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' REPLY IN SUPPORT OF MOTION TO DISMISS OR FOR SUMMARY JUDGMENT AND RESPONSE TO CROSS-MOTION FOR SUMMARY JUDGMENT

INTRODUCTION

For the past half century, the American public has been protected by a system of federal drug regulation that requires manufacturers to demonstrate the safety and efficacy of drugs for their intended uses before marketing them for those uses. The FDA regulations at issue in this case are an integral part of that regulatory system. Without the challenged regulations, manufacturers would be free to engage in virtually unlimited promotion of off-label uses of approved drugs, subject only to after-the-fact enforcement actions for misbranding. That is the regime that prevailed prior to 1962. It was highly profitable for drug manufacturers, but gravely detrimental to the public health.

Contrary to Allergan's claims, the First Amendment does not compel this Court to reset the regulatory clock to 1962. Allergan overstates the regulatory limitations on manufacturer speech regarding off-label uses and, at the same time, gravely understates the impact of its own constitutional challenge on the new drug approval process and the public health. The Act and its implementing regulations strike a careful balance with respect to information relating to off-label uses, preventing manufacturers from promoting drugs for off-label uses while allowing dissemination of truthful, non-promotional information regarding health and safety risks associated with those uses. That balance is a constitutional one, both on its face and as applied in this case. The draconian scenarios offered by Allergan have no basis in reality, and their hypothetical nature confirms the absence of a ripe constitutional controversy here.

Allergan's statutory challenges to FDA's regulations are equally misconceived. The regulations that Allergan is challenging have been in effect for many decades. They have been applied by FDA and the courts on countless occasions, without any suggestion that they are at odds with the Act. And Congress has amended the Act on multiple occasions without ever calling the regulations into question. This unbroken record of administrative, judicial, and legislative

acceptance confirms that the regulations, far from conflicting with the Act, are an appropriate and indeed vital complement to it. Finally, Allergan's objections to the equitable remedy of disgorgement are not only without merit, but entirely premature – as are all of Allergan's other claims. For all of these reasons, the government is entitled to summary judgment.

I. FDA'S REGULATIONS ARE NOT FACIALLY UNCONSTITUTIONAL

A. Allergan Understates the Breadth and Impact of Its Challenge and Overstates the Regulations' Impact on Speech Regarding Off-label Uses

In our opening brief, we explained why the provisions of the Act and regulations relating to promotion of unapproved uses of approved drugs are consistent with the First Amendment. Allergan's response suffers from two overarching defects. First, Allergan systematically understates the breadth of its challenge to the existing regulatory scheme and the drastic consequences of that challenge for the public health. Second, Allergan dramatically overstates the extent to which FDA's regulations prevent the dissemination of truthful information about unapproved uses, particularly the non-promotional dissemination of information relating to health risks associated with those uses. These two basic errors distort all of Allergan's more specific constitutional objections.

1. For the past half century, since the enactment of the 1962 Kefauver-Harris Amendments to the Act, manufacturers have been required to demonstrate, through rigorous clinical tests, that a drug is safe and effective for each of its intended uses before distributing the product to the public. That requirement is the cornerstone of evidence-based drug regulation in the United States.

The new drug approval process would be crippled if drug manufacturers could obtain approval of a drug for one use, then promote the drug for other, unapproved uses without first demonstrating through the approval process that the drug was safe and effective for each new use. Indeed, one of the central objects of the 1962 Amendments was to prevent drug manufacturers from

engaging in this kind of evasion. *See* S. Rep. No. 87-1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, 2901-2903 (if manufacturers were not required to demonstrate safety and effectiveness for new uses, "[t]he expectation would be that the initial claims would tend to be quite limited," and "[t]hereafter 'the sky would be the limit' and extreme claims of any kind could be made").

It is vital for manufacturers to demonstrate the safety and effectiveness of their drugs for new uses before they undertake to promote those uses. Patients can be – and have been – harmed and even killed by unapproved uses of approved drugs. Temple Decl. ¶ 5. And even widespread acceptance of an unapproved use in the medical community is no guarantee that the drug is safe or effective for that use, and no substitute for the rigorous clinical trials and careful scrutiny by FDA that the drug approval process requires. For example:

- Diethylstilbestrol (DES), approved to treat estrogen deficiency in premature ovarian failure, was prescribed by physicians to millions of women off-label to prevent miscarriage. The drug was later shown not only to be ineffective in preventing miscarriage and premature birth, but also to have caused severe long-term, and even multigenerational harms. Those harms included breast cancer in users of DES, and clear cell vaginal and cervical cancer and possible excess breast cancer risk in their daughters. Supp. Temple Decl. ¶ 9.
- Premarin/Prempro, an estrogen/hormone replacement therapy approved for treating menopausal symptoms and preventing postmenopausal osteoporosis, was widely prescribed off-label for long-term use to prevent the increase in coronary artery disease that follows menopause. Although that was a plausible use supported by some epidemiological evidence, it was not supported by data from well-controlled clinical trials. Later, a well-controlled, government-sponsored clinical trial demonstrated that this off-label use of the drug *increased* the risk of vascular disease (including stroke, thromboembolic disease, and heart attack) and

breast cancer. *Id.* ¶ 8.

- Encainide and Flecainide, approved for treating severe, life-threatening disturbances in the heart rhythm that were resistant to treatment with other drugs, were widely prescribed off-label to treat minor disturbances in heart rhythms that were associated with decreased survival in patients who had recently experienced heart attacks. A later study showed that this off-label use increased the likelihood of death from heart attacks by 2 ½ times. *Id.* ¶ 10.

Promotion of off-label uses by drug manufacturers increases the risk that a drug will be prescribed for uses for which it is unsafe, ineffective, or both. The information supplied by manufacturers is likely to be biased in favor of the drugs' claimed benefits, while minimizing the drugs' limitations and adverse effects, thereby influencing a physician's prescribing decisions toward unsupported uses. Wilkes Decl. ¶ 16; see also David Evans, *When Drug Makers' Profits Outweigh Penalties*, Washington Post, March 21, 2010, p. G1. The legislative history of the 1962 Amendments contains extensive testimony regarding the inherent bias in detailing information from drug companies.[1]

Although Allergan assures the Court (at 7) that it does not challenge the 1962 Amendments, the remedies it seeks would produce the same result by invalidating FDA regulations that are critical to the operation of the statutory scheme. If this Court were to strike down those regulations, drug manufacturers would be free to advertise prescription drugs for off-label uses without obtaining FDA approval for those uses; without conducting clinical trials to determine whether the uses they are promoting are safe and effective; and without having to provide adequate directions for use. They

[1] *See, e.g.*, 108 Cong. Rec. 19925 (Sept. 27, 1962) (Dr. Lena Baumgartner, Commissioner of the New York Department of Health, testified that "the physician is bombarded with seductive advertising which fails to tell the truth, the whole truth, and nothing but the truth. This often misleads him into prescribing a new drug without adequate warning or information about its possible side effects and, indeed, without any solid clinical evidence that the drug is effective or is even as safe as the advertisers claim.").

would be free to do so even with respect to prescription drugs like Botox, which have the potential to produce serious and life-threatening side effects.

Allergan tries to minimize these drastic regulatory consequences by stating (at 8) that, even if it prevails, manufacturers would still have to obtain FDA approval to market their drugs for uses recommended in their labeling. However, manufacturers would *not* have to obtain FDA approval in order to promote off-label uses through promotional activities that do not involve labeling, such as advertising. And if manufacturers can evade the drug approval process simply by relying on promotional media other than labeling to promote unapproved uses, the requirement of approval for new uses would become a dead letter – particularly if Allergan were to prevail in its efforts to redefine what constitutes "labeling" under the Act (pp. 22-23 *infra*).

Allergan also asserts (at 8) that it is only challenging limitations on its communications with physicians, and that limitations on direct-to-consumer (DTC) advertising of unapproved uses will remain in place. That is not so. The advertising regulation that prohibits prescription drug advertisements that promote unapproved uses (21 C.F.R. § 202.1(e)(4)(i)(a)) does not distinguish between DTC and physician advertising, and Allergan's complaint asks this Court to invalidate that regulation on its face, which would eliminate the restriction on off-label DTC advertising as well. *See* Compl. ¶ 124 ("Allergan thus seeks the entry of a judgment declaring that 21 C.F.R. § 202.1(e)(4)(i)(a) *is facially unconstitutional....*") (emphasis added).

Finally, Allergan notes (at 8) that false or misleading drug labeling and advertising would still be unlawful. But false labeling and advertising were unlawful long before the 1962 Amendments. The pre-1962 history of drug regulation demonstrated many times over that after-the-fact liability for false or misleading promotional claims did not deter such claims and protect the public from them. In fact, the inadequacy of after-the-fact liability was one of the concerns that led

to the enactment of the 1962 Amendments. Govt SMJ Mem. 3-4.

2. On the other side of the constitutional balance, Allergan's overarching theme is that FDA has adopted a "draconian" regime that "suppress[es] virtually all off-label speech" by manufacturers. Allergan SMJ Mem. 25. That theme is repeated on page after page of Allergan's brief: "blanket suppression of off-label speech" (at 19), "sweeping restrictions" (at 22), "indiscriminate prohibitions" (at 23), "criminalizing virtually all off-label speech" (at 26), "ban on off-label speech" (at 27), "prohibit[ing] virtually all manufacturer speech about off-label uses" (at 29). But, as Allergan itself notes, mere repetition does not make an assertion true, and it is not true here.

Despite Allergan's repeated references to "blanket suppression," the Act and regulations do *not* prohibit all, or even virtually all, truthful speech by manufacturers regarding off-label uses of their drugs. The regulatory provisions at issue in this case cast a narrower net, one that reaches efforts by manufacturers to promote unapproved uses but leaves room for non-promotional dissemination of health and safety information. Contrary to Allergan's assertions, the distinction between promotional and non-promotional communications regarding off-label uses is directly grounded in the terms of the Act and its regulations.

A manufacturer must prove that a drug is safe and effective for all uses "prescribed, recommended, or suggested" in a drug's labeling. 21 U.S.C. §§ 321(p), 355(a). If the drug is a prescription drug, the manufacturer's advertising may not "recommend or suggest" an unapproved use for the drug. 21 C.F.R. § 202.1(e)(4)(i)(a). "Prescribing," "recommending," and "suggesting" that a drug be used for unapproved purposes are all forms of promotion. Statements regarding unapproved uses that do *not* "prescribe," "recommend," or "suggest" that the drug be put to those uses are not promotional and do not trigger these provisions. Thus, for example, labeling and advertising may – and sometime must – include appropriate warnings regarding risks associated with

an unapproved use without triggering the new drug approval requirement and without running afoul of the prohibition against advertising that recommends or suggests unapproved uses. *See* Govt SMJ Mem. 36-37; Temple Dec. ¶¶ 12, 38, 40, 43.

Allergan is thus wrong when it suggests (at 16) that "the communication of even basic safety information" regarding unapproved uses of Botox "would implicitly convey efficacy, and thus may be deemed 'promotional.'" Depending on the wording and supporting evidence, much of the warning information discussed in Allergan's complaint would qualify as non-promotional safety information that would not constitute evidence of an intended use. Temple Dec. ¶¶ 19-20; *see* Govt SMJ Mem. 37. And FDA itself has required Allergan to disseminate safety information regarding unapproved uses of Botox. *See* Temple Dec. ¶¶ 38, 40, 43. It is peculiar for a drug manufacturer to assert that FDA will not permit it to disseminate safety information about unapproved uses at the same time that FDA is requiring it to do just that.

The distinction between promotional and non-promotional speech is also inherent in the concept of intended use, which plays a vital role in the Act's misbranding requirements (as well as the definition of "drug" in 21 U.S.C. § 321(g)(1)). A drug is misbranded if, *inter alia*, its labeling does not contain adequate directions for all intended uses. See 21 U.S.C. § 352(f); 21 C.F.R. §§ 201.5, 201.100(c)(1). Speech by a manufacturer that represents or suggests that a particular use is safe or effective is evidence that the use is an intended one, and hence one for which the drug's labeling must bear adequate directions. In contrast, statements by the manufacturer relating to a particular use (such as safety information) that do not represent or suggest that a use is effective are not evidence of an intended use, and absent other evidence that the use is intended, the manufacturer is not obligated to include directions for the use in the drug's labeling. Thus, while a manufacturer cannot use safety warnings as a vehicle for "back door" promotion, "[i]f the safety or warning

information does not expressly or implicitly promote the efficacy of the unapproved use, . . . it will not be viewed as evidence of intended use." Temple Decl. ¶ 10.

There is no basis for Allergan's suggestion (at 14) that the distinction between promotional and non-promotional speech is unconstitutionally vague. "Promotion" is a shorthand way of describing the distinction drawn by specific provisions of the Act and regulations. When the government brings an enforcement action that involves promotion of unapproved uses, the manufacturer's liability *vel non* turns on the specific language used by the manufacturer and the specific terms of the statutory provisions and regulations under which the manufacturer is charged, not on "promotion" as a free-floating concept.

For example, if a manufacturer were charged under 21 U.S.C. § 331(d) with distributing an unapproved new drug, whether the drug is a "new drug" would depend on the uses "prescribed, recommended, or suggested" in the drug's labeling. *Id.* § 321(n). Similarly, if the government charged that a drug lacks adequate directions for use under 21 U.S.C. § 352(f), liability would turn on whether the manufacturer's speech evidenced an "intended use" and whether that use was unapproved. *See* 21 C.F.R. §§ 201.5, 201.100(c)(1). The "prescribed, recommended, or suggested" standard and the "intended use" standard have been in effect since 1938 and 1952, respectively, and drug manufacturers have shown no difficulty in understanding them. The Supreme Court has held that "perfect clarity and precise guidance have never been required even of regulations that restrict expressive activity." *Ward v. Rock Against Racism*, 491 U.S. 781, 794 (1989) (citations omitted); see also *Nat'l Ass'n of Manufacturers v. Taylor*, 582 F.3d 1, 26 (D.C. Cir. 2009) ("an intent standard *is not* per se vague, even in a statute regulating speech").

FDA's guidance documents provide manufacturers with further clarity regarding the regulatory distinction between promotional and non-promotional speech. For example, FDA permits

manufacturers to disseminate truthful and non-misleading medical journal articles and sponsor unbiased educational programs, and it has issued a *Reprint Guidance* that is designed to facilitate the distribution of such information by manufacturers.[2] If a manufacturer distributes medical and scientific reprints regarding unapproved uses in accordance with the recommendations in the guidance, FDA will not consider the manufacturer's actions as evidence of intended use related to an unapproved use. *Id.* § V.[3] Allergan objects (at 12) that FDA guidance documents are not binding on the agency. But the *Reprint Guidance* reflects FDA's understanding that the course of conduct outlined in the guidance *is not unlawful*. More specifically, it reflects the agency's judgment that the recommended actions do not demonstrate intended use, and therefore do not trigger any of the regulatory consequences that arise when an intended use of a drug is unapproved. A manufacturer that engages in such actions faces no prospect of liability under the Act.

Allergan also claims (at 12-13) that the Department of Justice brings off-label prosecutions that are at odds with FDA's views regarding off-label speech by manufacturers, and hence that FDA's guidances have no real-world value. The GAO report on which Allergan purports to base that claim says nothing of the kind.[4] FDA's efforts to obtain compliance and the Department's enforcement actions are complementary, not conflicting. In this case, the United States and FDA

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[2] 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* (January 2009) (http://www.fda.gov/oc/op/goodreprint.html) (Reprint Guidance).

[3] See also *Guidance for Industry: Industry-Supported Scientific and Educational Activities* (November 1997) (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125602.pdf) (CME Guidance) (permitting industry sponsorship of unbiased educational and scientific programs). FDA also permits manufacturers to disseminate information on unapproved uses "in response to unsolicited requests for scientific information from health care professionals." 59 Fed. Reg. 59820, 59823 (Nov. 18, 1994).

[4] The report shows that FDA issued a number of warning letters to manufacturers regarding off-label speech but did not refer the matters to the Department. GAO, *Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses*, GAO -08-835, pp. 21-22 (July 2008). As the report makes clear, however, FDA did not make referrals to the Department because the companies that received the warning letters ceased promoting unapproved uses and otherwise complied with FDA's requests for corrective action. *Id.* at 22.

are both defendants, and the views expressed in the government's briefs regarding the meaning of the Act and its implementing regulations are the views of the Department of Justice as well as those of FDA. Thus, Allergan's suggestion that it is in jeopardy of being pursued by the Department on legal theories that conflict with the views of the law expressed in these briefs is baseless.

B. FDA's Regulations Are Not Subject to Strict Scrutiny

1. Allergan suggests (at 17) that the speech at issue in this case is "fully protected" speech, and that FDA's regulations therefore are subject to strict scrutiny rather than the more deferential review applicable to commercial speech. That suggestion is fundamentally misconceived.

With the exception of the intended-use regulation, which we address below, the regulations that Allergan is challenging are confined by their terms to drug advertising and drug labeling. Advertisements are the quintessential form of commercial speech, and product labeling constitutes commercial speech as well. See, *e.g.*, *Rubin* v. *Coors Brewing Co.*, 514 U.S. 476, 481 (1995). The kinds of advertising and labeling at issue here are especially clear examples of commercial speech because, as explained above, the regulations only attach regulatory consequences to labeling and advertising that "prescribe," "recommend," or "suggest" particular uses. *Cf. Nutritional Health Alliance* v. *Shalala*, 144 F.3d 220, 228 (2d Cir. 1998) (dietary supplement labeling containing health claims "is indisputably 'pure commercial' speech"). Labeling and advertising that refer to an unapproved use without prescribing, recommending, or suggesting the drug for that use are outside the purview of these regulations.

Allergan cites *Riley* v. *Nat'l Fed'n of Blind*, 487 U.S. 781, 796 (1988), for the proposition that strict scrutiny applies when commercial speech is intertwined with "informative and perhaps persuasive speech." But *Riley* and the cases on which it relies involve the First Amendment status of charitable solicitation, in which commercial speech "is characteristically intertwined with

informative and perhaps persuasive speech *seeking support for particular causes or for particular views on economic, political, or social issues . . . .*" *Vill. of Schaumburg* v. *Citizens for a Better Env't*, 444 U.S. 620, 632 (1980) (emphasis added); see *Riley*, 487 U.S. at 796. Nothing in *Riley, Schaumberg*, or any other case suggests that labeling and advertising are subject to strict scrutiny just because they contain "informative and perhaps persuasive speech" about the drug itself. Such a rule would subject virtually all regulation of drug labeling and advertising (as well as regulation of securities offerings, for example) to strict scrutiny.

Allergan also suggests (at 30) that heightened scrutiny applies because, in Allergan's view, speech regarding unapproved uses "is unfettered when made by independent scientists but completely prohibited when made by manufacturers." As already explained, off-label speech by manufacturers is very far from being "completely prohibited." But to the extent that the regulations do distinguish between manufacturers and independent scientists, the distinctions are constitutionally unobjectionable, and nothing about them calls for heightened constitutional scrutiny.

Physicians and patients receive drug labeling from the manufacturer, not from outside scientists, and only the manufacturer can be called on to provide labeling that enables the drug to be used safely and effectively. And to the extent that FDA prohibits offering a drug for unapproved uses in prescription drug advertising, the prohibition reflects obvious differences between manufacturers and independent scientists. Independent scientists have no incentive to skew their analyses of a drug's safety and effectiveness for unapproved uses, whereas drug manufacturers "will likely only seek to disseminate information that presents their product in a favorable light." *Wash. Legal Found.* v. *Friedman*, 13 F. Supp. 2d 51, 65 (D.D.C. 1998), *as amended*, 36 F. Supp. 2d 16 (1999), *vacated in part as moot*, 202 F.3d 331 (D.C. Cir. 2000); see Wilkes Decl. ¶¶ 15-17. Moreover, limiting promotion of unapproved uses by manufacturers provides a powerful incentive

to engage in the clinical testing required to support a supplement application, whereas independent scientists have no economic stake in the approval process.[5]

2. The only regulation at issue in this case that is not strictly confined to advertising or labeling is FDA's intended-use regulation (21 C.F.R. § 201.128). In practice, of course, the kinds of speech that are most likely to provide evidence of intended use are advertising, labeling, and other kinds of promotional communications, all of which lie at the heartland of commercial speech. But as *Wisconsin* v. *Mitchell*, 508 U.S. 476 (1993), and *Whitaker* v. *Thompson*, 353 F.3d 947 (D.C. Cir. 2004), make clear, the government is free in any event to use speech as evidence of intent or to prove an element of a violation, regardless of whether the speech is commercial (as in *Whitaker*) or is non-commercial (as in *Mitchell*). *See* Govt MSJ Mem. 20-21. Thus, far from being subject to strict scrutiny, the intended-use regulation does not require First Amendment scrutiny at all.

As Allergan notes (at 20), the concept of intent in FDA's intended-use regulation is an objective rather than subjective one, but that fact in no way diminishes the application of *Mitchell* and *Whitaker* here. Indeed, the same thing was true in *Whitaker* itself. *Whitaker* involved whether a particular product was a "drug," which turns on whether the product is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease." 21 U.S.C. § 321(g)(1)(B). The criteria used to determine intended use in the "drug" context are no less objective than the ones used to determine intended use in the misbranding context; to the contrary, they are exactly the same. *See*, *e.g.*, *Action on Smoking and Health* v. *Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980) (summarizing criteria); *Nat'l Nutritional Foods Ass'n* v. *Mathews*, 557 F.2d 325, 334 (2d Cir. 1977) (same); *United*

[5] Nothing in *Greater New Orleans Broad. Ass'n*, *Inc.* v. *United States*, 527 U.S. 173, 194 (1999), cited by Allergan (at 30), is to the contrary. *Greater New Orleans* involved a statute that discriminated between different advertisers promoting the same commercial activity. Here, the regulatory scheme differentiates between commercial speech by one party (a drug manufacturer) and non-commercial speech by other parties (independent scientists).

States v. *Livdahl*, 459 F. Supp. 2d 1255, 1259-60 & n.3 (S.D.Fla. 2005) (relying on 21 C.F.R. § 201.128 to determine whether product is a "drug"); *United States v. Kasz Enters., Inc.*, 855 F. Supp. 534, 538-40 (D.R.I. 1994) (same).[6] *Whitaker* therefore cannot be distinguished on the theory that it involves a different concept of intent.

Allergan argues (at 20) that *Mitchell* and *Whitaker* do not resolve the constitutionality of misbranding actions under 21 U.S.C. § 352, because a manufacturer's statements are themselves an element of the misbranding offense, not simply evidence of intended use or another non-speech element of an offense. That is correct but irrelevant, because Allergan has expressly stated that it is not challenging the constitutionality of the Act itself, including the Act's misbranding provisions. In particular, Allergan has never suggested that it is inappropriate, much less unconstitutional, to prohibit false or misleading statements in labeling (21 U.S.C. § 352(a)) or to require labeling to include adequate directions for intended uses (21 U.S.C. § 352(f)). See, *e.g.*, *Zauderer* v. *Office of Disciplinary Counsel of Supreme Court of Ohio*, 471 U.S. 626, 651 (1985) ("Because the extension of First Amendment protection to commercial speech is justified principally by the value to consumers of the information such speech provides, * * * appellant's constitutionally protected interest in *not* providing any particular factual information in his advertising is minimal.")

C. FDA's Regulations Are Appropriately Tailored under *Central Hudson*

To the extent that FDA's regulations implicate the First Amendment at all, they are subject – at most – to review under *Central Hudson* and its progeny. Allergan concedes (at 7-8, 22) that the provisions of the Act and regulations relating to unapproved uses further important public purposes.

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[6]Contrary to Allergan's suggestion, there is nothing "oxymoronic" or "counterintuitive" about FDA's use of an objective standard for determining intended use. The objective-intent standard reflects the common-sense point that "the FDA is not bound by the manufacturer's subjective claims of intent but can find actual therapeutic intent on the basis of objective evidence." *National Nutritional Foods*, 557 F.2d at 334.

Allergan argues, however, that the regulatory scheme fails to pass muster under *Central Hudson* because the same interests could be furthered by less restrictive means.

As the D.C. Circuit has held, "[t]he government does *not* have to show [under *Central Hudson*] that it has adopted the least restrictive means for bringing about its regulatory objective; it does *not* have to demonstrate a perfect means-ends fit; and it does *not* have to satisfy a court that it has chosen the best conceivable option." *Nat'l Cable & Telecomms. Ass'n* v. *FCC*, 555 F.3d 996, 1002 (D.C. Cir. 2009) (emphasis added). Instead, "[t]he only condition is that the regulation be proportionate to the interests sought to be advanced." *Id.* Given the essential role of new drug approval in protecting the public health, FDA's regulations cannot reasonably be viewed as disproportionate to the interests that they serve.

1. Allergan argues (at 23) that the regulatory scheme would be substantially less restrictive if it distinguished between promotional and non-promotional speech about unapproved uses. But as explained above, the existing scheme does just that, and leaves considerable room for manufacturers to provide physicians with non-promotional information about unapproved uses, particularly information about risks associated with such uses, without triggering either the misbranding or the new drug approval provisions of the Act.[7]

Allergan also argues that "the statutes and regulations left untouched by Allergan's challenge" (at 23) are themselves an effective alternative way to protect the public and encourage manufacturers to seek approval for off-label uses. But far from being "left untouched," the

[7] Allergan's demand for a "narrow[] and precise[]" definition of "promotional" is misconceived. As explained, "promotional" is a shorthand way of referring to more specific and self-explanatory statutory and regulatory terms, such "recommended" and "intended." Moreover, drug manufacturers are constantly developing new ways to convey their messages, such as recent foray into newer social media tools including Twitter, Facebook, interactive websites, and online physician and patient communities, as well as applications for mobile devices, such as Epocrates (a mobile drug information reference for physicians). Supp. Temple Dec. ¶¶ 25-26. FDA cannot anticipate all the new techniques manufacturers will use to promote their products, and any attempt to provide an exhaustive definition of "promotion" would only invite creative evasion. *Id*.

provisions that Allergan points to are the very ones that Allergan itself is attacking. For example, Allergan says that a ruling in its favor "would leave in place restrictions on DTC off-label advertisements" in 21 C.F.R. § 201.(e)(4)(i)(a). Yet Count III of Allergan's complaint asks this Court to invalidate that regulation, not just as applied but on its face. In similar fashion, Allergan argues that manufacturers would still have to obtain FDA approval before they could promote off-label uses in their labeling. Yet Count I of the complaint asks this Court to significantly narrow the range of materials that constitute labeling, a result that would greatly reduce existing incentives to seek FDA approval.[8]

2. Allergan also points to various supposed regulatory alternatives raised in its preliminary injunction papers. We explained in our opening brief why none of those palliatives is a plausible alternative to the current regulatory scheme. Although Allergan lists all of them again in its latest brief, it discusses only two in any detail: allowing off-label advertising that is accompanied by disclaimers, and taxing off-label sales.

Allergan itself concedes (at 24) that permitting manufacturers to advertise their drugs for unapproved uses as long as they include disclaimers "would surely provide less of an incentive"to seek FDA approval of unapproved uses. That concession disposes of the disclaimer alternative, for a regulation is adequately tailored "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) (emphasis added). Promotion of unapproved use with a disclaimer that the use is not approved by the FDA is not an adequate substitute for the rigorous FDA evaluation and approval process. Supp. Temple Decl.¶ 24. Allergan suggests that other features of the regulatory

[8] Allergan also notes (at 23) that it is not challenging the prohibition on false or misleading advertising in the Federal Trade Commission Act. See 15 U.S.C. § 52(a). Allergan neglects to mention that that provision does not apply to advertising of prescription drugs. See 21 U.S.C. § 352(n)(3)(B).

scheme would motivate manufacturers to seek approval, but here too, the features it points to are the ones that it is challenging in Counts I and III of the complaint. Allergan cannot have it both ways.

As for taxing manufacturers at a higher level for off-label sales, there is no practical way for FDA to determine whether any particular sale is for an approved use or an unapproved one. *See* Supp. Temple Dec. ¶ 29. Allergan suggests that FDA could collect sales data from manufacturers, but FDA has no legal authority to demand such data. *Cf.* 21 U.S.C. 374(a)(1)(B) (FDA authority to inspect manufacturer premises and records does not include authority to inspect "financial data [or] sales data other than shipment data"). Even if FDA did have such authority, manufacturer sales records would not ordinarily reflect whether particular sales were for an approved or unapproved use.

Alternatively, Allergan suggests that data regarding the volume of unapproved uses are available through the Medicare and Medicaid programs. Using Medicare and Medicaid reimbursement records to determine whether a drug has been prescribed for on-label or off-label uses is complex and in some cases impossible.[9] Moreover, two out of every three Americans – roughly 200 million people – are not eligible for Medicare or Medicaid, and their use of prescription drugs is entirely outside the scope of Medicare and Medicaid reimbursement records.[10] As a result, a tax based on Medicare and Medicaid records would leave an enormous volume of sales untaxed.

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[9] The great majority of prescription drugs that are reimbursed by the federal government are billed to Medicare Part D and Medicaid. Prescription drug reimbursement forms for these programs are submitted by pharmacies rather than physicians, and ordinarily do not reflect the diagnosis associated with the prescription. The only way that the use of the drug can be determined is by matching the pharmacy's drug reimbursement form with the corresponding reimbursement request by the treating physician, a difficult and laborious process. When drugs are administered in the course of in-patient hospital procedures under Medicare Part A, reimbursement records ordinarily do not identify the drugs at all, since reimbursement is based on the procedure performed rather than the drugs used in connection with the procedure. See generally 42 U.S.C. § 1395ww(d) (Prospective Payment System).

[10] As of 2008, 45.2 million persons participated in the Medicare program. See Board of Trustees of Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Funds, *Annual Report* 2 (2009) <http://www.cms.hhs.gov/ReportsTrustFunds/downloads/tr2009.pdf>. During FY 2007, an estimated 61.9 million persons were enrolled in Medicaid. Office of the Actuary, CMS, HHS, *2008 Actuarial Report on the Financial Outlook for Medicaid* 10 (2008) <http://www.cms.hhs.gov/ActuarialStudies/downloads/MedicaidReport2008.pdf>

Moreover, even if a tax on off-label sales were administratively feasible, there is no reason to think that it would provide manufacturers with significant incentives to seek approval of unapproved uses, because the lion's share of the tax burden would be likely to be borne by patients rather than manufacturers. Patient demand for prescription drugs tends to be highly inelastic, particularly when the drug is being used to treat serious medical conditions. See, *e.g.*, Simonsen, Skipper & Skipper, *Price Sensitivity of Demand for Prescription Drugs*, Economics Working Paper 2010-3, School of Economics and Management, Aarhus University (Jan. 15, 2010) <ftp://ftp.econ.au.dk/afn/wp/10/wp10_03.pdf>. And the greater the inelasticity of demand for a taxed good, the greater the extent to which the economic incidence of the tax will fall on the buyer rather than the seller. See, *e.g.*, Bernard Salanié, *The Economics of Taxation* 20 (2003).

3. As we have explained, speech that recommends or suggests an unapproved use is not protected at all under the commercial speech doctrine, because it proposes an illegal commercial transaction. Govt SMJ Mem. 25-26. Allergan responds that the Act does not make it illegal for a physician to prescribe (or for a patient to use) a drug for an unapproved use. But "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." *Wash. Legal Found.*, 202 F.3d at 332-33 (emphasis added); see also 21 U.S.C. § 331(a), (k) (illegal to distribute misbranded drug in interstate commerce or to take actions that render drug misbranded while it is held for sale after shipment in interstate commerce). Advertising that offers a drug for an unapproved use inescapably promotes this unlawful commercial activity. And as the Court of Appeals explained in *Whitaker*, there is nothing circular about using a manufacturer's promotional claims as evidence a product's intended use, then using the intended use to determine the regulatory requirements that apply to the product. *See Whitaker*, 353 F.3d at 953 ("one may recharacterize the analysis in a way that avoids the circularity" by focusing on the

evidentiary role of the speech in the determination of intended use); *see also Wisconsin v. Mitchell*, 508 U.S. at 489 (speech may be used to establish element of a crime).

II. THE AS-APPLIED CONSTITUTIONAL CLAIMS ARE WITHOUT MERIT

A. "Medically Accepted" Off-Label Uses

Allergan asks the Court (at 27-31) to invalidate the challenged regulations as applied to off-label uses that are treated as "medically accepted" for purposes of Medicare and Medicaid reimbursement. "Medical acceptance" of an unapproved use, as reflected in physician practices and standards of medical care, is no substitute for the rigorous clinical trials required for the FDA approval process. *See Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 613-14, 618-19, 630 (1973) (proof of effectiveness requires well-controlled scientific data and cannot be satisfied by impressions or beliefs of physicians, reports lacking in details, or personal testimonials); *Upjohn Co. v. Finch*, 422 F.2d 944, 954 (6th Cir. 1970) ("record of commercial success" and "widespread acceptance by the medical profession, do not, standing alone, meet the standards of substantial evidence prescribed by 21 U.S.C. § 355(d)"); Supp. Temple Decl. ¶¶ 21-22. And as a practical matter, allowing manufacturers to promote unapproved uses that are "medically accepted" is a recipe for disaster. As shown above, off-label uses of drugs such as DES have produced pervasive harm despite – in fact, because of – their widespread medical acceptance.

Allergan argues (at 28) that it is only asking the government to rely on its "medically accepted" standard "to relax the most onerous speech-restricting regulations – not to grant approval." But if the regulations that Allergan challenges were dispensed with, *there would be no need to seek approval* for "medically accepted" off-label uses. Companies would get approval for one use, then be free to promote "medically accepted" off-label uses in all media other than labeling. Drug manufacturers would not have to include adequate directions for such uses in their labeling (Count

IV, ¶ 130), and by keeping unapproved uses out of their labeling, they could avoid triggering the new drug approval requirement under 21 U.S.C. §§ 321(p) and 355(a) altogether. *See* Govt SMJ Mem. 18. In short, if Allergan's position were to become law, manufacturers would have neither the practical need nor any legal obligation to seek FDA approval before promoting off-label uses that are "medically accepted."

Allergan also suggests (at 27 n.13) that manufacturers have a First Amendment right to offer drugs to the public for any use that has been approved in other countries such as European Union members or Japan. Thalidomide was approved in Europe and caused devastating birth defects there; it had little impact in the United States because it was still under FDA review when the manufacturer withdrew it from the market. Supp. Temple Dec. ¶ 17. Similarly, an anticoagulant drug, Ximelagatran, was approved in Europe for treating venous thromboembolism and other conditions, but was denied approval by FDA because the drug was shown to cause severe and even fatal liver damage; the European countries that had approved it eventually withdrew it from their markets. *Id.* ¶ 18. Like "medical acceptance," foreign approval does not assure safety or effectiveness and is no substitute for careful premarket review by FDA.

B. Off-Label Uses Covered by Supplemental NDA or BLA

Count V alleges that the challenged regulations are unconstitutional as applied to unapproved uses that are the subject of a pending supplemental NDA or supplemental BLA. Count V is directed at Allergan's then-pending sBLA for adult upper limb spasticity. On March 9, 2010, FDA approved that sBLA. Supp. Temple. Decl. ¶ 31. Because Allergan is now free to engage in truthful and non-misleading communications regarding that approved use, the as-applied claim in Count V is moot with respect to that use. Moreover, to the extent that Allergan's previous inability to promote Botox for adult upper-limit spasticity provided the Article III injury underlying Allergan's other claims,

those claims are now moot as well.

Count V would be without merit even if it were not moot. Allowing manufacturers with pending sNDAs or sBLAs to begin promoting the unapproved use while the application is pending would enable manufacturers to promote uses that are unsafe and ineffective, and would encourage them to file supplemental applications prematurely and rely on the recursive nature of the review process to prolong their promotional campaigns. *See* Govt SMJ Br. 40.

Allergan now appears to concede (at 32) that the First Amendment does *not* require FDA to permit promotion of unapproved uses "as soon as an sBLA is filed." Instead, Allergan argues only that it is "so close" (*id.*) to obtaining FDA approval regarding adult upper limb spasticity that it should be allowed to begin promoting the use covered by its sBLA. Apart from pointing to its own sBLA, Allergan does not offer any guidance about how "close" is close enough. In any event, if an application *is* close to approval, having to wait a brief additional time for the approval itself is constitutionally unobjectionable. *Cf. Nutritional Health Alliance*, 144 F.3d at 228.

C. Information Regarding Off-Label Risks

Finally, Count VII alleges that Allergan has a constitutional right to communicate with physicians regarding off-label health risks of Botox for which FDA itself is requiring Allergan to provide warnings. As noted, the Act and regulations leave room for Allergan to provide truthful information about off-label risks in a non-promotional manner without triggering any of the regulatory limitations about which Allergan complains. Govt SMJ Mem. 9-10; Temple Decl. ¶¶ 10, 19-20. Allergan's only response (at 32-33) is to renew its unfounded insistence that the law does not distinguish between promotional and non-promotional communications.

Whether any particular speech by Allergan falls on the non-promotional side of the line depends, of course, on the details of what is said. It is chiefly for that reason that Allergan's claims

relating to speech about Botox's off-label risks are not ripe for review. Without concrete details about the proposed contents of specific communications, Allergan's assertion that the communications are prohibited by FDA's regulations is speculative at best, which renders Allergan's claims premature.[11] *Cf. Renne v. Geary*, 501 U.S. 312, 320 (1991) (plaintiff must "demonstrate a live dispute involving the actual or threatened application of [a statute or policy] to bar particular speech"). And now that Allergan's sBLA has been granted, the safety-related communications are the only ones still at issue in this case.

III. FDA'S REGULATIONS ARE CONSISTENT WITH THE ACT

In part IV of its brief, Allergan contends that the regulations that it challenges are contrary to the terms of the statute and Congressional intent. However, in adopting and implementing its regulations, FDA has acted reasonably and consistently with the Act and Congressional intent, and its statutory implementation is entitled to broad deference.[12] Each of Allergan's specific arguments regarding alleged statutory violations is without merit.

A. There Is No Controversy Regarding the Meaning of 21 U.S.C. § 352(a)

In Count II, Allergan sought a declaration regarding the meaning of 21 U.S.C. § 352(a). Although it is now clear that the parties agree on the meaning of the provision, Allergan asserts (at 34) that it is still entitled to declaratory relief clarifying the meaning of a provision that has been on

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[11] It is equally speculative whether any particular communications will be truthful and non-misleading. Allergan insists (at 5) that "it *is* known that this case involves 'truthful' speech" because Allergan is seeking relief only with respect to truthful and non-misleading communications. But that simply begs the question. A plaintiff cannot challenge the applicability of regulations to truthful speech unless he shows that his own speech will be truthful, and framing the requested relief in terms of truthful speech hardly suffices to make that showing.

[12] *See, e.g., Nat'l Ass'n of Home Builders v. Defenders of Wildlife*, 551 U.S. 644, 672 (2007) ("An agency's interpretation of the meaning of its own regulations is entitled to deference unless plainly erroneous or inconsistent with the regulation.") (citation and internal quotation marks omitted); *Nat'l Rifle Ass'n v. Reno*, 216 F.3d 122, 132 (D.C. Cir. 2000) ("as long as the agency stays within Congress' delegation, it is free to make policy choices in interpreting the statute, and such interpretations are entitled to deference")(citations and internal punctuation omitted); *Wyo. Outdoor Council v. U.S. Forest Serv.*, 165 F.3d 43, 52 (D.C. Cir. 1999) ("broad deference [to agency regulations] is all the more warranted when . . . the regulation concerns a complex and highly technical regulatory program").

the books for more than seventy years. Not so. "The availability of declaratory relief depends on whether there is a live dispute between the parties. . . ." *Powell v. McCormack*, 395 U.S. 486, 518 (1969). In the absence of a "substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality," declaratory relief is not warranted. *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 127 (2007).

B. FDA's Interpretation of "Labeling" is Consistent with *Kordel*

The parties are also in agreement that the meaning of "accompanying," as used in the definition of "labeling" in 21 U.S.C. § 321(m), has been settled by *Kordel v. United States*, 335 U.S. 345 (1948), and *United States v. Urbuteit*, 335 U.S. 355 (1948). *Kordel* explained that "[n]o physical attachment * * * is necessary," that "[i]t is the textual relationship that is significant," and that "accompanying" should be read as requiring an "integrated" transaction, a requirement that is satisfied where the literature and the drug share a common origin and common destination and the literature is used in the sale of the drug. *Id*. at 348, 350.

Allergan repeatedly asserts (at 34-38) that FDA construes the term "labeling" to include promotional literature that is "untethered" to the drug and that, contrary to *Kordel*, FDA asks only whether the literature contains information about the drug. That is not FDA's position. Allergan purports to see that construction in 21 C.F.R. § 202.1(*l*)(2), but Allergan misunderstands that regulation.

Section 202.1(*l*)(2) was issued pursuant to 21 U.S.C. § 352(n), which governs prescription drug advertising. By its terms, Section 352(n) excludes "any printed matter which the Secretary determines to be labeling * * * ." Section 202.1(*l*)(2), which lists items that "are hereby determined to be labeling," was issued to implement this exclusion. In keeping with the terms of Section 352(n), its purpose is to limit the domain of the Act's prescription drug advertising requirements, by making

clear what kinds of materials are *not* subject to those requirements. It was never meant to suggest that the items in the list will be regulated as labeling without regard to *Kordel*'s construction of "accompanying," and it has not been applied by FDA in that manner.

Although Allergan purports to concede (at 37-38) that *Kordel* governs the meaning of "accompanying," it simultaneously urges the Court (at 35-36) to hold that "'labeling' . . . mean[s] materials that are sent along with a shipment of drugs – i.e., that accompany those drugs," and that "'accompanying' . . . refers to a physical location." That same position was rejected by the Court in *Kordel* and *Urbuteit*. See Govt MSJ Mem. 32-34. The Court's opinions in those cases make clear that printed material that has the necessary "textual" and "functional" relationship to a drug constitutes labeling even if the printed material is distributed separately (*Kordel*) or at a different time (*Urbuteit*). Allergan's revisionist formulation would significantly narrow the definition of "labeling" adopted in *Kordel* and *Urbuteit*, and would produce a *pro tanto* narrowing of the Act's new drug approval process, since the definition of "new drug" is tied to the drug's labeling.

C. The Intended-Use and Adequate-Directions Rules Reasonably Implement the Act

Allergan next argues (at 38) that FDA's "intended use regulations" have "staggering breadth," are "irrational," and turn the statute into a "Catch-22." These regulations, however, are consistent with and reasonably and permissibly implement the statutory provisions requiring FDA approval for each new use of an approved drug before a manufacturer can offer the drug for that use.[13] As discussed above, the statutory provisions governing new drug approval, 21 U.S.C. §§ 321(p), 355(a), 355(b)(1)(F), and misbranding for failure to contain adequate directions for use, *id.*

[13] *See, e.g., Weinberger v. Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609, 613 (1973); *Wash. Legal Found.*, 202 F.3d at 332 (under the FDCA, a manufacturer "demonstrate[s] that its product is safe and effective for each of its intended uses").

§ 352(f)(1), must be read in tandem to effectuate Congress's intent that drugs not be marketed for a use without first obtaining FDA approval under § 355(a).

In determining the uses for which the manufacturer is offering its product, nothing in the statute confines FDA to examining only the labeling. 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." 21 U.S.C. § 321(g)(1)(B)-(C) (emphasis added). Thus, Congress granted FDA the authority to consider any relevant evidence in determining the "intended use" of a drug. *See United States v. Nova Scotia Food Prods. Corp.*, 568 F. 2d 240, 246 (2d Cir. 1977) ("[W]hen we are dealing with the public health, the language of the [FDCA] should not be read too restrictively, but rather as 'consistent with the Act's overriding purpose to protect the public health'") (quoting *United States v. Bacto-Unidisk*, 394 U.S. 784, 798 (1969)).

21 C.F.R. § 201.128, which describes "example[s]" of what "may" be viewed as evidence of intended use, does not conflict in any way with the provisions of the Act, nor does Allergan identify a conflict. Instead, Allergan insists (at 11) that the intended-use regulation treats all statements by a manufacturer regarding unapproved uses as evidence of intended use, regardless of the contents or circumstances of the speech. But that is not what the rule says. It says that intended use "*may*, for example, be shown by labeling claims, advertising matter, or oral or written statements" by the manufacturer or "*may* be shown by the circumstances"(emphasis added). As shown by the word "may" (which Allergan conspicuously omits from its discussion), the rule merely reflects the common-sense point that statements by the manufacturer regarding an unapproved use *may* indicate that the use is an intended one. Whether any particular statement *does* indicate that a use is intended depends on what the statement actually says and the circumstances in which the

statement is made. The regulation does not prohibit speech, but merely identifies potential categories of evidence for determining intended use, a common-sense approach that is fully consistent with the First Amendment under *Whitaker*.

Allergan insists (at 39) that § 201.128 obligates it to include adequate directions for off-label uses simply because it knows that physicians are prescribing Botox off-label, even if those uses are not intended by Allergan. But the language that Allergan quotes ("knows, or has knowledge of facts that would give him notice, that a drug * * * is to be used for [new] conditions, purposes, or uses") is taken out of context. The quoted language is part of a larger passage discussing labeling responsibilities when a drug's intended use "change[s] after it has been introduced into interstate commerce by its manufacturer" – for example, when "a packer, distributor, or seller" offers the drug for a new use. When the intended use undergoes this kind of change at the hands of a downstream vendor, § 201.128 provides that the vendor "is required to supply adequate labeling" for the new use, and the manufacturer is also responsible for providing adequate labeling if he "knows, or has knowledge of facts that would put him on notice," that the drug has acquired a new intended use. This discussion does not refer to, and is not directed at, the situation in which physicians are prescribing a drug for off-label uses. As the rule makes clear at the outset, "intended use" "refer[s] to the objective intent of the persons legally responsible for the labeling of drugs," and prescribing physicians are not legally responsible for drug labeling.

Allergan argues (at 40) that 21 C.F.R. § 201.100(c)(1), which requires prescription drug labeling to bear adequate information for physician use, conflicts with the exemption from adequate directions for use contained in 21 U.S.C. § 353(b)(2).[14] As explained previously, Allergan is wrong.

[14] Allergan has previously suggested that 21 U.S.C. § 352(f)(1) does not permit FDA to take advertising into account in determining the intended uses for which adequate directions are required. That suggestion was rejected by the courts nearly sixty years ago, and no one has renewed it since then. See, *e.g., Alberty Food Prods.* v. *United States*, 194 F.2d

See Govt SMJ Mem. 29-30. Section 201.100(c)(1) exempts prescription drug labeling from § 352(f)(1), which otherwise requires drugs to bear adequate directions for use by *laypersons*, on the condition that the prescription drug's labeling provide adequate directions for the *health care professionals* under whose supervision the drug is used. *See United States v. Evers*, 643 F.2d 1043, 1052 (5th Cir. 1981) (explaining statutory basis for § 201.100(c)(1)); *United States v. Articles of Drug (Rucker Pharm.)*, 625 F.2d 665, 670, 675 (5th Cir. 1980); *United States v. Undetermined Quantities* ..., 145 F. Supp. 2d 692, 701-702 (D. Md. 2001). Section 353(b)(2), on which Allergan relies, does not exempt prescription drugs from the adequate-directions requirement in § 352(f)(1) altogether, but instead applies "only at the point at which the drug is actually prescribed and dispensed." *Evers*, 643 F.2d at 1051; *Rucker Pharm.*, 625 F.2d at 674. As the Fifth Circuit squarely held in *Evers*, § 352(f)(1) continues to apply to prescription drugs prior to the point of dispensing, and § 201.100(c)(1) is a proper exercise of FDA's statutory authority to create appropriate exceptions from that requirement.

Allergan argues (at 40) that § 352(f)(1) "cannot" apply at all times prior to dispensing, because another labeling provision, 21 U.S.C. § 353(b)(4), applies by its terms to prescription drugs "at any time prior to dispens[ing]." But § 353(b)(4) merely provides that prescription drug labeling must bear, "*at a minimum*," an "Rx only" legend (emphasis added). There is no inconsistency between that "minimum" requirement and the general adequate-directions requirement in § 352(f)(1). As a result, § 353(b)(4) does not call into question *Evers*' conclusion that prescription drugs are subject to § 352(f)(1) prior to dispensing.[15]

463, 464 (9th Cir. 1952) (labeling must contain adequate directions for uses promoted in advertising); see also *Alberty Food Prods. Co.* v. *United States*, 185 F.2d 321, 325 (9th Cir. 1950) (directions for use must identify all intended uses).

[15] Allergan suggests that it is inconsistent for FDA to exempt prescription drugs from bearing "adequate directions" for use (21 C.F.R. § 201.5(a)) while simultaneously requiring them to bear "adequate information" for use (*id.* § 201.100(c)(1)). There is no inconsistency, because the first regulation requires directions adequate for "the layman,"

D. FDA's Advertising Regulation Is Valid

Allergan contends (at 40-41) that 21 C.F.R. § 202.1(e)(4)(i)(a) is not a valid interpretation of 21 U.S.C. § 352(n). Section 352(n) sets forth basic requirements for prescription drug advertising and requires advertisements to present "'such other information in brief summary relating to side effects, contraindications, and effectiveness' *as shall be required in regulations*" (emphasis added), thereby authorizing FDA to give substance to the requirement through regulations.

Section 202.1 carries out that Congressional directive. Subpart (e) of § 202.1 describes what is required for the "true statement of information in brief summary relating to side effects, contraindications, and effectiveness." Subpart (4) of § 202.1(e) provides that the summary of effectiveness "shall not recommend or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement."[16] Thus, § 202.1(e)(4)(i)(a) is both explicitly authorized and a permissible implementation of 21 U.S.C. § 352(n) , and fully consistent with Congress' statutory framework governing marketing of approved products for off-label uses.

E. FDA's Regulations Properly Implement the Statute

Allergan asserts (at 41-42) that the Court must undo FDA's long-standing regulatory approach to the promotion of off-label uses because these regulations are unsupported by "a clear statement of congressional support" and represent "elephants in mouseholes." Allergan does not cite any authority for the "clear statement" standard, nor is the government aware of any. Consistent with basic principles of administrative law, Congress explicitly authorized FDA to "promulgate

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while the second requires information adequate for "practitioners licensed by law to administer the drug."

[16] Subpart (6)(i) of section 202.1 provides that an advertisement may be false or misleading if it "contains a representation or suggestion, not approved for use in the labeling, that a drug is . . . useful in a broader range of conditions . . . than has been demonstrated by substantial evidence or substantial clinical experience." These two subsections must be construed *in pari materia* so that they will "they will harmonize with each other and be consistent with their general objective scope." *Rathbun v. Autozone, Inc.*, 361 F.3d 62, 68 (1st Cir. 2004); *see also Lamoille R. Co.* v. *ICC*, 711 F.2d 295, 323 (D.C. Cir. 1983).

regulations for the efficient enforcement of this Act," 21 U.S.C. § 371(a), and FDA "is empowered not only to construe its governing statute, but additionally to make safety judgments delegated to it by Congress." *United States v. Algon Chem. Inc.*, 879 F.2d 1154, 1159 (3d Cir. 1989).

Moreover, far from "an elephant in a mousehole," the challenged regulations directly further the Congressional intent underlying the 1962 Amendments. The Act requires that each intended use of a drug be proven to be safe and effective and that the labeling for these drugs, which also must be approved by FDA, contain adequate directions for each use. These provisions cannot be separated from each other without destroying the *raison d'etre* of the 1962 Amendments to require FDA approval of the safety and effectiveness of *each* new use of an approved drug. FDA regulations implement these provisions in a way that avoids their circumvention, and FDA's longstanding approach has been upheld in countless circumstances. *See, e.g., United States v. Rutherford*, 442 U.S. 544, 554 (1979) ("we are reluctant to disturb a longstanding administrative policy that comports with the plain language, history, and prophylactic purpose of the [FDCA]"); *Hynson, Westcott and Dunning, Inc.*, 412 U.S. at 618-19 ("Lower courts have upheld the validity of [FDA drug approval] regulations, and it is not disputed here that they express well-established principles of scientific investigation"); *Evers*, 643 F.2d at 1051; *Action on Smoking and Health*, 655 F.2d at 239.

Moreover, while Congress has amended the Act many times in the intervening decades, it has not changed FDA's overall approach to manufacturer promotion of off-label uses, with the exception of a narrow, temporary provision (since expired) regarding manufacturer dissemination of medical and scientific articles.[17] Congress is well aware of how FDA regulates off-label uses, and

[17] As part of the Food and Drug Administration Modernization Act of 1997 (FDAMA), Congress specified conditions under which a drug or medical device manufacturer could disseminate medical and scientific information discussing unapproved uses of approved drugs and cleared or approved medical devices to healthcare professionals and certain entities. See 21 U.S.C. § 360aaa. In 2006, that provision expired. See 21 U.S.C. § 360aaa *note*. After the sunset of that provision, FDA issued the Reprint Guidance, discussed above and in our opening brief at pages 9-10, explaining FDA's post-FDAMA policy in the distribution of medical articles described in FDAMA.

has chosen only to make limited and temporary changes. *See Fla. Dep't of Revenue v. Piccadilly Cafeterias, Inc.*, 128 S. Ct. 2326, 2336 (2008) ("Congress is presumed to be aware of an administrative or judicial interpretation of a statute and to adopt that interpretation when it reenacts a statute without change.") (quoting *Lorillard v. Pons*, 434 U.S. 575, 580-581(1978)); *Rucker Pharm.*, 625 F.2d at 674 ("An agency's long-standing construction of its statutory mandate is entitled to great respect, especially when Congress has refused to alter the administrative construction.") (citations and internal punctuation omitted).[18] Accordingly, the Court should decline Allergan's invitation to eviscerate FDA's longstanding approach in implementing the 1962 Amendments.

IV. ALLERGAN'S DISGORGEMENT CLAIM IS FRIVOLOUS

Allergan's claim that the Act precludes the courts from granting the equitable remedy of disgorgement is both unripe and wrong on the merits. The claim would be ripe *if* the government had brought an enforcement action against Allergan under 21 U.S.C. § 332; *if* the government had prevailed in such an action; and *if*, having prevailed, the government had sought disgorgement. But none of those things has happened, and it is entirely speculative whether any of them, much less all of them, will ever take place. If Allergan ever *is* faced with a demand for disgorgement, it will be free to litigate FDA's legal authority at that time.

On the merits, three courts of appeals have directly rejected the very argument Allergan makes here. *See United States v. RX Depot, Inc.*, 438 F.3d 1052 (10th Cir. 2006); *United States v. Lane Labs-USA, Inc.*, 427 F.3d 219, 223 (3d Cir. 2005); *United States v. Universal Mgmt. Servs.,*

[18] Allergan chides the government (at 42) for not addressing *Founding Church of Scientology v. United States*, 409 F.2d 1146 (D.C. Cir. 1969), in which the D.C. Circuit found that certain claims made in religious literature were excluded from FDA regulation. But the D.C. Circuit made clear that its holding related only to religious literature: "[w]ere the literature here introduced clearly secular, we might well conclude that under existing law it constituted 'labeling' for purposes of the [FDCA]. Such a conclusion might be justified by a broad reading of the statute, consistent with its high purpose of protecting the public health and Pocketbook against health frauds." 409 F.2d at 1159. Allergan's citations in the same section to *Int'l Union v. OSHA*, 938 F.2d 1310 (D.C. Cir. 1991), which involved alleged excessive delegation of legislative power to OSHA, are likewise inapposite.

Inc., 191 F.3d 750, 761 (6th Cir. 1999). Allergan asserts that these cases should be disregarded because they predate *United States v. Philip Morris USA, Inc.*, 396 F.3d 1190 (D.C. Cir.), *cert. denied*, 546 U.S. 960 (2005). But *Phillip Morris* does not purport to overrule (nor could it) *Porter v. Warner Holding Co.*, 328 U.S. 395 (1946), the case on which these decisions rest. And the statute in *Phillip Morris* is readily distinguishable from the provision here. See Govt SMJ Mem. 44-45.

Alternatively, Allergan suggests that *Porter*'s reasoning was repudiated in *Meghrig v. KFC Western, Inc.*, 516 U.S. 479 (1996). But *Meghrig* did not purport to call *Porter* into question, and the Supreme Court has continued to cite *Porter* after *Meghrig*. *See, e.g., Miller v. French*, 530 U.S. 327, 340-41 (2000). Moreover, even on its own terms, *Meghrig*'s reasoning does not cast any doubt on *RX Depot*, *Lane Labs*, and *Universal Management*.[19] Thus, if this Court reaches the question of disgorgement, which it should not, it ought to follow those unanimous and on-point decisions.

CONCLUSION

For the foregoing reasons, the defendants' motion for summary judgment should be granted, and the plaintiff's motions for summary judgment and for an injunction should be denied.

[19] In *Meghrig*, the Court held that § 6972(a) of the Resource Conservation and Recovery Act (RCRA), which authorizes district courts "to restrain any person [responsible for toxic waste], to order such person to take such other action as may be necessary, or both," did not authorize a private party suing under § 6972(a)(1)(B) (permitting citizen suits against persons who contributed to hazardous wastes that pose an imminent and substantial endangerment) to seek recovery of past cleanup costs. 516 U.S. at 479. The Court did not suggest, much less hold, that all statutes authorizing courts to "restrain" statutory violations precluded orders granting restitution or disgorgement. Instead, it rejected the creation of a *private* right for monetary relief based on features unique to RCRA. See *id.* at 485-88.

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DECLARATION OF MICHAEL S. WILKES, M.D., Ph.D

I, Michael S. Wilkes, M.D., Ph.D., do hereby declare under penalty of perjury, pursuant to 28 U.S.C. § 1746, that the following is true and correct to the best of my knowledge, information, and belief.

Professional Background

1. I am a Professor of Medicine, Director of Global Health, and I recently stepped down as Vice Dean for Education at the School of Medicine, University of California at Davis (UCD). In my capacity as Vice Dean, I oversaw five other Deans and was the chief academic officer of the school.

2. I have been employed at the University of California since 1988 (from 1988 through 2001 at the University of California at Los Angeles (UCLA) and from 2001 to the present at UCD). I held a variety of positions at UCLA: Associate Director, UCLA Center for Educational Development and Research; Senior Chair, "Doctoring," a new UCLA innovative curriculum; Assistant, Associate, and full Professor of Medicine; Chair "Fundamentals of Clinical Medicine" and "Clinical Reasoning and Epidemiology" courses; Chair of the Medical Ethics course; and Co-chair of the Behavioral Medicine Training Program for residents. I was an elected member of the Faculty Executive Committee at the UCLA School of Medicine. I have also taught at the Columbia University School of Public Health and at the University of Connecticut School of Medicine. I have been a visiting professor at numerous schools in California, the United States, and internationally. My topics of expertise include medical education, curriculum development, improving physician practice, the impact of direct to consumer advertising, and the impact of marketing on physician practice.

3. Since 1988 and 2002, respectively, I have worked as a volunteer physician both at the Venice Family Clinic in Los Angeles and the Joan Viteri clinic in Sacramento. I am a consultant to several international education groups but have no commercial relationships with any of them. I am also a principal investigator for the National Institutes of Health on several major research projects intended to improve community practice by physicians (end-of-life care and genetics) and to the Centers for Disease Control and Prevention (cancer care). I have worked as a consultant to the Olive View Hospital (Los Angeles County) and as an emergency room physician in Bellevue Hospital in New York City. I have been the Editor-in-Chief of the Western Journal of Medicine and the Associate Editor of Medical Education. I am a reviewer for the New England Journal of Medicine, the Annals of Internal Medicine, the Journal of the American Medical Association, Lancet, the British Medical Journal, and the Journal of General Internal Medicine. I have recently and briefly discussed, with the Deputy Commissioner of Food and Drugs, the possibility of my working at the Food and Drug Administration (FDA) while on sabbatical from my University positions. No offers have been extended.

4. I received UCD's highest teaching honor in 2008 and the Alpha Omega Alpha Distinguished Teacher Award from the American Association of Medical Colleges in 1997. I also received the 1996 National Award for Innovation in Medical Education (Society of General Internal Medicine); the 1996 Outstanding Educator of the Year (United States Association of Teachers of Preventative Medicine); and the 1995 Award for Excellence in Education (UCLA School of Medicine), among other awards.

5. I received my medical degree from the University of Connecticut School of Medicine in 1985. I completed residencies at the New York University Medical Center/Bellevue Hospital, Columbia University and the New York City Department of Public Health, and the UCLA Department of Internal Medicine, in 1986, 1988, and 1991, respectively.

I received a Masters of Public Health from the Columbia University School of Public Health in 1987 and my Ph.D. in Public Health from the UCLA School of Public Health in 1992. My undergraduate degree is from Vassar College.

6. A true and correct copy of my curriculum vitae, including a list of my presentations and publications, is attached to this declaration as Exhibit 1.

7. I have extensively studied the education of physicians -- medical students, residents, and physicians in active practice. I have also conducted research into the effects of industry advertising on physician practices including, but not limited to, the effects of continuing medical education and the most effective means of communicating information. I have also studied and published papers on the impact of direct to consumer advertising on physicians, patients, and health care systems. I have studied, lectured, and written articles on the effects of industry promotion on physician prescribing patterns. In December 1997, I executed a declaration I had written on this subject, which the government submitted to the court in Washington Legal Foundation v. Friedman, CA No. 94-1306 (D.D.C.). This declaration is an updated version of the substantially similar declaration I wrote in 1997, and is consistent with the views I have expressed in various articles I have written over the last twenty years.

Physicians' Evaluation of Critical Clinical Information

8. Medicine is constantly changing. Physician education, therefore, must not only provide an initial foundation of factual knowledge, but also prepare physicians to adapt to new information and learn continuously throughout their careers. Physicians need to keep up to date on scientific advances, new discoveries, effectiveness research, systems-based practice (for example, new ways to reduce error) and, of course, new methods of treatment.

9. Medical education, as it now exists, inconsistently and inadequately addresses the physicians' need for future learning and for adapting to changes in medicine. Existing medical education also poorly prepares doctors to evaluate clinical data and to critically evaluate numerical (statistical) data presented to them in research formats (e.g., papers, meetings, and lectures). Studies over the years have consistently shown that doctors are not at all comfortable understanding research findings or interpreting statistical information about drugs or other treatments.[1]

10. In my role as Vice Dean overseeing Education at UCD and before that as Director of the Doctoring Curriculum at UCLA, I have directed a comprehensive effort to revise the medical school curriculum to provide medical students with the ability to critically analyze information provided to them. Included in the curriculum is an emphasis on continued learning in general and specifically the process of critically analyzing new information including, but not limited to, information provided by the companies selling drugs, biologics, and medical devices. Such longitudinal and sustained training programs are exceedingly rare, and even our programs have had limited successes.

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[1] Berwick DM et al., "When doctors meet numbers," 71 Am. J. Med. 991-98 (1981); Novack L et al., "Evidence-based medicine: assessment of knowledge of basic epidemiological and research methods among medical doctors," 974 Postgrad. Med. J. 817-22 (2006); Schor R et al., "Tolerance of uncertainty of medical students and practicing physicians," 38 Med. Care. 272-80 (2000); Oliveri RS et al., "Hospital doctors' self-rated skills in and use of evidence-based medicine -- a questionnaire survey," 10 J. Eval. Clin. Pract. 219-26 (2004); Weiss ST and Samet JM, "An assessment of physician knowledge of epidemiology and biostatistics," 55 J. Med. Educ. 692-97 (1980); Windish DM et al., "Medicine residents' understanding of the biostatistics and results in the medical literature," 298 J. Am. Med. Assoc. 1010-22 (2007); Swift L et al., "Do doctors need statistics? Doctors' use of and attitudes to probability and statistics," 28 Stat. Med. 1969-81 (2009); Wulff HR et al., "What do doctors know about statistics?," 6 Stat. Med. 3-10 (1987); Friedman SB and Philips S, "What's the difference? Pediatric residents and their inaccurate concepts regarding statistics," 68 Pediatrics 644-46 (1981); Saint S et al., "Journal reading habits of internists," 15 J. Gen. Intern. Med. 881-84 (2000); Christakis DA et al., "Do physicians judge a study by its cover? An investigation of journal attribution bias," 53 J. Clin. Epidemiol. 773-78 (2000).

11. Based on my extensive experience as a medical school professor and dean, in conducting research on medical education, in developing curricula, and as a practicing physician, it has been my observation that most doctors know little to nothing about the FDA approval process or off-label prescribing. Medical schools do not typically require instruction on the new drug application (NDA) requirements of the Federal Food, Drug and Cosmetic Act or the history of the 1938 enactment and the 1962 amendments. In the course of my career, and as part of my academic pursuits, I have discussed off-label prescribing practices and off-label promotion with hundreds of practicing physicians in a wide range of practice areas. Most of the physicians with whom I have spoken are not aware that the NDA requirements were the result of lethal problems that resulted from aggressive marketing practices by pharmaceutical manufacturers; do not fully appreciate the meaning of "off-label prescribing"; have no clear idea what indications for a given drug are for "off-label" or "on-label" uses; and do not know how to find information relevant to the approval status of the drug. Similarly, many members of the medical profession (e.g., physicians, physicians' assistants, and nursing practitioners) assume that, if a drug can be legally prescribed for a use, it surely must have been proven safe and effective for that use as evidenced by adequate and well controlled studies; that the experts at the FDA have done their job with regard to premarketing approval; that the drug being promoted by manufacturers is safe and effective for that promoted use; and that promotional material is accurate and balanced. See Chen DT et al., "U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: result of a national survey," Pharm. and Drug Safety (2009).

12. In considering the needs for continuing physician education, one must also take into account certain facts about medical practice: the typical physician is constantly surrounded by various competing demands on his or her time and must make decisions about critical

matters -- often in seconds or minutes. Individual physicians are essentially left to fend for themselves while also dealing with long work hours, great responsibilities, family commitments, and health care system dysfunctions.

13. Thus, while it is crucial that physicians be able to adapt to new information, it is equally important that the information provided to physicians be reliable, comprehensive, complete, honest, and accurate -- with respect to both positive and negative information -- for a complete and unbiased picture. Our patients' lives depend on this.

The Impact of Pharmaceutical Promotion on Physicians

14. The marketing of drugs and devices is a lucrative, multi-billion dollar industry, and the drug and device industries are well aware of the power of appealing to physicians to increase their sales. Prescriptions for off-label uses comprise a significant segment of that market: conservative estimates are that across the board 21 percent of prescription drugs are for off-label uses, and these estimates rise to substantially higher levels for some specialties. See Radley DC, Finkelstein SN, Stafford RS, "Off-label prescribing among office-based physicians," 166 Arch. Intern. Med. 1021-26 (2006).

15. Drug companies have used a variety of methods to promote off-label uses to doctors, including the use of "opinion leaders," sponsorship of "seminars," hiring marketing specialists to pen papers that masquerade as research, and distributing favorable reprints of journal articles while withholding unfavorable reprints. Promotion of off-label uses is often based on pseudo-science sometimes published in obscure medical journals, or, worse yet, in more reputable journals where companies have curried favor with the publisher or written the articles themselves (known as scientific ghost writing). Companies are clever at selecting what material to provide to physicians through marketing campaigns. They often take small preliminary investigations, funded by the manufacturer, published in obscure journals, written

by ghostwriters, and present their results to make them sound like major research studies. See Frank D, "Sponsorship, authorship, and accountability," 345 New Eng. J. Med. 825-27 (2001). At the same time, they ignore and fail to mention larger negative studies published in major journals. Major pharmaceutical companies (Pfizer, Eli Lilly, Bristol-Myers Squibb, and others) have paid billions of dollars in fines for unlawful off-label promotion of many drugs in the past few years. See Mello MM et al., "Shifting terrain in the regulation of off-label promotion of pharmaceuticals," 360 New Engl. J. Med. 1557-66 (2009).

16. Even when manufacturers are not engaged in overtly deceptive practices, the information they provide to physicians is likely to reflect bias. It is not uncommon for drug manufacturers to heavily promote the positive and completely omit dangers and side effects associated with their products. See Landerfeld CS and Steinman MA, "The Neurontin legacy: marketing through misinformation and manipulation," 360 New Eng. J. Med. 103-06 (2009). Manufacturers frequently do not include negative studies on a drug or those showing no benefit. Moreover, off-label promotion claims by the industry are typically not critically assessed. In some situations, a manufacturer may overlook or ignore early signs of harm. The physician is provided only the glowing studies and must rely on drug salespeople for interpretation.

17. These marketing activities can significantly alter physicians' prescribing behaviors and result in increased sales for the promoted products. Many doctors do not know to ask whether the promoted use is for an approved indication or for an off-label use, and lack the background knowledge and skills to critically evaluate the information provided in the context of off-label marketing. No matter how sincerely a physician believes that he or she is making an objective decision in the patient's interest, the foundation for that decision may often be incomplete, biased, and, therefore, flawed.

18. In addition, research on the promotion of dietary supplements has shown that the public is unable to carefully appraise even simple data on safety and effectiveness. See France R et al., "Policy makers' paradigms and evidence from consumer interpretations of dietary supplement labels," 39 J. of Consumer Affairs 27-51 (2005). As such, those who are favorably predisposed toward a product or even the industry hold attitudes that are difficult to change even in the face of clear evidence to the contrary. There is no reason to assume that physicians are any different. We are all subject to our biases, our prior assumptions, and the limitations of our understanding.

19. Given the assumptions held by prescribing professionals and the many demands on their time that occur during their practices, it is particularly dangerous when pharmaceutical companies push the boundaries of honesty and scientific integrity through overzealous promotion of off-label uses. However, even where the marketing is more measured, manufacturers are unlikely to provide the fully comprehensive and objective information that physicians need. It is particularly dangerous when the manufacturer is the only source of information about the unapproved use because, without other readily available information and the time, ability, and inclination to evaluate that information, the physician is unable and unlikely to critically assess the new use.

20. The consequences of the manufacturers' actions can -- and have been -- grave. Patients are deprived of approved treatments known to be effective and, in some cases, the off-label treatment may cause fatal consequences. Even where there are no physical harms, if a physician is deceived into prescribing a drug or medical device that he or she is led to believe will be effective and it only costs the patient money, there is still a harm. It allows both physician and patient to hope for something that is no more than a straw dog. For example, gabapentin was marketed by Pfizer Pharmaceuticals for many indications for which it was never

approved. In fact, these off-label uses accounted for the vast majority of gabapentin prescriptions, as it was recognized that gabapentin was not very effective for its approved indication (as a supplemental medication to help control seizures). It is also worth pointing out that, just because a drug is deemed safe for one indication in a small population of patients where the risks of non-treatment may be great, this does not mean the same drug is safe when used in large numbers of patients for minor symptoms.

21. The same pattern is seen in many other marketing campaigns for prescription drugs. Although many physicians believe they critically analyze data provided by pharmaceutical and medical device industry representatives, studies have shown that most physicians are unaware that they are hearing information promoting -- or extolling the virtues of -- a drug or medical device rather than an objective presentation of the products' benefits, limitations, and negative aspects. Physicians' attitudes towards drug sales representatives tend to be positive because of their relatively frequent detailing visits. A 2002 survey of a national random sample of physicians (n = 2,608) found that 74% judged the information provided by sales representatives to be useful and 81% judged the information on drugs to be accurate, even though that is not necessarily the case. See Kaiser Family Foundation, National Survey of Physicians (Part II), Doctors and Prescription Drugs, Highlights and Chartpack (March 2002) (www.kff.org). Another study compared initial prescriptions for psychiatric out-patients during periods with and without sales representative visits, and found significant associations between timing of sales visits and prescribing frequency. Market research also indicates that a pharmaceutical company's spending on sales representatives increases physician prescribing for that company's products. See Schwartz TL et al., "Newly admitted psychiatric patient prescriptions and pharmaceutical sales visits," 13 Ann. Clin. Psych. 159-62 (2001); Neslin S,

"ROI Analysis of Pharmaceutical Promotion: An Independent Study" (May 21, 2001), Scott Levin (http://www.rxpromoroi.org/rapp/definition.html).

22. In a study by Cho and Bero, published in 1996, researchers evaluated the quality, relevance, and structure of drug studies published in symposium proceedings and examined the relationship between drug company sponsorship and study outcome. The study found that significantly more articles with drug company support than without such support favored the subject drug. Although symposia have the potential to be valuable sources of information about drugs, in reality they are typically industry-sponsored and are used to market drugs and medical devices. See Cho MK & Bero LA, "The quality of drug studies published in symposium proceedings," 124 Annals Inter. Med. 485-89 (1996). Although the authors offered several theories for this outcome, the study demonstrated that physicians who rely on publications of symposia proceedings for information about new uses for approved products tend to receive only positive information and often are not provided with the information needed to critically assess the article and its conclusion. Id. at 488-89. Further, many physicians and nearly all students and residents are not aware of industry sponsorship of these symposia and the limited or non-existent peer review for data presented at the symposia using the usual definition of review.

23. My own research has confirmed that industry presentations favor the positive aspects of the company's own products and downplay -- or completely ignore -- the negative. In a study I conducted with Dr. Martin F. Shapiro, M.D., M.PH, Ph.D., a professor of medicine at UCLA, we examined the effect of pharmaceutical advertising on practicing physicians. We conducted this study, in part, because of our concern that medical knowledge in general, and knowledge about pharmaceutical products in particular, becomes dated very quickly. To keep physicians current with respect to pharmaceutical products, an effective educational program

must contain four critical elements: accuracy, honesty of claims, clarity, and references. Because industry advertising is very effective at influencing physician prescribing, physicians will be misled, and patients will be at risk, unless these four elements are present. We asked expert peer reviewers to evaluate various advertisements which, unlike the more subtle forms of promotion such as sponsorship of continuing medical education (CME) programs and the distribution of enduring materials (e.g., reprints of scientific journal articles), is recognized as an effort to increase the company's sales. Among other things, the reviewers assessed potential educational value and any deficiencies in the advertisements. We found that most advertisements had little or no educational value and, with respect to most drugs, serious deficiencies in substance (including misrepresentations about the drug's safety, cost, and benefit). Graphs were mislabeled or drawn to exaggerate a drug's benefit or downplay its harms, references that were cited were unavailable and written requests for copies went unanswered, and advertisements touted relative risks (a 25% decrease in heart attacks) as opposed to the more useful and honest absolute risks (a 0.50% reduction in heart attacks). These promotional deficiencies existed for *approved* uses; in my view, if companies were allowed to promote their products for *off-label* uses, these shortcomings would be even more pronounced. Drug companies would be far more likely to promote products for uses that have not been substantiated based on clear, compelling, and well-designed scientific studies.

24. Because many doctors do not have the background, time, or skill to critically analyze all statements made in the marketing of off-label uses, because the public does not have the analytical skills to evaluate drug research (which is why they visit the doctor as the learned intermediary in the first place), and because the pharmaceutical industry has an economic incentive to promote sales, it is the FDA that must serve the vital evaluative role. It stands to reason that an FDA evaluation of manufacturers' new claims of a drug's effectiveness and

safety needs to precede any promotional activity for new uses rather than follow it (assuming the company even decides to seek FDA approval for a new indication). Premarket approval, for Allergen's products or those of any other company, provides the public with protection and allows the doctor to focus on the patient's best interest. If, and when, a company acquires substantial evidence of a drug product's effectiveness for a new indication, the high road expected by the medical profession and the public requires the company to prove effectiveness for a particular use and submit a supplemental application for an FDA review. The other alternative -- to wait until actual harm comes to patients because of unproven claims -- is unacceptable. Given our current system of enormous economic rewards from the marketing of drugs and medical devices, physicians, as a proxy for their patients, need objective, honest, accurate, information that is as free of real and perceived conflict of interest as possible.

Continuing Education Programs

25. Drug and medical device companies often promote their products under the guise of "education." The most effective form of CME for physicians would include complete objectivity in course design, content, and presentation. I participate in approximately eight CME programs per year; I have planned approximately 40 CME programs per year, none of which has any involvement with pharmaceutical or device companies. This independence from industry, however, is the exception rather than the rule for CME; I am familiar with interactions between industry and other types of CME providers. In my experience, drug and medical device companies typically expect, in return for the funding they provide for these programs, some benefits to the company and its products. At a minimum, the industry hopes to influence the selection of the speaker and the topic of the presentation.

26. In a study by Bowman and Pearl, the authors analyzed the prescribing patterns of physicians who attended different CME programs. Each CME course was heavily subsidized by

a different drug company. The courses focused on similar drugs. The physicians' prescribing patterns were recorded both before and six months after the course. The study showed that physicians increased their prescriptions for the products of the sponsoring company and decreased their prescriptions for competitors' products. The results of this study are significant because, if physicians were, in fact, critically assessing the data provided in the courses, the prescriptions for essentially similar drugs would not have so closely correlated with the various companies which sponsored the respective programs. See Marjorie A. Bowman & David L. Pearle, "Changes in drug prescribing patterns related to commercial company funding of continuing medical education," 8 J. Contin. Educ. Health Prof. 13-20 (1988). Other studies have shown the same result: drug company funding of CME events is directly related to an increase in use by physicians of the funding company's products. See Avorn J et al., "Scientific and commercial sources of influence on the prescribing behavior of physicians," 73 Am. J. Med. 4-8 (1982); Stern RS, "Drug promotion for an unlabeled indication -- the case of topical tretinoin," 331 New Engl. J. Med. 1348-49 (1994).

27. As noted, physicians often accept the presentation at CME events or that provided in written materials without critically assessing such information. While physicians believe they are relying on an objective source of information, studies have demonstrated that programs sponsored by industry about new uses for their products are often biased. In another study by Bowman, the research demonstrated that, even in a program with more than one sponsor, the speakers mentioned the positive aspects of their own sponsor's products more often than the negative aspects. See Bowman MA, "The impact of drug company funding on the content of continuing medical education," 6 Mobious 66-69 (1986); see also Bero LA et al., "The publication of sponsored symposiums in medical journals," 327 New Engl. J. Med. 1135-40 (1992).

Disclaimers

28. Simply adding a disclaimer to the promotion of a new, unproven use for a drug or device, such as "the indications described are not approved by the FDA," would not be an effective means to help physicians critically evaluate information supplied by drug manufacturers. Manufacturers might follow such a disclaimer with mention of references to studies claiming effectiveness and safety, all in an attempt to legitimize the market pitch to follow. The impact of the disclaimer -- or even the fact that there is a disclaimer at all -- may be drowned out by the other marketing information. As already pointed out, such studies frequently are not robust, involve small study populations, are written by ghost writers, and/or are published in obscure medical journals. There also have been numerous occasions when drug manufacturers have promoted off-label drug uses to physicians in dangerous and misleading ways. In my view, if these promotional efforts were made together with a disclaimer that a use is not FDA-approved, many physicians would likely conclude that there is reliable evidence of safety and effectiveness. Further, because, as discussed above, many physicians generally have a limited understanding of the FDA approval process, and the significance of a use being "off-label," physicians are unlikely to fully appreciate the implications of the disclaimer. For example, a physician might conclude that the FDA approval for one use means that the product is safe for another use. I believe a mere disclaimer, therefore, would not be an effective way to address the underlying, serious problems with the off-label promotion of approved drugs and medical devices.

Conclusion

29. I believe that the public's health depends on the FDA's requirement of premarket approval for *each* use for which a drug is promoted by manufacturers. If a company has the data to prove safety and effectiveness, then not only should this provide no hardship but it should

provide financial gain by allowing promotion of the drug as an approved indication. If the outcome of this suit were that the evidentiary standard for prescription drugs were lowered, countless people would be harmed by the promotion of Botox and the hundreds of other products that would be aggressively promoted to doctors for indications that were never proven effective or safe. This does not even include the billions of health care dollars (most spent by the elderly) that would be wasted on prescriptions that provide the public no benefit.

Executed on March 27, 2010.

Michael S. Wilkes

Michael S. Wilkes, M.D., Ph.D

Exhibit 1

CURRICULUM VITAE

MICHAEL S. WILKES, M.D., Ph.D.

PERSONAL HISTORY:

Business Address: University of California, Davis
School of Medicine
One Shields Avenue
Building MSI-C
Davis, CA 95616

Phone: (530) 752-0321
Fax: (530) 752-1532
E-mail: michael.wilkes@ucdmc.ucdavis.edu

EDUCATION:

1976-81	Vassar College, Film History Phi Beta Kappa, General and Departmental Honors, Koppelmann Scholarship In Communications	B.A.
1978	Dutchess County, New York Paramedic Program	
1981-85	University of Connecticut, School of Medicine • Scholar in Medicine • Scholar in Psychiatry	M.D.
1984-85	National Fund for Medical Education Fellowship Research on adolescent health issues in Sri Lanka, under auspices of World Health Organization	
1985-86	New York University Medical Center/Bellevue Hospital Internal Medicine (Primary Care Track)	Resident
1986-88	Columbia University and New York City Department of Health, Preventive Medicine	Resident
1987	Columbia University School of Public Health	M.P.H.
1988-90	Robert Wood Johnson Clinical Scholar UCLA School of Medicine	Clinical Scholar
1990-91	UCLA Department of Internal Medicine	Resident
1992	UCLA School of Public Health	Ph.D.
2002-2004	Fellow – California Health Leadership Program (California Health Care Foundation)	

LICENSURE:

State of California, G064198

PROFESSIONAL EXPERIENCE:

2007-present **Director Global Health**, University of California, Davis

2008-present **Head,** IVIMEDS (consortium of international health science schools) collaboration of resource sharing and software development for developed and developing health science schools

2007-2009 **Co-chair,** University of California System-Wide Task force to develop a new, multi-campus, transdisciplinary, problem based, technology-based School of Global Health

2007 – present **Assistant Editor**, Essential Evidence / POEMS (online text and resource guide) Wiley and Sons.

2001-2007 **Vice Dean for Medical Education (Chief Academic Officer)**, School of Medicine, University of California, Davis

(Leadership in undergraduate medical education, graduate medical education, graduate nurse practitioner program, continuing medical education, masters in public health program, community outreach, integrated learning with other schools of health sciences, development of new 140,000 sq ft education building, rural health initiative, community outreach, and oversight of six student clinics. Direct reports included Deans of Curriculum, Student Affairs, Medical Humanities/ethics, and Admissions & Community Outreach and a staff of 78 faculty and staff. School budget of $18 million excluding research and clinical budget)

2001-Present **Professor** of Internal Medicine, University of California, Davis

2002-present **Creator**/Director, UC Davis Doctoring Curriculum, Course Chair, Doctoring 3 & 4

11/98-12/02 **Editor,** Western Journal of Medicine

5/98-3/04 **Associate Editor**, Medical Education

2001 **Professor of Medicine**
UCLA Division of General Internal Medicine and Health Services Research

1990-2001 **Creator and Senior Chair** UCLA Doctoring Curriculum

1998-2001 **Chair,** Faculty Executive Committee, University of California, Los Angeles (elected twice as chair by medical school-wide faculty vote.)

9/97-8/98 **Atlantic Fellow** in Public Policy, North American Office, British Foreign Office
(Faculty of Medicine, University of Newcastle, England)

1997-2001 **Associate Professor of Medicine**
UCLA Division of General Internal Medicine and Health Services Research

1992-2001 **Director,** High Risk Comprehensive Adolescent Medicine Clinic,
Venice Family Clinic (UCLA's Urban Teaching Site)

1991-2001 **Associate Director,** UCLA Center for Educational Development and Research

Senior Chair, "**Doctoring**," UCLA's innovative clinical curriculum
(Oversaw a faculty of 470 and staff. Directed curriculum development, faculty development, and evaluation)

Chair, UCLA Fundamentals of Clinical Medicine course (second year)

Chair, UCLA Clinical Reasoning and Epidemiology course, "Patients and Populations" (second and third year)

1990-2001 **Chair**, Medical Ethics course, (first, second, third, and fourth years)

1991-present Consultant, RAND, Santa Monica, CA

1991-1997 Assistant Professor of Medicine, UCLA Division of General Internal Medicine & Health Services Research

1996 Acting Associate Dean for Education

1990-1992 Co-Chair, Behavioral Medicine Training Program (Internal Medicine residents)

1987-1990 Assistant Clinical Professor
Columbia University of Public Health
Classes dealt with AIDS, aging and health policy, medical, public health, and social policy issues.

1983-85 Clinical Instructor
University of Connecticut School of Medicine
Department of Surgery, Paramedic Training Program

GLOBAL CONSULTING:

2009 External Reviewer, University of Queensland

2009-present Consultant, Kaiser Permanente Task Force to Establish a Medical School

2003-present UNAN University, Leon, Nicaragua – Faculty Development and Curriculum Planning

1997-present University of Newcastle, England – Technology Assisted Learning Curriculum Development

2008 Consultant, Medical Education, King Fahad Medical City, Riyadh, Saudi Arabia

2008 Consultant, Medical Education, PHAM NGOC THACH Medical School, Vietnam

2008 Consultant, AIDS research and outreach. Ravicherla Integrated Development and Education Society (NGO), Nuzvid, India

2007 Republic of Georgia, Tbilisi State Medical University. National Medical Education and Planning Evaluation (US Department of Defense)

2004 Belarus, Tbilisi State University – Curriculum consultant

2002 University of Tokyo, Japan – Faculty of Medicine

2000 Brazil, Consulting Medical Education and Curriculum Reform, Ministry of Health

PROFESSIONAL ACTIVITIES:

2008-Present Chair, NBME – National Board of Medical Examiners, Committee on Integrated cases

	(Assessment for Communication, Professionalism, Cultural Competency, and Ethics tied to clinical medicine)
2008-Present	LCME Member (Survey Team)
2005-Present	Columnist, McClatchy Newspapers (Sacramento Bee)
June 2004-Present	International Campaign to Promote and Revitalize Academic Medicine, Working Party Retreat, Chesham, United Kingdom
1991-Present	Weekly Medical Commentator, National Public Radio (Weekend Edition)
1988-Present	Volunteer Physician, Venice Family Clinic
1997	Medical Director, "Vital Signs" ABC Prime Time Television show (Thursday 9-10pm) Buena Vista Pictures. Show consisted of multiple real doctors' stories describing interesting and difficult patient encounters that changed the physician in some manner.
June 1995	Visiting Professor, University of Vermont, School of Medicine
June 1995	Visiting Professor, University of Alberta, School of Medicine
1994 & 2002	Visiting Professor - Vassar College Program In Science, Technology and Society
1989-1992	Contributing Editor, The Los Angeles Times
1988-1990	Consulting Physician, Olive View Hospital (LA County Hospital)
1988-1991	Columnist, New York Times Sunday Magazine
1989-1991	Ship's Physician and Officer, Princess Cruises
1988-90	Medical Consultant, NBC's "Today Show"
1986-88	Emergency Room Physician, Bellevue Hospital, New York
1986-87	Medical Producer, ABC's "World News Tonight with Peter Jennings" Produced medical stories for Dr. Timothy Johnson.
1982-84	Medical Correspondent, WFSB-TV-3 evening news, CBS Television affiliate in Hartford, CT. Wrote, produced, and narrated on-air reports on health issues for the evening news.
1978-79	County Paramedic Coordinator, New Haven,CT. Coordinated emergency medical services including 60 paramedics and 240 emergency medical technicians.

COMMITTEES AND COMMUNITY SERVICE:

2003-Present	Member, Yolo County Board of Health
2002-Present	Member, Strategic Alliance For Error Reduction (SAFER) in California Healthcare Advisory Board, Agency for Healthcare, Research and Quality (AHRQ)
1994-Present	Elected Member, Venice Family Clinic, Board of Directors

2004-2006	Chair, Yolo County Board of Health
2000-2003	Chair, Health Sciences Institute Task Force, University of California, Office of the President
1998-2002	Member, International Committee of Medical Journal Editors
1995-2002	Vice-President for Medical Services, Venice Family Clinic Board of Directors
1993-1995	Wildwood Elementary School, Education Committee of the Board
1990-1994	Member, Venice Family Clinic Medical Advisory Board
1988-1992	Chairman, Board of Trustees, Samantha Smith World Teen Program Poland Spring, Maine
1986-88	Member, New York Academy of Medicine's Committee on Public Health

UC Davis School of Medicine

2003-Present	Chair, MPH Board of Overseers
2002 – 2007	Chair, task force on medical school relation and Education Building Committee
2002-2007	Chair, Admissions Policy Committee, School of Medicine, University of California, Davis, California
2002-2007	Member, Committee on Educational Policy, UC Davis School of Medicine
2002-2007	Member, Student Progress Committee, UC Davis School of Medicine
2002-2007	Member, Fourth Year Oversight Committee, UC Davis School of Medicine
2002-2007	Member, Graduate Medical Education Advisory Committee

UCLA School of Medicine

1998-2001	Chair, Faculty Executive Committee, University Academic Senate, elected by faculty, School of Medicine, UCLA
1995-2001	Member, Faculty Executive Committee, UCLA School of Medicine Executive Governing Body, School of Medicine
1993- 2001	Member, Medical School Admissions Policy and Oversight Committee
1990-1997	Member, UCLA Ethics Committee
1990-2001	Chair, 4 Year Doctoring Curriculum (physical diagnosis, ethics, communication skills, epidemiology/clinical reasoning, cultural issues, geriatrics, etc)

REVIEWER:

2004 – present	NIH Committee Reviewer- National Human Genome Research Institute (NHGRI)
2002	Kaiser Permanente Clinician-Patient Communication Research Initiative
1997 – present	Medical Education
1992 – present	Annals of Internal Medicine

1992 – present	Journal of the American Medical Association
1992 – present	Journal of General Internal Medicine
1992 – present	Journal of Obstetrics and Gynecology
1992 – present	Lancet
1992 – present	New England Journal of Medicine
1992 – present	Academic Medicine

AWARDS:

2008	Woodward Lecturer and Visiting Professor, Penn State College of Medicine
2008	Distinguished Teacher of the Year, University of California, Davis (entire campus)
2005-2007	*Best Doctor* (Internal Medicine & Adolescent Medicine), Sacramento Magazine / Solano Magazine
2006	SGIM "Best Published Research Paper of the Year" (awarded May, 2006)
2006	Academy Health "Article of the Year' Award (awarded June, 2006)
2002-2005	California Health Care Foundation Leadership Fellowship
2001	The Christine & Helen S. Landgraf Memorial Cancer Research Award
2002	AOA, UC Davis School of Medicine Chapter, Faculty Award
1999	Time Inc. Health Freddie Awards Finalist in the International Health and Medical Film Competition
1999	UCLA School of Medicine Faculty Grand Marshal, Graduation (elected by Senior Class)
1997	American Association of Medical Colleges, Alpha Omega Alpha(AOA), "Distinguished Teacher Award" Washington, DC
1997	UCLA Lucien B. Guze "Golden Apple Award" (given to faculty member by students for outstanding clinical teaching)
1997	UCLA School of Medicine Kaiser Permanente Teaching Award (given to faculty members for innovative education)
1997	Atlantic Fellow/Harkness Fellowship: Provided by HM: British Foreign Office and Commonwealth Foundation.
1996	National Award for "Innovation In Medical Education" Society of General Internal Medicine
1996	"Outstanding Educator of the Year" United States, Association of Teachers of Preventative Medicine
1996	"Best of the Boards" Award for Teaching Clinical Epidemiology, American College of Physicians (ACP)
1995	University of California "Distinguished Wellness Lecturer" Award
1995	Award for "Excellence in Education" UCLA School of Medicine
1991	United Nation's "Peace Messenger" Award (for Samantha Smith World Teen Program)

1986 Outstanding Young Men in America

1984-85 National Fund for Medical Education: SmithKline-Beckmann Scholar

RESEARCH GRANTS AND FELLOWSHIP RECEIVED:

National Institution of Health/National Human Genome Research Institute (NHGRI) 2009-2013
"Increasing Confidence and Changing Behaviors in Primary Care Providers Engaged in Managing Ethical, Legal and Social Aspects of Patients Requesting Genetic Testing"
$1,902,020
Principal Investigator

American Association of Medical Colleges 2005-2008
"Cultural Competence in Medical Student Education: An Integrated and Developmentally Informed Curriculum"
$200,000
Principal Investigator

National Cancer Institute 2005-2010
"Statewide Initiative to Disseminate End-of-Life Education"
$4,200,000
Principal Investigator

Center for Disease Control 2004-2010
"Interventions to Improve Shared Decision Making: Prostate Cancer Screening
$2,600,000
Principal Investigator

National Institute of Health (NIH) 2003-2006
"Interactive ELSI Curriculum for Primary Care Residents"
$1,400,00
Principal Investigator

National Institute of Health (NIH-NINDS) 2002-2005
"Management Decisions in Financial Conflicts of Interest"
Co-Investigator

National Institute of Health (NIH) 2002-2005
"Consumer Influence on Treatment of Depression"
$566,000
Co-Investigator

Substance Abuse and Mental Health Services Administration 2002-2005
"Targeted Capacity Expansion Initiative for Substance Abuse Prevention and HIV Prevention in Minority Communities"
$343,000
Co-Investigator

Agency for Healthcare Research and Quality 2002-2004
"Addressing Patients' Multiple Concerns in Primary Care"
$450,000
Co-Investigator

Center of Disease Control (CDC) 2001-2004
"Professional Education on Prostate Cancer Screening: Primary Healthcare Providers"
$900,000

Principal Investigator

Paul G. Allen Foundation 2000-2004
"e Doctoring-Curriculum Development"
$200,000
Principal Investigator

Arthur Vining Davis 1997-2000
"Innovative Approaches to Community-Based Faculty Development"
$200,000
Principal Investigator

Culpepper Foundation 1995-1997
"Longitudinal Curriculum - Development of Evidence-Based Medicine"

$300,000
Principal Investigator

Stein Oppenheimer Award 1995-1996
"Development of Managed Care/Ethics Education Committee"
$16,000
Co-Principal Investigator

Office of Research and Developmental Field Program 1994-1996
Department of Veteran Affairs
$10,000
Principal Investigator

DHHS #ROI-901088 1990-1991
"Study of Pharmaceutical Promotion Accuracy"
$26,000
Principal Investigator

RESEARCH PAPERS:

1. Jacobs, T.A. and **Wilkes**, **M.S.** "Cremation Patterns for Patients Dying of AIDS in New York City, 1982-86" New York State Journal of Medicine 1988;628-632

2. **Wilkes**, **M.S.**, Jacobs, T.A., Milberg, J., and Stoneburner, R. "Autopsy Patterns in Patients Dying of Immunodeficiency Syndrome in New York City" Arch Of Path Lab Med 1988;112:1221-1223

3. **Wilkes**, **M.S.**, Fortin, A.H., Felix, J.C., Jacobs, T.A., and Thompson, W. "Value of Necropsy in Acquired Immunodeficiency Syndrome" Lancet 1988:85-88

4. **Wilkes**, **M.S.**, Schichor, A., Rea, M.M., Silva, K.T., and Aponso H. "Survey of Adolescent Health Issues in Sri Lanka" International Journal of Adolescent Medicine and Health 1988;3:163-172

5. **Wilkes**, **M.S.**, Jacobs, T.A., Fortin, A.H., Felix, J.C., and Link, N. "Attitudes of House Officers Toward the Autopsy" Journal of General Internal Medicine 1990;5:122-125

6. **Wilkes**, **M.S.** and Blum, S. "Current Trends in Routine Newborn Male Circumcision in New York State, 1980-86" New York State Journal of Medicine 1990;90;243-246

7. **Wilkes**, **M.S.**, Fortin, A.H., and Jacobs, T.A. "Physicians Attitudes Toward the Autopsy of Patients with AIDS" New York State Journal of Medicine 1991;386-389

8. **Wilkes**, **M.S.** and Kravitz, R.L. "Medical Researchers and the Media's Attitudes Toward Dissemination of Medical Information" Journal of the American Medical Association 1992;268:999-1003

9. **Wilkes**, **M.S.**, Doblin B.H., and Shapiro, M.F. "Pharmaceutical Advertisements in Leading Medical Journals: Experts' Assessments" Annals of Internal Medicine 1992;116:912-919

10. Hodgson, C.S., **Wilkes**, **M.S.**, and Wilkerson, L. "First Year Medical Students' Attitudes Toward Access to Medical Care in Cost Containment" Academic Medicine 1993;68(Suppl):S70-S74

11. **Wilkes, M.S.**, Malotte, C.K., Shlian, D., and Leaf, D. "Serum Cholesterol and Health Risk Factors in a University Population" Medicine, Exercise, Nutrition, and Health 1994;3:141-147

12. **Wilkes, M.S.**, Skootsky, S.A., Hodgson, C.S., and Wilkerson, L. "Health Care Reform as Perceived by First-Year Medical Students" Journal of Communitiy Health 1994;19:253-269

13. **Wilkes, M.S.**, Skootsky, S.A., Hodgson, C.S., Slavin, S.J., and Wilkerson, L. "Entering First-Year Students' Attitudes Toward Managed Care" Academic Medicine 1994;69:307-309

14. **Wilkes**, **M.S.**, Slavin, S.J., and Usatine, R. "Doctoring: A Longitudinal Generalist Curriculum" Academic Medicine 1994;69:191-193

15. Mackel, J.V., Farris, H., Mittman, B.S., **Wilkes, M.S.**, and Kanouse, D.E. "A Windows-Based Tool for the Study of Clinical Decision-Making Source" Medical Information 1995;8 Pt 2:1687

16. Usatine, R., Hogson, C.S., Marshall, T., Whitman, D.W., Slavin, S.J., and **Wilkes, M.S.** "Reactions of Family Medicine Community Preceptors to Teaching Medical Students" Family Medicine 1995;27:566-570

17. Slavin, S.J., **Wilkes,M.S.**, and Usatine, R. "Doctoring III: Innovation in Education in the Clinical Years": Academic Medicine 1995;70(12):1091-1095

18. Coulter, I.D. and **Wilkes, M.S.** "Medical Schools, the Social Contract, and Population Medicine: McMaster Revisited" Journal of Manipulative and Physiological Therapeutics 1995;18(80:554-558)

19. **Wilkes, M.S.** and Kravitz, R.L. "Policies, Practices, and Attitudes of North American Medical Journal Editors" Journal of General Internal Medicine 1995;10(8):443-450

20. **Wilkes, M.S.** "The Changing Role of Medical Education in the Face of Pressure to Reform Health Care" Drug Information Journal 1995;29:461-468

21. Usatine, R. and **Wilkes**, **M.S.** "Addressing Phone Medicine in the Medical School Curriculum" Academic Medicine 1996;71(5)

22. **Wilkes**, **M.S.** and Schriger, D. "Caution: The Meter Is Running" Western Journal of Medicine 1996:165(1-2):74-79

23. Usatine, R., **Wilkes**, **M.S.**, Slavin, S.J., and Wilkerson, L. "A Model Smoking-Intervention Curriculum for Medical School" Academic Medicine 1996;71(1 Suppl):S96-S98

24. Usatine, R., Slavin, S.J., and **Wilkes**, **M.S.** "Teaching Clinical Decision-Making and Cost-Effectiveness in Medical School: A Simulated Back Pain Case" Advances in Medical Education, Kluwer Academic Publishers, 1997:807-808

25. Usatine, R., Slavin, S.J., and **Wilkes**, **M.S.** "Addressing Telephone Medicine in Medical School Education" Advances in Medical Education, Kluwer Academic Publishers, 1997;200-202

26. Shuchman, M. and **Wilkes**, **M.S.** "Medical Scientist and Health News Reporting: A Case of Miscommunication" Annals of Internal Medicine 1997;126:976-982

27. Slavin, S.J., **Wilkes**, **M.S.**, and Usatine, R. "Faculty Perceptions of Learning While Teaching of Doctoring" Advanced in Health Sciences Education 1997;2:9-16

28. **Wilkes**, **M.S.** "The Public Dissemination of Medical Research: Problems and Solutions" Journal of Health Communication 1997;2:3-15

29. **Wilkes**, **M.S.** and Slavin S.J. "Heart Transplant Selection Criteria: Attitudes of Ethnically Diverse Medical Students" The Journal of Clinical Ethics 1998;9(2):147-155

30. **Wilkes**, **M.S.**, Coulter, I.D., and Hurwitz, E. "Medical, Law, and Business Students' Perceptions of the Changing Health Care System" Social Science & Medicine 1998;47(8):1043-1049

31. Coulter, I.D., Adams, A., Coggan, P., **Wilkes**, **M.S.**, and Gonyea, M. "A Comparative Study of Chiropractic and Medical Education" Alternative Therapies in Health and Medicine 1998:4(5):64-75

32. **Wilkes, M.S.**, Usatine, R., Slavin, S., Hoffman, J.R., "Doctoring: University of California, Los Angeles. Academic Medicine 1998;73(1):32-40

33. **Wilkes**, **M.S.**, Coulter I.D., Hurwitz, E.L. "The Relationship of Specialty and Training Site on Resident's Attitudes Toward a Changing Health Care System" Research in the Sociology of Health Care 1998;15:129-144

34. **Wilkes**, **M.S.** and Bligh, J. "Evaluating Educational Interventions" British Medical Journal 1999;318:1269-1272

35. **Wilkes, M.S.**, Shuchman, M. "Managing/Understanding Chronic Disease: A Call for Papers" Western Journal of Medicine 1999; 170(6):326-7

36. **Wilkes**, **M.S.**, Middlekauff H., and Hoffman, J.R. "Evidence-Based Case Review - Heart Failure: Part I., First Hospitalization and Post-Hospital Care" Western Journal of Medicine May 1999;170:268-273

37. Bell, R.A., **Wilkes**, **M.S.**, and Kravitz, R.L. "Advertising - Induced Prescription Drug Requests: Patients Anticipated Reactions to a Physician Who Refuses" Journal of Family Practice June 1999; 48:446-452

38. **Wilkes**, **M.S.**, Middlekauff H., and Hoffman, J.R. "Heart Failure- An Evidential Based Approach, Part II" Western Journal of Medicine June 1999;170:339-342

39. Doostan, D. and **Wilkes**, **M.S.** "Treating the Developmentally Disabled" Western Journal of Medicine August 1999; 171:92-101

40. Kai, J., **Wilkes**, **M.S.**, Paramjit, G. "Learning to Value Ethnic Diversity – What, Why, and How?" Medical Education August 1999; 33(8):616-623

41. Bell, R.A., Kravitz, R.L ., and **Wilkes**, **M.S.** "Direct to Consumer Prescription Drug Advertising and the Public" Journal of General Internal Medicine November 1999;13:651-657

42. Skootsy, S.A., Stuart, S. J., and **Wilkes**, **M.S.** "Attitudes Toward Managed Care and Cost Containment Among Primary Care Trainees at Three Training Sites" American Journal of Managed Care November 1999, 5(11):1397-1404

43. Bellas, P., Asch, S. and **Wilkes**, **M.S.** "What Students Bring With Them to Medical School: Attitudes Toward Health Promotion and Prevention" American Journal of Preventative Medicine 2000;18:3 : 242-248

44. Bell, R.A., **Wilkes, M.S.**, Kravitz, R. "The Educational Value of Consumer-Targeted Prescription Drug Print Advertising" Journal of Family Practice 2000;49:1092-1098

45. Edelstein, Ronald A., Reid, Helen M., Usatine, Richard, **Wilkes, M.S.** "A Comparative Study of Measures to Evaluate Medical Students' Performances" Academic Medicine 2000 75:825-833

46. Bell, R.A., Kravitz, R.L., **Wilkes, M.S.** "Direct-to-Consumer prescription drug advertising, 1989-1998. A Content Analysis of Conditions, Targets, Inducements, and Appeals" Journal of Family Practice 2000;49(4):329-35

47. **Wilkes**, **M.S.** and Anderson, M. "A Primary Care Approach to Adolescent Health Care" Western Journal of Medicine. March 2000;172:177-182

48. **Wilkes**, **M.S.**, Bell, R., and Kravitz, R. "Direct to Consumer Advertising: Trends, Impact, and Implications" Health Affairs Journal March 2000;19:110-128

49. Danovitch, I. and **Wilkes, M.S.** "Managed Care" Medical Education 2001;35:1169

50. **Wilkes, M.S.** and Hoffman, J. "An Innovative Approach to Educating Medical Students About Pharmaceutical Promotion" Academic Medicine December 2001;76;12:88-94

51. **Wilkes, M.S.**, Milgrom, E., Hoffman, J.R. "Towards More Empathic Medical Students: A Medical Student Hospitalization Experience" Medical Education 2002;36:528-533

52. **Wilkes**, **M.S.** and Raven, B. "Understanding Social Influence in Medical Education" Academic Medicine June 2002;77;6:481-488

53. Cooper, R.J., Schriger, D.L., Wallace, R.C., Mikulich, V.J., **Wilkes, M.S.** "The Quantity and Quality of Scientific Graphs in Pharmaceutical Advertisements" Journal of General Internal Medicine. April 2003;18:294-297, 2003

54. Slavin S.J., **Wilkes M.S.,** Usatine R.P., Hoffman J.R. "Curricular Reform of the 4th Year of Medical School: the Colleges Model" Teach Learn Med. Summer 2003; 15(3): 186-93.

55. Mitchell M., Srinivasan M., West D.C., Franks P., Keenan C., Henderson M., **Wilkes M.** "Factors Affecting Resident Performance: Development of a Theoretical Model and a Focused Literature Review" Academic Medicine April 2005; 80(4):376-89.

56. Kravitz, R.L., Epstein R.M., Feldman M.D., Franz C.E., Azari R, **Wilkes, M.S.,** Hinton L., Franks P. "Influence of Patients Requests for Direct-to-Consumer Advertised Antidepressants: a Randomized Controlled Trial" Journal of American Medical Association. April 27, 2005; 293(16): 1995-2002. **(SGIM Best Published Research Paper of the Year (awarded May, 2006) (AcademyHealth Article of the Year Award (awarded June, 2006)**

57. **Wilkes M.S.,** Srinivasan M., Flamholtz E. "Effective Organizational Control: Implications for Academic Medicine" Academic Medicine November 2005: 80(11): 1-10.

58. Bell D.S., Sobolevsky S., Day F.C., Hoffman J.R., Higa J.K., **Wilkes, M.S.** "The Stadium Diagram, a Web-based Tool for Visualizing the Expected Outcomes of Alternative Clinical Management Strategies." AMIA Annu Symp Proc. 2005:36-40.

59. **Wilkes M.S.,** Hoffman J.R., Usatine R., Baillie S., " An Innovative Program to Augment Community Preceptors' Practice and Teaching Skills." Academic Medicine April 2006: 81(4): 332-341.

60. Hoffman J.R., **Wilkes M.S.,** Day F.C., Bell D.S., Higa J.K., " The Roulette Wheel: An Aid to Informed Decision Making." PloS Med 3 (6): e137. DOI: 10.1371/journal.pmed.0030137

61. Bell D.S., Hays R.D., Hoffman J.R., Day F.C., Higa J.K., **Wilkes M.S.** "A Test of Knowledge About Prostate Cancer Screening: Online Pilot Evaluation Among Southern California Physicians." Journal of General Internal Medicine April 2006; 21(4): 310-4.

62. **Wilkes, M.S.**, Howell, L. "Technology as an instrument to improve quality, accountability, and reflection in academic medicine." Academic Psychiatry, November 2006; 30 (6): 456-64.

63. Cooper, R.J., Gupta, M., **Wilkes, M.S.,** Hoffman, J.R. "Conflict of Interest Disclosure Policies and Practices in Peer-Reviewed Biomedical Journals." Journal of General Internal Medicine, December 2006; 21(12):1248-52.

64. Coulter, ID, **Wilkes, M.S., Der-Martirosian,C.** "Altruism Revisited: A Comparison of Medical Students, Law Students and Business Students Altruistic Attitudes" Medical Education 2007; 41:341-345.

65. Srinivasan, M., **Wilkes, M.S.**, Stevenson, F., Nguyen, T., Slavin, S., "Comparing Problem-Based Learning with Case-Based Learning: effects of a major curricular shift at two institutions." Academic Medicine, January 2007; 82(1):74-82.

66. Srinivasan, M., Pratt, D.D., Collins, J., Bowe, C.M., Stevenson, F.T., Pinney, S.J., **Wilkes, M.S.,** "Developing the Master Educator: cross disciplinary teaching scholars program for human and veterinary medical faculty." Academic Psychiatry, November-December 2007; 31(6):452-64.

67. Srinivasan, M., Hauer, K.E., Der-Martirosian, C., **Wilkes, M.,** Gesundheit, N., "Does Feedback Matter? Practice-based learning for medical students after a multi-institutional clinical performance examination." Medical Education, September 2007; 41(9):857-65.

68. Heritage, J., Robinson, J.D., Elliott, M.N., Beckett, M., **Wilkes, M.S.,** "Reducing Patients' Unmet Concerns in Primary Care: the difference one word can make." Journal of General Internal Medicine, October 2007; 22(10):1429-33.

69. Bourgeois JA, Ton H, Onate J, McCarthy T, Stevenson FT, Servis ME, **Wilkes M.S**., "The doctoring curriculum at the University of California, Davis School Of Medicine: leadership and participant roles for psychiatry faculty." Acad Psychiatry. 2008 May-Jun;32(3):249-54.

70. **Wilkes, M.,** Johns, M., "Informed Consent and Shared Decision Making: A Requirement to Disclose to Patients Off-Label Prescriptions." PLoS Medicine. November 2008; 5(11):e223:1-4.

RESEARCH PAPERS – NON-PEER REVIEWED

1. Wilkes, M.S. "Conflict, What Conflict?" Western Journal of Medicine 172;1:6-8, 2000

2. Wilkes, M.S. "Chronic Back Pain: Does Bed Rest Help?" Western Journal of Medicine 72; 2:121, 2000

3. Wilkes, M.S. Monthly editorial in Western Journal of Medicine

CHAPTERS:

1. **Wilkes**, **M.S.** "Acquired Immune Deficiency Syndrome (AIDS)" Columbia University, College of Physicians and Surgeons Complete Medical Guide, 2nd Edition Chapter 22, pgs. 476-489, 1989

2. **Wilkes**, **M.S.** "Women in the Work Place" The Good Housekeeping Illustrated Guide to Women's Health, Hearst Books Chapter 17, 1995

3. **Wilkes, M.S.** and Anderson, M. "Approach to the Adolescent Patient" Women's Health: Principles and Clinical Practice Chapter 3, pgs. 13-18, 2002

4. Ton, H., Hilty, D.M., **Wilkes, M.S.** "Teaching in Small Group Settings" Handbook of Career Development in Academic Psychiatry and Behavioral Sciences. American Psychiatric Publishing, Inc., Chapter 16, pgs. 183-195, 2006

5. **Wilkes, M.S.** "Making Curricular Changes to Include the Problem of Violence and Abuse" Building Academic Capacity and Expertise in the Health Effects of Violence and Abuse: A Blueprint for Advancing Professional Health Education Academy on Violence and Abuse, Chapter 3, pg. 10, 2007

LETTERS TO THE EDITOR:

1. Ioannidis, J.P., Ahmed, T., Awasthi, S., Clarfield, A.M., Clark, J., Dandona, L., Howe, A., Lozano, J.M., Li, Y., Madani, H., Marusic, A., Mohammed, I., Purcell, G.P., Rhoads, M., Sliwa-Hahnle, K., Straus, S.E., Edejer, T.T., Tugwell, P., Ward, R., **Wilkes, M.S**.., Smith, R. "Open Letter to the Leader of Academic Medicine." BMJ January 2007, 334 (7586):191-3.

2. Wilkes, M.S. and Hoffman JR. "The Truth About the Drug Companies: How They Deceive Us, and What To Do About It; On the Take: How Medicine's Complicity With Big Business Can Endanger Your Health." Journal of American Medical Association July 2005

3. **Wilkes, M.S**., Hoffman, J.R. "Students Benefit from Experience of Hospitalization" Medical Education 2002;36:586-587

4. Hoffman, J.R., **Wilkes, M.S**., Schriger, D.L., Morgan, M.T. "Editorial Independence and The Journal" JAMA May 1999, 281(19):1793-4

5. Wilkes, M.S. and Bazzano, Alicia. "Deadly Medicine" Lancet September 1995, 346(8976):686

EDITORIALS AND COMMENTARIES:

1. **Wilkes, M.S.** "Hormone Surge" Medical Education Aug 2003;37(8):674-5.
2. **Wilkes, M.S.** "Changing Clinical Practice" Medical Education 2001;35:924
3. **Wilkes, M.S.** "Educational Interventions Can Change Clinical Behavior" Western Journal of Medicine March 2000;172:163.
4. Hoffman, J.R. and **Wilkes, M.S**. "Direct to Consumer Advertising of Prescription Drugs" British Medical Journal 1999;318:1301-1302
5. **Wilkes**, **M.S.** "Community-Bespoke Doctoring" Lancet 1994;343(8898):613-614
6. Monthly *Editor's Pick* column in Western Journal of Medicine
7. Mainstream Media Radio Commentary—Medical Expert

GENERAL PUBLICATIONS (Select Pieces):

1. Syndicated Column, Sacramento Bee (www.sacbee.com) [search: Dr. Wilkes]
2. Weekly National Public Radio Commentary Second Opinion (www.KCRW.org) [search: second opinion]
3. "Curricular Reform of the 4th Year of Medical School: The Colleges Model" (Slavin & Others) Teaching and Learning in Medicine, 2003; 15:186-193
4. "Chronic Back Pain: Does Bed Rest Help?" Western Journal of Medicine. February 2000:172:121
5. "NMR: Private Radiologists vs. The State of Connecticut" Northeast Sunday Magazine of the Hartford Courant
6. "Educating Miriam and Michael" Northeast Sunday Magazine of the Hartford Courant
7. "Examining the Physical Exam" Social Issues Resource Series
8. "Autopsy – The Bare Truth" Social Issues Resource Series
9. "Journalist Heal Thyself" UCLA Magazine, P. 64
10. "Trauma Centers: An Advantage?" New York Times Sunday Magazine
11. "Medical Breakthroughs On Line" New York Times, July 7, 1995
12. "The Vitamin Uprising" New York Times Sunday Magazine, October 2, 1994
13. "Diagnoses from the Next Seat" UCLA Physician's Forum, 1990;10710:3-7
14. Regular Column, Los Angeles Times, October 1989-1992 (titles available upon request)
15. "Pitching Doctors" New York Times Sunday Magazine, November 5, 1989

16. "Suffering in Silence" New York Times Sunday Magazine, July 23, 1989
17. "What is Too Old" New York Times Sunday Magazine, June 8, 1989
18. "Asking and Telling" New York Times Sunday Magazine, February 2, 1989
19. "Holy Secrets" New York Times Sunday Magazine, October 2, 1988
20. "Who is to Decide" New York Times Sunday Magazine, August 21, 1988
21. "Tuberculosis and AIDS: A New Twist" Boston Globe, October 5, 1987
22. "The Myth of the Annual Physical Exam" Social Issues in Health Care Resources Series, (3) 1987
23. "Malpractice, a Losing Game" Social Issues in Health Care Resources Series, (3) 1987
24. "An Ounce of Prevention – A Look at the Annual Physician Exam" New York Times Sunday Magazine, September 28, 1986
25. "Medical Malpractice" Washington Post Sunday Magazine, March 2, 1986
26. "Medical Malpractice: Who's Winning – Who's Losing?" Connecticut Magazine, September 1985
27. "The Saddest Child" Connecticut Magazine, 1984;59 +
28. "The Depressed Child: A New Diagnosis" Connecticut Magazine, October 1984
29. "The Need for Medical Autopsies" Connecticut Magazine, September 1984
30. "Autopsy - A Dying Science" Boston Globe Sunday Magazine, May 6, 1984

Revised winter 08