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# Marketing Off-Label Uses to Physicians: FDA's Draft (Mis)Guidance

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When President Clinton signed the United States Food and Drug Administration (USFDA) Modernization Act into law in 1997, he hedged his support for several of its more controversial elements. "While I am satisfied with the resolution of the issues in this legislation," he asserted, "I am also pleased that Congress included sunsets to certain of the Act's provisions so that, at the appropriate time, we can evaluate whether the appropriate compromises were reached."<sup>1</sup> One such provision, which relaxed the previously operative prohibition against promoting off-label uses of drugs to physicians, expired in the fall of 2006.<sup>2</sup> This February, the FDA promulgated a draft policy to replace the defunct statute<sup>3</sup>—so the "appropriate time" to assess the effectiveness of the relevant compromises, past and present, seems to be now.

The 1997–2006 regime looked like this: Industry representatives could give physicians peer-reviewed journal articles assessing the effectiveness of a drug for uses other than those for which it had been approved—subject to the condition that the manufacturer begin or continue the process of earning regulatory approval for the new indications.<sup>4</sup> Exceptions to that requirement were available in a variety of cases, including when the patient population that might benefit from the off-label use was so small that it was

not worth the company's resources to conduct the necessary studies.<sup>4</sup> The point was to balance competing concerns. On one hand, Congress wanted to ensure that "health care practitioners [could] obtain important scientific information about uses that are not included in the approved labeling of drugs."<sup>5</sup> On the other, the legislature took care to "encourage that these new uses be included on the product label," by insisting on the statute's "strong incentives to conduct the research needed and file a supplemental application for [regulatory approval of] such uses."<sup>5</sup>

The new proposed policy would do away with the need for companies to work toward approval for the off-label uses they promote to physicians. While acknowledging that such marketing efforts technically may violate laws against hawking "misbranded" food, drug, and cosmetic products,<sup>6</sup> the FDA has effectively announced that, going forward, it will not be bothered by the promotion of off-label drug uses in the form of companies' giving peer-reviewed journal articles to physicians. The agency, in other words, has decided that it cares about only one of the issues that Congress expressed concern with in 1997: the "important public policy reasons for allowing manufacturers to disseminate truthful and non-misleading medical journal articles."<sup>7</sup>

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1. President William Jefferson Clinton, Signing Statement on FDA Modernization Act, 21 Nov 1997.

2. 21 U.S.C. §360aaa NOTE (e).

3. See United States Food and Drug Administration. 2008. *Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*. Available at: <http://www.fda.gov/oc/op/goodreprint.html> (accessed 16 May 2008). *Federal Register*, February 20, 2008, Vol. 73 No. 34 at 9342. Hereinafter "Draft Guidance".

4. 21 U.S.C. §360aaa et seq. The statute imposed several more modest demands as well, among them that companies submit materials to FDA prior to distributing them to physicians. *Id.*

5. Food and Drug Administration Modernization Act of 1997, H.R. Conf. Rep. 105-399, 9 Nov 1997, at 99-100.

6. See Draft Guidance, *supra* n.3, §III ("the [Food, Drug & Cosmetics] Act and FDA's implementing regulations generally prohibit manufacturers of new drugs or medical devices from distributing products in interstate commerce for any intended use that FDA has not approved as safe and effective or cleared through a substantial equivalence determination").

7. See Draft Guidance, *supra* n.3.

The FDA's gambit triggers a number of legal concerns for critics of burdensome government and reckless industry alike. Advocates of the old framework may argue that the draft "Guidance" raises red flags about an administrative agency's ability to decide for itself, irrespective of statutes passed by Congress, what kinds of "misbranded" drug marketing it views as troublesome. At the same time, the First Amendment concerns that prompted a conservative legal group to challenge FDA regulations implementing the 1997 law still linger in the background.<sup>8</sup>

Constitutional matters aside, it remains debatable whether expanding the promotion of off-label uses will, on balance, help or hurt patients. To be sure, off-label prescriptions are already both ubiquitous and necessary; more than 20% of scripts are apparently written for indications other than those approved by the FDA (Radley et al. 2006), many of which include pediatric applications of products tested only in adults (Harris 2008). And as Congress recognized in 1997, liberalizing off-label marketing policies allows physicians to be informed more rapidly and predictably about potentially life-saving applications for therapeutics already present in their armamentarium. As long as physicians are writing these prescriptions, why not make it easier for them to see the relevant literature?

There are, it turns out, a few good answers to that question. First, the selection of articles distributed to physicians by industry is likely to be biased, because companies have little incentive to share studies casting doubt on the utility of particular off-label indications. Second, the requirement that information passed on by industry be limited to peer-reviewed journal articles may do little, in practice, to ensure the scientific quality of the evidence contained therein. There are literally thousands of biomedical journals for drug companies to choose from, many of which offer ineffective safeguards to prevent investigators' competing interests from tainting the validity of their findings (Bodenheimer 2000; van Kolschooten 2002).<sup>9</sup> Although doctors might ideally be trained to account for these bias and quality concerns, investigations suggest that busy doctors tend to be susceptible to persuasion by information passed on by drug companies, regardless of its validity (Ziegler et al. 1995; Wazana 2000). Third, a rapid proliferation of off-label prescriptions, which might plausibly follow from a rapid proliferation of off-label marketing to physicians, could make it more difficult to track drug safety. The FDA has a poor record of monitoring the real effects of drugs for their *approved* uses—a regulatory failure that has led to substantial public health costs and public outcry (Fontanarosa 2004; Harris 2004). Any regulatory policy that actually augmented the challenge of monitoring what harms and benefits a given

8. See *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 2000). Although doing away with the "work toward approval" requirement removes one obstacle to free speech in the marketplace, the remaining limitation that, apparently, only peer-reviewed journal articles may be shared imposes a burden that First Amendment absolutists may chafe at.

9. The possibility of abject fraud by pharmaceutical companies is, of course, another problem. See *infra* n.11 (referring to misdeeds around the promotion of the drug Neurontin).

drug causes would certainly run counter to the recent Institute of Medicine report urging the FDA to do a better job assessing post-approval drug safety and effectiveness.<sup>10</sup> Finally, and most straightforwardly, the omission of a requirement that companies pursue approval for the off-label uses they promote eliminates any incentive for industry to invest in studies beyond those necessary to earn preliminary approval. The effect of this policy change could be quite radical: the FDA might be left out of the regulatory loop for many of the indications for which companies market drugs to physicians. In the most extreme case, a drug-maker could seek approval for a relatively narrow use, and then market its product broadly for other indications—to the point that government-approved use represented only a small fraction of actual use in the marketplace.

Some of these concerns were as troublesome under the 1997–2006 regime as they would be under the new framework the FDA has proposed. Indeed, in retrospect (and in the wake of the Neurontin debacle),<sup>11</sup> it seems that the Clinton-era compromise was inadequate to assure that companies provided physicians with *accurate and useful* information. That realization weighs in favor of a change in policy, to be sure, but not to one designed to elicit an increase in indiscriminate industry marketing, while doing nothing to remedy the same old shortcomings.

On the contrary, a more rational government response would be one that tightened rules about the articles companies could give to physicians promoting off-label uses, perhaps by requiring that such marketing efforts include an up-to-date and comprehensive selection from the literature.<sup>12</sup> Furthermore, sound regulation of off-label marketing

10. See generally *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, *Institute of Medicine Report*. September 22, 2006.

11. See Warner-Lambert to Pay \$430 Million to Resolve Criminal and Civil Health Care Liability Relating to Off-Label Promotion, Press Release, U.S. Department of Justice, May 13, 2004. Available at [www.usdoj.gov](http://www.usdoj.gov) (accessed 16 May 2008); "Warner-Lambert's strategic marketing plans, as well as other evidence, show that Neurontin was aggressively marketed to treat a wide array of ailments for which the drug was not approved... Warner-Lambert promoted Neurontin even when scientific studies had shown it was not effective."

12. Concededly, such restrictions might exacerbate the First Amendment concerns that already plague regulatory efforts in this area. A full discussion of the Free Speech Clause as it applies to the FDA's authority to define "misbranded" products is outside the scope of this essay—not because Constitutional objections to such regulation are unimportant or unpersuasive (for they are well worth considering), but because they raise questions that warrant more comprehensive treatment than is possible in this forum. See Helm K Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion, 18 *Fordham Intell. Prop. Media & Ent. L.J.* 117, 157–162 (2004) (discussing recent legal challenges to the FDA's efforts to regulate marketing of off-label indications). For present purposes, suffice it to say that relaxing certain Clinton-era formalities, such as the mandate for the FDA to pre-screen materials sent to doctors (see *supra* n.4), might ameliorate some Constitutional problems while sacrificing little in the way of effective public health regulation.

should, at the very least, consider how to mitigate the drug safety monitoring problem identified by the Institute of Medicine nearly 18 months ago—rather than blithely making matters worse.

In the end, perhaps the best that can be said of the FDA's draft guidance is that it may not make much difference. Because the document is likely to be controversial, activists on all sides of the issue will undoubtedly attempt to delay its implementation—and if they can keep the agency in a state of “paralysis by analysis” until January 2009, a new Presidential administration and political reality in Washington may effectively force the FDA to go back to the drawing board. In the meantime, the previous law's sunset has left industry and physicians alike in the dark. ■

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