advances this goal. Unlike the prohibition on advertising of compounded drugs struck down in *Thompson* v. *Western States Med. Ctr.*, 535 U.S. 357, 374 (2002), the regulation is not motivated by "a fear that people would make bad decisions if given truthful information" about prescription drugs. Instead, it rests on the premise – amply supported by the legislative history of the 1962 legislation – that drug manufacturers, when left to their own desires, frequently make *un*truthful claims about new uses, and that encouraging manufacturers to evaluate and demonstrate the safety and effectiveness of their drugs before marketing them for new uses protects the public from promotional claims that are unsubstantiated at best, and false at worst. See *Rutherford*, 442 U.S. at 558 ("Since the turn of the century, resourceful entrepreneurs have advertised a wide variety of purportedly simple and painless cures for cancer, including liniments of turpentine, mustard, oil, eggs, and ammonia; . . . colored flood-lamps; . . .; mineral tablets; and 'Fountain of Youth' mixtures of spices, oil, and suet").

The Supreme Court has observed that the pre-1962 alternative of pursuing false or misleading drug claims after the fact, by enforcing the FDCA's misbranding provisions, was a "slow,

cumbersome method" "utterly unsuited to the need." *USV Pharm. Corp.* v. *Weinberger*, 412 U.S. 655, 665 (1973). Under "the more cumbersome 1938" law that preceded the enactment of the Kefauver-Harris Amendments, "good medical practice [was] hampered, and the consumer [was] misled until, perhaps years later, the Government ha[d] gathered the necessary evidence to sustain its burden of proving the [misbranding] violation in court." *Id.* Thus, § 202.1(e)(4)(i)(a) is not impermissibly overbroad under *Central Hudson* merely because it is not confined to false or misleading advertising.

Nor do any the alternatives suggested by Allergan (PI Mem. 27-28) render § 202.1(e)(4)(i)(a) impermissibly overbroad. Contrary to Allergan's suggestion, allowing manufacturers to promote unapproved uses as long as they disclose that the uses have not been approved (*id.* at 27) would greatly undermine the incentive to conduct the kind of lengthy and rigorous testing needed to demonstrate safety and effectiveness under § 355. Requiring submission of supplemental applications when an unapproved use "pass[es] a threshold of prevalence or sales" (*id.*) – a suggestion that shines a telling light on Allergan's professed concern for the public health -- would be virtually unadministrable: FDA would have to know not only the uses to which the manufacturer's drug is being put, but what portion of the drug's total sales are attributable to each separate use, information that at best would have to be aggregated from countless individual patients and/or physicians and is often unobtainable. Moreover, even unapproved uses that generate small sales can pose a serious public health risks – for example, by diverting patients with serious illnesses from effective to ineffective drugs. Taxing manufacturers for off-label sales more heavily than for on-label sales (*id.*) would allow manufacturers to buy their way out of the new drug approval process, and would involve the very administrability and enforceability problems that are posed by the notion of requiring supplemental NDAs only when garnered by an unapproved use becomes

"too" profitable. Finally, nothing in *Central Hudson* and its progeny requires Congress to choose between allowing manufacturers to promote unapproved uses and prohibiting physicians from prescribing unapproved uses altogether (*id.*).

Contrary to Allergan's hyperbole, § 202.1(e)(4)(i)(a) does not "require prescription decisions to occur in a no-speech zone" (PI Mem. 40). As discussed, the Act leaves open numerous avenues for manufacturers to provide prescribing physicians with important safety information about unapproved uses. See Temple Decl. ¶¶ 8-12, 14-18. Nothing in § 202.1(e)(4)(i)(a), which is aimed solely at promotional speech rather than the non-promotional dissemination of safety information, stands in the way of that process.

3. As noted, a drug's labeling must contain adequate directions for use by patients. See 21 U.S.C. § 352(f)(1); 21 C.F.R. § 201.5; *Article of Drug*, 625 F.2d at 672-73. Because prescription drugs are not safe for use except under the supervision of a licensed practitioner, labeling cannot render a prescription drug safe for use by laymen. See *Articles of Drug*, 625 F.2d at 673. However, § 352(f) authorizes FDA to issue exceptions from the adequate labeling requirement, and FDA has exercised that authority by exempting prescription drugs that comply with 21 C.F.R. § 201.100. That regulation, in turn, requires prescription drug labeling to include, *inter alia*, "adequate information for its use . . . under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, *including all purposes for which it is advertised or represented*." *Id.* § 201.100(c)(1) (emphasis added). Thus, although OTC drug labeling must have adequate directions for use by laymen, prescription drug labeling must bear adequate directions ("adequate information") for use by physicians or other practitioners.

Allergan does not suggest that the First Amendment prevents Congress or FDA from requiring adequate directions for use of all drugs, including prescription drugs. Instead, Allergan

contends that Congress has excused prescription drug manufacturers from *any* obligation to include adequate directions for use in their labeling, and that § 201.100(c)(1) is invalid because it conflicts with that supposed Congressional design. Compl. ¶¶ 127-30. Absent § 201.100(c)(1), Allergan would be free to promote unapproved uses of Botox without including those intended uses in the drug's labeling, thereby skirting the approval process in 21 U.S.C. § 355 and 42 U.S.C. § 262.

Allergan relies on 21 U.S.C. § 353(b)(2), which exempts "[a]ny drug dispensed by filling or refilling a written or oral prescription of a practitioner licensed by law to administer such drug" from most of the misbranding requirements in 21 U.S.C. § 352, including the requirement of adequate directions for use in § 352(f)(1), if the drug "bears a label" containing specified information, including "the directions for use and cautionary statements, if any, contained in such prescription."

Allergan contends that § 353(b)(2) grants prescription drugs a global exemption from the adequate-directions requirement in § 352(f)(1). Allergan is wrong; as the language of § 353(b)(2) indicates, and as the Fifth Circuit has squarely held, the exemption relieves prescription drug labeling from compliance with § 352(f)(1) only at the point that the drug is prescribed *and* dispensed. *United States* v. *Evers*, 643 F.2d 1043, 1051 (5th Cir. 1981); see also *Articles of Drug*, 625 F.2d at 674. By its terms, § 353(b)(2) addresses the labeling of the drug as "dispensed [to the patient] by filling or refilling a written or oral prescription," and for that reason requires the labeling to include "the directions for use . . . contained in such prescription." Thus, as the court in *Evers* found, "it provides a much narrower protection for the distribution of the drug, for it exempts the provisions of [21 U.S.C. § 352] only at the point at which the drug is actually prescribed and dispensed . . . ." 643 F.2d at 1051. Because exemptions are to be read narrowly, and because § 353(b)(2) does not completely exempt prescription drugs from the adequate direction requirement in § 352(f)(1), there is no conflict between § 352(f)(1) and the adequate directions requirement in § 201.100(c)(1).

Allergan also takes issue with the requirement in § 201.100(c)(1) that prescription drug labeling contain adequate directions for use "for the purposes for which it is intended," including all purposes for which it is advertised or represented," rather than just the uses identified in the labeling itself. Compl. ¶ 131. Allergan suggests that if labeling must include adequate directions for all intended uses, then prescription drug manufacturers who intend new uses of their drugs will find themselves placed between Scylla and Charybdis: if the manufacturer does not add directions for the new intended use to the labeling, it will violate § 201.100(c)(1) and thus commit misbranding, but if it does add directions for the new use, it will be in violation of the prohibition against distribution of unapproved new drugs in 21 U.S.C. § 355.

This asserted dilemma ignores the regulatory realities. Although a drug manufacturer must obtain FDA approval under § 355 before it can distribute a drug for new use, a manufacturer that files a supplemental NDA or BLA for a new use will not be charged with misbranding under § 352(f)(1) merely because the manufacturer waits for FDA approval of the application before changing the drug's existing labeling to reflect the new use. Nor will the manufacturer be prohibited from distributing the drug with its original approved labeling during the interim, as long as the manufacturer is not otherwise promoting the unapproved use. Simply stated, Allergan's "dilemma" is created only by its impatience to begin promoting a new use for a drug before that use has been approved by FDA.

4. Allergan also takes issue with FDA's longstanding interpretation of "labeling" under the Act. The FDCA defines "labeling" to include "all . . . 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)*; see also* 21 C.F.R. § 1.3(a). To provide additional guidance for manufacturers, and to help to delineate the line between "labeling" and "advertising" for prescription drugs, 21 C.F.R.

§ 202.1(*l*)(2) more specifically identifies the materials relating to prescription drugs that may be deemed to be "labeling" under Section 321(m). The regulation provides that labeling includes specified types of "printed, audio, or visual matter descriptive of a drug," such as brochures, booklets, and reprints, "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. . . ." 21 C.F.R. § 202.1(*l*)(2).

Allergan claims that this regulation is invalid because it is inconsistent with 21 U.S.C. § 321(m). Compl. ¶¶ 99-108. According to Allergan, the regulation "radically expand[s]" the scope of the statutory definition of labeling (*id.* ¶ 25) by abandoning the statutory requirement that the material "accompan[y] such article." In Allergan's view (PI Mem. 33, 35), material does not "accompany" a drug for purposes of Section 321(m) unless the two travel in each other's company, going to the same destination by the same route at the same time.

Allergan's narrow and self-serving approach to the definition of "labeling" has been considered and expressly rejected by the Supreme Court. The Court long ago endorsed a broad construction of "labeling" to include promotional materials that supplement, explain, or are otherwise textually related to the article. See *Kordel v. United States*, 335 U.S. 345, 350 (1948); *United States v. Urbuteit*, 335 U.S. 355 (1948). The Court's decisions also make clear that the definition of "labeling" requires neither physical nor temporal proximity between the "written, printed, or graphic matter" and the article that it concerns.

In *Kordel*, the Supreme Court held that literature mailed separately from the product may constitute "labeling." As the Court explained, "[t]he literature was used in the sale of the drugs. It explained their uses. . . . It constituted an essential supplement to the label attached to the package. Thus the products and the literature were interdependent . . . ." 335 U.S. at 348. The Court held that,

for purposes of the definition of "labeling" in § 321(m), "[o]ne article or thing is accompanied by another when it supplements or explains it, in the manner that a committee report of the Congress accompanies a bill. No physical attachment to the other is necessary. It is the textual relationship that is significant." *Id.* at 350. To require a physical relationship between the material and the product, in the Court's view, would defy common sense and open an "obviously wide loophole." *Id*. at 349. Far from "limit[ing] its holding to the facts of the case," as Allergan claims, *Kordel* explicitly "affirm[s] [a] broad definition of 'labeling' under the [FDCA]." *WLF*, 202 F.3d at 333.

The same day that it decided *Kordel*, the Supreme Court also decided *United States v. Urbuteit*, 335 U.S. 355 (1948). The issue in *Urbuteit* was whether literature constituted "labeling" even though it was distributed after the shipment of the defendant's medical devices. Applying *Kordel*, the Court found the temporal gap to be immaterial because "the advertising matter that was sent was designed to serve and did in fact serve the purposes of labeling." 335 U.S. at 357. The Court explained that § 321(m) should be applied using "functional standards" to properly serve the consumer protections purposes of the statute. *Id.* at 357-58. See also *United States v. 47 Bottles, More or Less, ... Jenasol*, 320 F.2d 564, 568-69 (3d Cir. 1963) (promotional leaflets shipped separately from product were "labeling"); *Walls v. Armour Pharm. Co.*, 832 F. Supp. 1467, 1482-83 (M.D. Fla. 1993) ("labeling" includes "letters sent by drug manufacturers to physicians to provide information about a drug"), *aff'd in part and rev'd in part*, 53 F.3d 1184 (11th Cir. 1995).

FDA's regulation, 21 C.F.R. § 202.1(*l*)(2) is fully consistent with the statutory interpretation adopted in *Kordel* and *Urbuteit*. The regulation construes "labeling" to include specified printed and audiovisual materials "descriptive of a drug . . . 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." By requiring that the materials describe the drug, contain

information about the drug supplied by the manufacturer or other responsible persons, and be disseminated by or on behalf of those persons, the regulation fully honors the "textual relationship" and "functional standard" benchmarks established in *Kordel* and *Urbuteit*.

Allergan argues that when a manufacturer wishes to promote an approved drug for unapproved uses, promotional material that does not physically accompany the drug should be regarded as advertising, rather than labeling, to avoid supposed First Amendment problems. But for all of the above reasons, the provisions of the Act and regulations that relate to promotion of unapproved uses do not trench upon the First Amendment, regardless of where the line between labeling and advertising is drawn. The consequence of adopting Allergan's narrow definition of labeling would not be to avoid a potential constitutional problem, but instead to enable Allergan to promote unapproved uses of Botox without having to comply with the § 352 misbranding provisions that govern labeling. There is no reason for the Court to allow that result.

5. Finally, in Count II, Allergan challenges what it characterizes as FDA's interpretation of § 352(a), which provides that a drug is misbranded if its labeling is "false or misleading in any particular." According to Allergan, the government regards all statements by a manufacturer relating to the safety and effectiveness of an unapproved use as automatically false or misleading, regardless of the actual state of the scientific evidence concerning the use, simply because the FDA has not approved the use. Allergan argues that if a statement about a drug's safety and effectiveness for an unapproved use is not otherwise false or misleading, the fact that the FDA has not approved the use does not automatically render it false or misleading, without more, for purposes of § 352(a).

We agree. It is *not* FDA's position that any statement by a manufacturer about the safety or effectiveness of an unapproved use is automatically false or misleading merely because the use has

not yet been approved by FDA.[11] To be sure, references in labeling to unapproved uses *can* be false or misleading – for example, by implying that FDA has approved the use, or by failing to disclose that the use is unapproved, or by falsely implying that the safety and effectiveness of the drug are settled questions. But it does not follow, and FDA does not contend, that every statement regarding the safety and effectiveness of an unapproved use, regardless of its contents and other circumstances, is false or misleading simply because FDA has not yet reviewed and approved the use.[12]

B. The Challenged Statutory Provisions and Regulations Are Constitutional As Applied To Allergan (Counts V-VII)

For the foregoing reasons, the provisions of the Act and regulations challenged by Allergan are constitutional on their face, and the regulations are consistent with the Act. As we now show, the Act and regulations are equally valid as applied to Allergan.

1. As noted, FDA has required Allergan to take specific steps to alert physicians to serious health risks associated with common unapproved uses of Botox. Allergan alleges that it wishes to provide physicians with additional information about these health risks, including ways to minimize those risks. Compl. ¶¶ 76-87. Count VII asserts that the FDCA and FDA regulations are

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[11] In this regard, we note that 21 C.F.R. § 201.56(a)(3), a provision whose validity Allergan has not challenged, prohibits prescription drug labeling from including claims about uses "if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness." If FDA regarded statements about safety and effectiveness as inherently false or misleading in the absence of FDA approval, the prohibition in § 201.56(a)(3) on claims that are not supported by adequate evidence would be superfluous: *regardless* of how much evidence might support a safety or effectiveness claim, the claim would render the drug misbranded under § 352(a). The existence of § 201.56(a)(3) confirms that FDA does not regard statements about safety and effectiveness of unapproved uses as *ipso facto* false or misleading simply because the use has not been approved by the agency. Temple Decl. ¶ 11.

[12] Contrary to Allergan's suggestion, the government's prosecution in *United States* v. *Warner Lambert Co.*, Crim. No. 04-10150 (D. Mass. 2004), was not based on such a theory. In *Warner Lambert*, the defendant promoted its drug as safe and effective for uses that had been *rejected* by FDA. See Sentencing Memorandum at 24-25 (defendant "continued to promote Neurontin for monotherapy by saying that it was effective for it, without ever mentioning the material fact that the FDA had rejected its application for monotherapy based on its finding that the clinical trial performed did not establish effectiveness"). It is in that context that the government stated, in the sentence quoted by Allergan, that it is false or misleading to "suggest[] that [a] drug is safe and effective for uses which have not been approved by the FDA." *Id.* at 9. We note too that the charges in *Warner Lambert* were based on inadequate directions for use under § 352(f)(1), not on false or misleading labeling under § 352(a). See *id.* at 1-2.

unconstitutional as applied to these proposed communications. *Id.* ¶¶ 152-57. Allergan argues that it has a constitutional right to engage in truthful speech about unapproved uses "about which the FDA has required Allergan to speak," and that the government lacks a legitimate interest in "suppressing" further truthful speech about those uses. *Id.* ¶¶ 154-55. Allergan further claims that "all non-pre-approved speech violates the FDA's regulatory regime," and that this supposed pre-approval requirement is an unconstitutional prior restraint. *Id.* ¶ 156.

The premise underlying Count VII is false. A manufacturer wishing to warn physicians of serious risks associated with unapproved uses and to offer guidance on how to minimize those risks will not find its path barred by FDA. As already shown above, and as further explained by Dr. Temple, the Deputy Director for Clinical Science for FDA's Center for Drug Evaluation and Research, Allergan's contrary premise is wrong.

The FDCA and FDA's regulations do not prohibit manufacturers from disseminating truthful, non-misleading information about risks associated with unapproved uses. FDA does not construe the Act or regulations to prohibit the communication of non-promotional safety information about unapproved uses. Temple Decl. ¶¶ 8-12. A manufacturer is free to warn about the adverse consequences of an unapproved use as long as the warning does not explicitly or implicitly promote the effectiveness of the drug for that use. *Id.* If the communication is not promotional, it will not be viewed as evidence of intended use, and therefore will not trigger the obligation either to include adequate directions for use or to submit a new drug application. *Id.*

Indeed, far from prohibiting manufacturers from disseminating warnings relating to unapproved uses, FDA has affirmatively encouraged them to do so. For example, when a drug manufacturer distributes copies of medical or scientific articles regarding unapproved uses for the manufacturer's drug, FDA's *Reprint Guidance* urges the manufacturer to attach a "prominently

displayed" statement that "disclos[es] . . . all significant risks or safety concerns known to the manufacturer concerning the unapproved use" that are not disclosed in the article itself. *Reprint Guidance* at 7. And on multiple occasions, including this one, FDA has affirmatively required manufacturers to disseminate warning information about risks associated with unapproved uses. Temple Decl. ¶ 12.

Here, depending on the wording and supporting evidence, much of the warning information that Allergan alleges it wants to provide would qualify as non-promotional safety information that would not constitute evidence of an intended use. Temple Decl. ¶¶ 19-20. For example, Allergan may be able to provide information on how the risk increases with the number of injection sites (see Compl. ¶ 80); explain that the full effect of an injection of Botox may not be apparent until a significant period of time after the injection (id. ¶ 81); explain that the effects of Botox and all BTX products may spread from the area of injection to produce symptoms consistent with BTX effects; explain that treatment with Botox and other BTX products can result in swallowing or breathing difficulties; explain that 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 (see id. ¶ 82); explain that for both unapproved uses and approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia; and explain that because there are currently multiple marketed BTX products with different dose-to-potency ratios, there is a concern about medication errors such as overdosing based on incorrect unit administration from interchanging the products. Temple Decl. ¶ 19.

Whether Allergan's communications *will* be truthful and non-misleading, and whether Allergan *will* refrain from promoting the unapproved uses at issue, depend on what Allergan actually

says. That is one reason why Allergan's First Amendment claims relating to its proposed communications are not ripe. *Cf. Nutritional Health Alliance*, 144 F.3d at 226 (First Amendment challenge to FDA's standards for evaluating health claims not ripe because "without a specific proposed health claim to review, on evidence of record before the FDA, we cannot determine whether the 'significant scientific agreement' requirement actually bars any truthful, non-misleading speech").

Allergan's related claim that "all non-pre-approved speech violates the FDA's regulatory regime," and that it therefore cannot convey warnings to physicians without submitting to an administrative prior restraint (Compl. ¶ 156), is equally misconceived. None of the forms of communication proposed in the complaint (¶¶ 83-87) requires prior FDA review or approval. FDA approval is not required for promotional labeling or advertising, much less for forms of communication that (depending on their contents) may not even constitute labeling or advertising in the first instance. FDA approval is required only for changes in FDA-approved labeling that appears on the drug product or inside its packaging. See *id.* Allergan does not allege that it wishes to provide additional warnings, above and beyond those required by FDA, in its FDA-approved labeling. And even if it did, FDA's regulations allow manufacturers to change FDA-approved labeling to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product" immediately, subject to potential disapproval of the labeling changes after the fact. See 21 C.F.R. § 314.70(c)(6)(iii). Allergan's prior restraint claim therefore fails for the simple reason that Allergan's proposed speech is not subject to prior FDA approval.[13]

[13] Even if prior approval *were* required, the First Amendment does not prohibit Congress from requiring manufacturers to submit claims about the safety and effectiveness of drugs for review and approval before the claims are disseminated to the public. See, *e.g.*, *Nutritional Health Alliance*, 144 F.3d at 227-28 (requirement that health claims on dietary

2. In Count V, Allergan asserts that the government's interests relating to promotion of unapproved uses lapse as soon as a manufacturer files a supplemental NDA or BLA that seeks approval to market the drug for such uses. Compl. ¶¶ 136-43. Allergan argues that if Congress's goal is to provide an incentive for manufacturers to seek FDA review and approval of previously unapproved uses, that goal is fully realized when the manufacturer files a supplemental application, and no further interest is served by limiting promotion of the unapproved use while the application is under review, even if the application fails to demonstrate that the drug is safe and effective for the new use and will ultimately be disapproved by FDA. *Id.* ¶ 140.

The basic flaw in this argument is that the filing of a supplemental application is a means to an end, not an end in itself. Congress' goal is not simply to encourage manufacturers to file new applications for unapproved uses, but to enable FDA to evaluate the effectiveness and safety of the drugs for those uses in order to protect patients from drugs that are unsafe, ineffective, or both. While some supplemental applications are approved, others are disapproved because, *inter alia*, the data do not demonstrate safety and effectiveness for the new use. See Temple Decl. ¶ 6. Allowing every manufacturer that submits a supplemental application to begin promoting the use immediately upon filing the application would therefore necessarily mean allowing manufacturers to promote uses for which the drug is *not* safe and effective – precisely the result that Congress sought to avoid when it enacted the Kefauver-Harris Amendments in 1962.

For example, Provigil (modafinil) was approved by FDA to treat excessive daytime sleepiness associated with narcolepsy, shift work disorder, and sleep apnea. Temple Decl. ¶ 5. The drug's sponsor filed a supplemental NDA for attention deficit hyperactivity disorder (ADHD). *Id.*

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supplement labels be submitted to FDA for prior approval is not unconstitutional prior restraint, even when review process may take up to 540 days).

Rather than waiting for approval of the supplemental NDA, the sponsor began promoting and distributing Provigil for ADHD while the application was pending, in contravention of the governing statute and regulations Allergan now challenges. *Id.* However, an FDA advisory panel ultimately recommended disapproval of the application for use of the drug for ADHD because it received reports of a rare, but sometimes fatal, rash developing in children who took the drug. *Id.* FDA agreed with the panel and notified the sponsor that the supplemental application could not be approved, and the sponsor withdrew the application. *Id.* The regime proposed by Allergan would open the door to this kind of promotion of drugs that are unsafe – even, as in the case of Provigil, potentially fatal – for the unapproved use. Contrary to Allergan's suggestion, the government has an overwhelming compelling interest in avoiding that outcome.

Moreover, allowing manufacturers to begin promoting unapproved uses as soon as they file supplemental applications would create a powerful financial incentive for manufacturers to file such applications prematurely, before the safety and effectiveness of the drug for the new use has been adequately investigated and substantiated. The mere submission of the application would entitle the manufacturer to begin promoting the unapproved use and thereby begin increasing its revenues immediately, even if the application contains deficiencies that would prevent FDA approval. If FDA determines that an NDA or BLA cannot be approved as submitted, it issues a "complete response letter," which identifies deficiencies in the application that foreclose approval and, where applicable, recommends actions by the manufacturer that might lead to eventual approval. See 21 C.F.R. §§ 314.110, 601.3. Thus, a prematurely submitted and inadequately supported application need not bring the review process to a close, but could lead to the submission of a revised application and further review, during which time the manufacturer would (under Allergan's scheme) continue to enjoy the right to promote the drug. Manufacturers would therefore have a significant incentive

to "shoot first and answer questions later," which in turn would increase the frequency with which drugs are promoted for unsafe or ineffective uses.

3. Finally, Allergan argues that it is unconstitutional to restrict the promotion of unapproved uses that are "widely accepted." Compl. ¶¶ 144-51. More specifically, Allergan argues that manufacturers are constitutionally entitled to promote drugs for unapproved uses for which the government reimburses health care providers under Medicare and Medicaid. *Id.* ¶¶ 146-49. Allergan reasons that if the government has "recognized the validity" of an unapproved use through its reimbursement decisions, it has no valid interest in limiting promotional speech for that use. *Id.* ¶ 149.

What this argument overlooks is that the Medicare and Medicaid programs do not make drug reimbursement decisions using the same criteria and procedures used by FDA. As the federal gatekeeper for drug safety, FDA examines the results of "adequate and well-controlled investigations, including clinical investigations," and determines on the basis of those investigations and other data whether the drugs are safe and effective for their intended uses. In making coverage determinations, the Medicare and Medicaid programs use the FDA's threshold approval determinations when such determinations are available, but also use non-governmental drug compendia, peer-reviewed medical literature, and prevailing medical practices. See Complaint ¶¶ 62-63.

But the fundamental premise of federal drug regulation as embodied in the original enactment of the FDCA in 1938 and the Kefauver-Harris Amendments has been that the safety and effectiveness of new drugs can be established only through the rigorous process of clinical investigations and expert review mandated by § 355, and that the judgments of individual physicians about the safety and effectiveness of drugs, however sincere and however widely held, are often

unreliable. The Supreme Court has pointed out that "[t]he hearings underlying the 1962 Act [*i.e.*, the Kefauver-Harris Amendments] show a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous." *Hynson,* 412 U.S. 609, 619 (1973). And "[t]he [FDCA's] 'substantial evidence' requirement [for approval of new drug applications] reflects the conclusion of Congress, based upon hearings, that clinical impressions of practicing physicians and poorly controlled experiments do not constitute an adequate basis for establishing efficacy." *Cooper Laboratories, Inc.* v. *FDA*, 501 F.2d 772, 778-79 (D. C. Cir. 1974); see also *E.R. Squibb and Sons, Inc.* v. *Bowen*, 870 F.2d 678, 685 (D.C. Cir. 1989) ("the FDA's exclusion of 'anecdotal evidence indicating that doctors "believe" in the efficacy of a drug[ ] [is] amply justified by the legislative history' of the 1962 amendments").

The standards used by Medicare and Medicaid in making reimbursement decisions are not a substitute, much less a constitutionally compelled substitute, for the standards used by FDA in approving or disapproving new drug applications. A drug reimbursement mistake costs money. A drug approval mistake can cost lives.

C. Allergan's Challenge to the Authority of District Courts to Order Disgorgement Under the Act is Unripe and Without Merit (Count VIII)

Allergan's disgorgement claim in Count VIII is obviously unripe. It assumes that the government will elect to bring a civil action based on violations of the Act with respect to Allergan's off-label activities, that the action will be successful, and that the government will then seek disgorgement of financial gains under the FDCA rather than other remedies. To suggest that this speculative and attenuated chain of events presents a such a chill on Allergan's activities with respect to off-label use as to give rise to a present First Amendment case or controversy defies credibility and would require this Court to issue an advisory opinion. If, nonetheless, the court wishes to

engage in the speculation invited by Allergan in Count VIII, it must conclude that disgorgement is a remedy available to the government for violations of the Act.

The Third, Sixth, and Tenth Circuits have recently considered the availability of monetary equitable relief, disgorgement and restitution, for violations of the Act, and they have each readily concluded that such relief is permissible. *United States v. RX Depot, Inc.*, 438 F.3d 1052 (10th Cir.), *cert. denied*, 549 U.S. 817 (2006);*United States v. Lane Labs-USA, Inc.*, 427 F.3d 219, 223 (3d Cir. 2005); *United States v. Universal Mgmt. Servs., Inc.*, 191 F.3d 750, 761 (6th Cir. 1999).

The decisions by these three Circuits all rest on the traditional analysis of the scope of equitable relief established by the Supreme Court in *Porter v. Warner Holding Co.*, 328 U.S. 395 (1946), and *Mitchell v. Robert DeMario Jewelry, Inc.*, 361 U.S. 288, 293 (1960). In *Porter*, the Court construed a provision of the Emergency Price Control Act of 1942 ("EPCA") that authorized the courts to grant "a permanent or temporary injunction, restraining order, or other order" for charging excessive rents, 328 U.S. at 397, to also allow for restitution because: "Unless otherwise provided by statute, all the inherent equitable powers of the District Court are available for the proper and complete exercise of that jurisdiction . . . . Moreover, the *comprehensiveness of this equitable jurisdiction is not to be denied or limited in the absence of a clear and valid legislative command*." Id. at 397-98 (internal citations and quotations omitted and emphasis added). In *Mitchell*, 361 U.S. at 290-92, the Court reaffirmed the district courts' inherent authority to grant monetary equitable remedies, absent an express statutory prohibition, and did so with respect to the precisely the same statutory language that Congress used in § 332(a) of the FDCA.

Relying on *Porter* and *Mitchell*, the Sixth, Third, and Tenth Circuits each have held that district courts may order monetary equitable relief for violations of the FDCA. In *Universal Management*, the Sixth Circuit affirmed the district court's award of restitution in connection with

an injunction against a manufacturer of medical devices sold without required FDA approval. In *Lane Labs*, the Third Circuit affirmed a restitution order against a manufacture who distributes a drug without the requisite FDA approval, holding that "[t]hough the FDCA does not specifically authorize restitution, such specificity is not required where the government properly invokes a court's equitable jurisdiction under this statute." *Id.* 427 F.3d at 223. Most recently, in *RX Depot*, the Tenth Circuit reversed a district court's rejection of disgorgement as an ancillary remedy in an injunction action against a business that facilitated the importation of drugs that lacked required approval from FDA. The court reasoned that, "under *Porter* and *Mitchell*, when a statute invokes general equity jurisdiction, courts are permitted to utilize *any equitable remedy* to further the purposes of the statute *absent a clear legislative command or necessary and inescapable inference* restricting the remedies available." *Id.* 438 F.3d at 1055 (emphasis added).

Contrary to Allergan's suggestion, nothing in *Philip Morris USA, Inc.*, 396 F.3d 1190 (D.C. Cir.), *cert. denied*, 546 U.S. 960 (2005), requires a different result. The statutory provision at issue in that case was fundamentally different from the FDCA's § 332. In *Phillip Morris*, a divided panel of the D.C. Circuit ruled that disgorgement is unavailable under § 1964(a) of the Racketeer Influenced and Corrupt Organizations Act ("RICO"), because the "text and structure" of RICO created the "necessary and inescapable inference" to restrict the courts' jurisdiction. *Id.* at 1197. The court's conclusion was based on the "appropriate orders" specified by Congress in § 1964(a):

> to prevent and restrain violations of [RICO] by issuing appropriate orders, including, but not limited to: ordering any person to divest himself of any interest, direct or indirect, in any enterprise; imposing reasonable restrictions on the future activities or investments of any person, including, but not limited to, prohibiting any person from engaging in the same type of endeavor as the enterprise engaged in, the activities of which affect interstate or foreign commerce; or ordering dissolution or reorganization of any enterprise ....

Id. at 1192. The D.C. Circuit construed these "appropriate orders" as "all aimed at separating the

RICO criminal from the enterprise so that he cannot commit violations *in the future*," *id*. at 1198-99 (emphasis in original), and stated it would "expand on the remedies explicitly included in the statute only with remedies similar in nature to those enumerated," *id.* at 1200.

By contrast, 21 U.S.C. § 332 contains no list of "appropriate orders" from which such a restriction on the district courts' equitable powers can be inferred. Section 332(a) simply provides that "[t]he district courts of the United States . . . shall have jurisdiction, for cause shown, to restrain violations of [the Act]." This unqualified grant of equitable authority contains nothing from which an implicit limitation on the court's remedial powers can be inferred.

In both *Lane Labs* and *Rx Depot*, the defendants argued, as Allergan does here, that *Philip Morris* precludes the granting of equitable monetary relief under the Act. Neither court had trouble rejecting the argument. The *Lane Labs* court explained that "RICO's grant of equitable jurisdiction was far less broad than the FDCA's grant we consider here," and "[t]here is nothing comparable in the text or structure of the FDCA that provides the 'necessary and inescapable inference' that Congress had limited the equitable power of district courts to . . . 'restrain violations of [the Act].'" *Id*. at 233. *Rx Depot* dismissed *Philip Morris* as irrelevant to the FDCA on the same ground, and noted that "*Philip Morris* did not question the continued validity of *Porter* and *Mitchell*, the cases we rely on here." 438 F.3d at 1059. This Court should follow the Supreme Court's reasoning in *Porter* and *Mitchell* and the holdings in *Universal Management*, *Lane Labs*, and in *Rx Depot*.

CONCLUSION

For all of the foregoing reasons, the Court should dismiss plaintiff's complaint or enter summary judgment in defendants' favor.

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