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# BOUND GUIDANCE: FDA RULEMAKING FOR OFF-LABEL PHARMACEUTICAL DRUG MARKETING

## INTRODUCTION

On December 30, 1993, the United States Food and Drug Administration (“FDA”) approved gabapentin, a drug marketed and distributed by Parke-Davis Pharmaceuticals Company, for “adjunctive therapy in the treatment of partial seizures . . . in patients above the age of 12 years.”<sup>1</sup> The drug was hailed as a welcome advance in the study of epilepsy, a field that scientists are only beginning to understand.<sup>2</sup> In clinical trials, gabapentin’s results were impressive. In one study, gabapentin corresponded with a fifty percent reduction in seizures for twenty-three percent of epileptic patients, in comparison to a nine percent reduction in the placebo group.<sup>3</sup> Gabapentin’s potential use, however, may well extend beyond treatment of seizures. Although it will not be a ‘miracle solution’ to all ailments involving neuropathic pain,<sup>4</sup> numerous studies suggest that gabapentin may have uses far beyond the scope of its FDA approval.<sup>5</sup>

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<sup>1</sup> Alicia Mack, *Examination of the Evidence for Off-Label Use of Gabapentin*, 9 J. MANAGED CARE PHARMACY 559, 559 (2003).

<sup>2</sup> See James Le Fanu, *In Sickness and in Health: Breaking the Pain Barrier*, TELEGRAPH (U.K.), Dec. 15, 2002 (Health), available at [http://www.telegraph.co.uk/health/health\\_advice/4712479/In-sickness-and-in-health-breaking-the-pain-barrier.html](http://www.telegraph.co.uk/health/health_advice/4712479/In-sickness-and-in-health-breaking-the-pain-barrier.html); Sally Squires, *New Drug For Epilepsy: Patients Have Waited 15 Years for an Advance in Medication*, WASH. POST, Aug. 10, 1993 (Health), at 9 (“Despite its long and well-documented history, epilepsy remains a poorly understood condition.”).

<sup>3</sup> See PARKE-DAVIS, NEURONTIN (GABAPENTIN) CAPSULES, NEURONTIN (GABAPENTIN) TABLETS, NEURONTIN (GABAPENTIN) ORAL SOLUTION 7–8 (2009), available at [http://www.pfizer.com/files/products/uspi\\_neurontin.pdf](http://www.pfizer.com/files/products/uspi_neurontin.pdf) (physician prescribing information for Neurontin).

<sup>4</sup> See David Perlman, *New Drugs Being Tested for Pain Relief*, S.F. CHRON., Feb. 14, 1998, at A4.

<sup>5</sup> See, e.g., Udo Bonnet et al., *Treatment of Acute Alcohol Withdrawal with Gabapentin: Results from a Controlled Two-Center Trial*, 23 J. CLINICAL PSYCHOPHARMACOLOGY 514 (2003); Atul C. Pande et al., *Gabapentin in Bipolar Disorder: A Placebo-Controlled Trial of Adjunctive Therapy*, 2 BIPOLAR DISORDERS 249 (2000); Michael Rowbotham et al., *Gabapentin for the Treatment of Postherpetic Neuralgia: A Randomized Controlled Trial*, 280 JAMA 1837

Parke-Davis' marketing budget makes it clear that encouraging these potential alternative uses for the drug was a priority. In 1998 alone, Parke-Davis budgeted over \$11 million for professional education events, such as dinner meetings with doctors, intended to "[m]aximize [o]pportunities in '[e]merging [[u]napproved] [u]ses.'"<sup>6</sup> In total, Parke-Davis allocated approximately \$40 million for its Neurontin advertising budget in 1998.<sup>7</sup> Due in part to its marketing practices, Neurontin has been prescribed by physicians for a plethora of uses outside the scope of its FDA approval, including treatment of bipolar disorder, attention deficit disorder, restless leg syndrome, and migraine headaches.<sup>8</sup> As much as seventy-eight percent of Neurontin's \$1.3 billion in sales for 2000 can be attributed to uses outside the scope of the drug's FDA approval "without clinical evidence of safety or effectiveness."<sup>9</sup>

The use of drugs like gabapentin for purposes not approved by the FDA is referred to as off-label use.<sup>10</sup> Although drug companies are not allowed to promote drugs for off-label uses, the FDA "does not regulate the practice of medicine and recognizes that physicians may determine that prescribing a drug off label constitutes good care."<sup>11</sup> Thus, despite the marketing restrictions, manufacturers utilize a number of methods to promote off-label uses of pharmaceuticals, including paying for professional education sessions, hiring speakers, engaging in direct mail campaigns, and reprinting favorable journal articles.<sup>12</sup> In recent years, many of these tactics have come under fire in a barrage of qui tam lawsuits brought against pharmaceutical

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(1998) (describing use of gabapentin for treatment of shingles).

<sup>6</sup> Michael A. Steinman et al., *Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents*, 145 ANNALS INTERNAL MED. 284, 287 tbl.2 (2006), available at <http://www.annals.org/cgi/reprint/145/4/284.pdf>.

<sup>7</sup> See *id.*

<sup>8</sup> See Mack, *supra* note 1, at 562–65.

<sup>9</sup> *Id.* at 562.

<sup>10</sup> See, e.g., Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008) (noting that "off-label prescribing" means "the prescription of a medication in a manner different from that approved by the FDA").

<sup>11</sup> U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-08-835, FDA'S OVERSIGHT OF THE PROMOTION OF DRUGS FOR OFF-LABEL USES 2 (2008) [hereinafter GAO REPORT], available at <http://www.gao.gov/new.items/d08835.pdf>. Although physicians are permitted to prescribe off label, the FDA explains that, as a matter of good medical practice, physicians have a responsibility "to base [any off-label] use on firm scientific rationale and on sound medical evidence." See U.S. Food & Drug Administration, "Off-Label" and Investigational Use of Marketed Drugs, Biologics and Medical Devices, <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm116355.htm>.

<sup>12</sup> See Steinman et al., *supra* note 6, at 287 tbl.2.

companies under the False Claims Act.<sup>13</sup> As a result, while pharmaceutical companies are facing record-breaking fines for their unlawful business practices—Pfizer's \$2.3 billion settlement for off-label marketing included the largest criminal fine in history and was its fourth settlement over illegal marketing since 2002—these same companies continue to engage in off-label marketing.<sup>14</sup>

Pfizer's strategy for Neurontin is no exception to this trend. According to Dr. Kay Dickersin of the Johns Hopkins Bloomberg School of Public Health, Pfizer, through its Parke-Davis division, used "a publication strategy meant to convince physicians of Neurontin's effectiveness and misrepresent or suppress negative findings."<sup>15</sup> For example, although physicians prescribe Neurontin to treat depression,<sup>16</sup> recent studies have shown that its use doubles the risk of suicidal behavior.<sup>17</sup> However, despite the drug's generic status and the ongoing controversy surrounding its off-label use, Neurontin continues to generate substantial income for Pfizer, grossing \$387 million in sales in 2008.<sup>18</sup>

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<sup>13</sup> See, e.g., Jack Dew & Jack Zemlicka, *Amended False Claims Act Has Lawyers Advising Caution: Universities, Hospitals Among Potential Targets*, WIS. L.J., Aug. 25, 2009, <http://www.wislawjournal.com/article.cfm/2009/08/31/Amended-False-Claims-Act-has-lawyers-advising-caution-Universities-hospitals-among-potential-targets> (noting that Eli Lilly settled with the Department of Justice for \$1.4 billion based on allegations that it promoted Zyprexa for off-label uses); Andrew Jack, *Pfizer Agrees to Plead Guilty in Painkiller Case*, FIN. TIMES, Sept. 3, 2009, at 15, available at <http://www.ft.com/cms/s/0/d86bc890-9821-11de-8d3d-00144feabdc0.html> (noting that Pfizer agreed to a \$2.3 billion settlement with the U.S. government based on allegations that it illegally promoted its painkiller, Bextra).

<sup>14</sup> See Gardiner Harris, *Pfizer Pays \$2.3 Billion to Settle Marketing Case*, N.Y. TIMES, Sept. 32, 2009, at B4.

<sup>15</sup> S. Swaroop Vedula et al., *Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use*, 361 NEW ENG. J. MED. 1963 (2009); Stephanie Saul, *Experts Conclude Pfizer Manipulated Studies*, N.Y. TIMES, Oct. 8, 2008, at B4 (internal quotation marks omitted).

<sup>16</sup> See Sarah Yasmin et al., *Adjunctive Gabapentin in Treatment-Resistant Depression: A Retrospective Chart Review*, 63 J. AFFECTIVE DISORDERS 243, 246 (2001) (stating that gabapentin is potentially helpful in the "management of treatment-resistant depression").

<sup>17</sup> See U.S. Food & Drug Administration, *Serious Health Risks with Antiepileptic Drugs* (Feb. 5, 2008), <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107332.htm> (finding that use of certain antiepileptics, including gabapentin, increases the risk of suicidal thoughts and behaviors by an estimated 2.1 per 1,000 patients); see also Bernadette Tansey, *Doctors Warned of Drugs' Danger: Anti-Epilepsy Medications Tied to Risk of Suicide*, S.F. CHRON., Feb. 1, 2008, at C1 (discussing the FDA's findings).

<sup>18</sup> Posting of Jim Edwards to BNET, *What Docs Didn't Know About Pfizer's Neurontin*, <http://industry.bnet.com/pharma/10003276/what-docs-didnt-know-about-pfizers-neurontin/?tag=shell;content> (July 24, 2009); see also Margaret Cronin Fisk et al., *Pfizer Faces First Trial on Neurontin Suicide Claim*, BLOOMBERG.COM, July 24, 2009, <http://www.bloomberg.com/apps/news?pid=20601127&sid=a1CYnBA5tGV4>. Pfizer's patents on the gabapentin molecule and its only approved use have expired, bringing the drug into the public domain as a generic drug. However, Pfizer has subsequently filed patents on a new form of gabapentin intended to treat neurodegenerative diseases such as Alzheimer's, Huntington's and Parkinson's disease. FED. TRADE COMM'N, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY*, at A-31 to -32 (2002), available at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>.

Rather than addressing these recent high-profile litigations, this Note will focus on the regulatory underpinnings of off-label marketing. While the FDA does not regulate a physician's decision to prescribe FDA-approved drugs for off-label uses, its recent "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" ("Guidance") does offer regulatory guidelines that permit manufacturers to use medical journals as promotional materials.<sup>19</sup> This Note will argue that this guidance is problematic for a number of reasons. First, despite its claims to the contrary, the Guidance attempts to implement a legislative rule under the guise of a non-legislative document.<sup>20</sup> Second, and more importantly, the measures proposed in the Guidance are insufficient both to protect the public and keep physicians properly informed of medical advances regarding off-label uses of prescription drugs. In effect, the current Guidance allows pharmaceutical companies to market their products for uses that have not been approved as safe and effective by the FDA.

Section I will outline the notice and comment rulemaking procedures under both the Administrative Procedure Act and the Good Guidance Practices adopted by the FDA. Section II will then recount the evolution of regulations restricting the distribution of journal articles promoting off-label uses of drugs by pharmaceutical manufacturers, while Section III will explore the current regulatory structure. Section IV will then evaluate whether the current Guidance satisfies the qualities of a guidance document, or whether it should have been promulgated as a legislative rule. Finally, Section V will recommend that the FDA replace the current Guidance with a legislative rule that prohibits manufacturers from distributing journal articles that primarily promote off-label uses for their drugs.

## I. NOTICE AND COMMENT RULEMAKING

In 1938, Congress passed the Food, Drug, and Cosmetic Act ("FDCA") in response to public outcry against the marketing of untested drugs,<sup>21</sup> delegating additional power to the FDA.<sup>22</sup> In order

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<sup>19</sup> U.S. FOOD & DRUG ADMIN., 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 (2009) [hereinafter GOOD REPRINT PRACTICES], available at <http://www.fda.gov/oc/op/goodreprint.html> (Guidance went into effect in January 2009).

<sup>20</sup> See discussion *infra* Section IV.

<sup>21</sup> See Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription*

to act within Congress's authority, the FDA must comply with the minimum requirements imposed by the APA's notice-and-comment procedures.<sup>23</sup> In addition, the FDA has created additional, self-imposed procedural requirements for interpreting the Congressional Act or carving out new legislative rules.<sup>24</sup> Taken together, these requirements shape the FDA's exercise of its rulemaking power.

Much of the FDA's regulatory power, including its ability to regulate off-label drug use, stems from its informal rulemaking authority. The Administrative Procedure Act ("APA") defines a rule as "the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency . . . ."<sup>25</sup> This definition includes legislatively binding rules, as well as policy statements, such as guidance documents, intended to establish non-binding best practices for agencies.<sup>26</sup> According to the APA, informal rules must undergo "notice and comment"<sup>27</sup> unless the agency is attempting to promulgate "interpretative rules, general statements of policy, or rules of agency organization, procedure, or practice."<sup>28</sup>

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*Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform*, 48 RUTGERS L. REV. 883, 893 (1996) ("In 1937, however, over one hundred people died and others were seriously injured as a result of ingesting a drug known as Elixir Sulfanilamide, a product which had never been tested for safety before marketing. The public outcry over the Elixir Sulfanilamide incident spurred Congress to undertake the necessary process of reforming federal drug law." (footnote omitted)).

<sup>22</sup> See *id.* at 894. The 1938 Food, Drug, and Cosmetic Act required that all new drugs be tested and reviewed for safety by the FDA before commercial distribution. *Id.* at 894.

<sup>23</sup> See James Hunnicutt, Note, *Another Reason to Reform the Federal Regulatory System: Agencies' Treating Nonlegislative Rules as Binding Law*, 41 B.C. L. REV. 153, 156-57 (1999) ("When a court reviews an agency's actions, the court looks first to the agency's organic statute and second to the APA as the default statute.").

<sup>24</sup> *Id.* at 177-78.

<sup>25</sup> Administrative Procedure Act § 1, 5 U.S.C. § 551(4) (2006).

<sup>26</sup> See Robert A. Anthony, *Interpretive Rules, Policy Statements, Guidances, Manuals, and the Like—Should Federal Agencies Use Them to Bind the Public?*, 41 DUKE L.J. 1311, 1315 (1992) [hereinafter Anthony, *Bind the Public*].

<sup>27</sup> Agencies utilizing the notice-and-comment procedure must publish a general notice of proposed rulemaking in the Federal Register, including "(1) a statement of the time, place, and nature of [the] public rule making proceedings; (2) reference to the legal authority under which the rule is proposed; and (3) either the terms or substance of the proposed rule or a description of the subjects and issues involved." 5 U.S.C. § 553(b)(1)-(3). The agency must then provide at least thirty days for interested parties to submit their data, views, or arguments for agency consideration. See *id.* § 553(c)-(d).

<sup>28</sup> *Id.* § 553(b)(A). In 2007, the Office of Management and Budget published a "Final Bulletin for Agency Good Guidance Practices," calling for the increased use of notice-and-comment procedures for significant guidance documents. See Final Bulletin for Agency Good Guidance Practices, 72 Fed. Reg. 3432 (Jan. 25, 2007).

Notice-and-comment rulemaking exists to allow for public participation and input into the informal rulemaking process.<sup>29</sup> Such participation “increases accountability and oversight, provides better quality information for both decision makers and participants, minimizes excessive influence of powerful interests, and promotes proceduralist values that enhance the fairness and legitimacy of a rule.”<sup>30</sup> Agencies can impose stricter procedures for notice-and-comment rulemaking, but the procedures outlined in the APA provide a baseline for agency action: reviewing courts turn first to the agency’s rulemaking procedures, and then to the APA procedures.<sup>31</sup>

The FDA is one of many agencies that impose stricter procedures than are required by the APA for non-legislative rulemaking.<sup>32</sup> Under section 553(b) of the APA, interpretative rules and general statements of policy do not have to go through notice-and-comment proceedings.<sup>33</sup> Despite this exemption, the FDA, however, still imposes requirements akin to notice and comment on its interpretative rules and general policy statements, placing both under the umbrella of guidance documents. FDA guidance documents include “documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency’s interpretation of or policy on a regulatory issue.”<sup>34</sup> Guidance documents are subject to two different levels of public scrutiny based on the nature of the document. Level 1 guidance documents “(i) [s]et forth initial interpretations of statutory or regulatory requirements; (ii) [s]et forth changes in interpretation or policy that are of more than a minor nature; (iii) [i]nclude complex scientific issues; or (iv) [c]over highly controversial issues.”<sup>35</sup> Level 2 guidance documents include all guidance documents not classified as Level 1 that “set forth existing practices or minor changes in interpretation or policy.”<sup>36</sup>

For Level 1 guidance documents, the FDA must publish a notice of proposed rulemaking in the Federal Register and invite public comment, requirements that largely<sup>37</sup> mirror the APA notice-and-

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<sup>29</sup> See Stephanie Stern, *Cognitive Consistency: Theory Maintenance and Administrative Rulemaking*, 63 U. PITT. L. REV. 589, 594 (2002).

<sup>30</sup> *Id.*

<sup>31</sup> See Hunnicutt, *supra* note 23, at 156–57 (“When a court reviews an agency’s actions, the court looks first to the agency’s organic statute and second to the APA as the default statute.”).

<sup>32</sup> Good Guidance Practices, 21 C.F.R. § 10.115 (2009).

<sup>33</sup> 5 U.S.C. § 553(b)(A).

<sup>34</sup> 21 C.F.R. § 10.115(b).

<sup>35</sup> *Id.* § 10.115(c)(1)(i)–(iv).

<sup>36</sup> *Id.* § 10.115(c)(2).

<sup>37</sup> See *id.* § 10.115(g)(1)–(3).

comment procedures for legislative rules.<sup>38</sup> Even after the Level 1 document has been finalized, the public can continue submitting comments for consideration should the agency deem it appropriate to undertake future revisions.<sup>39</sup> In comparison, Level 2 guidance documents are implemented as soon as the FDA posts the document on the Internet.<sup>40</sup> The FDA still allows for the submission of public comments following publication of Level 2 guidance documents, and reserves the right to revise the documents when appropriate.<sup>41</sup>

## II. THE EVOLUTION OF OFF-LABEL REGULATION

As a default rule, the FDCA prohibits the marketing of drugs for uses the FDA has not approved.<sup>42</sup> However, both Congress and the FDA have sought to make a limited exception to the rule in the case of marketing through scholarly journal articles.<sup>43</sup> On December 8, 1995, the FDA published two draft guidance documents addressing the dissemination of journal articles: “Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data” and “Guidance for Industry Funded Dissemination of Reference Texts” (collectively, “Guidance Documents”).<sup>44</sup> The Guidance Documents permit dissemination of journal articles promoting off-label uses so long as: (1) the principal subject of the article is a use approved by the FDA; (2) the article is published in a peer-reviewed journal; (3) the information that is different from the drug’s FDA approval is clearly labeled; and (4) the reprint discloses all material facts without being false or misleading.<sup>45</sup> The FDA allowed interested parties to submit comments until January 5, 1996, and finalized the Guidance Documents on October 8, 1996, noting that the guidelines “strike the proper balance between the need for an exchange of reliable scientific

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<sup>38</sup> *See id.*

<sup>39</sup> *See id.* § 10.115(g)(3)(i)–(ii).

<sup>40</sup> *See id.* § 10.115(g)(4)(i)(A)–(B).

<sup>41</sup> *See id.* §§ 10.115(g)(4)(i)(C) & (g)(4)(ii).

<sup>42</sup> *See* 21 U.S.C. §§ 331(d), 355(a) (2006) (banning the introduction of drugs into interstate commerce without FDA approval); *see also* 21 C.F.R. § 202.1(e)(6) (2009) (setting forth the circumstances under which drug advertisements are false, lacking in fair balance, or misleading, and therefore in violation of the FDCA’s prohibition against misbranded drugs); Letter from Henry A. Waxman, Chairman, Committee on Oversight and Government Reform, to Andrew C. von Eschenbach, Commissioner, U.S. Food & Drug Admin. (Nov. 30, 2007), available at [http://online.wsj.com/public/resources/documents/waxmanletter\\_113007.pdf](http://online.wsj.com/public/resources/documents/waxmanletter_113007.pdf) (arguing against a proposed agency loophole that would allow circumvention of FDA approval for off-label drug use).

<sup>43</sup> *See* Food & Drug Administration Modernization Act, 21 U.S.C. § 360aaa-1 (2006); GOOD REPRINT PRACTICES, *supra* note 19.

<sup>44</sup> Advertising and Promotion; Draft Guidances; Republication, 60 Fed. Reg. 63,384 (Dec. 8, 1995).

<sup>45</sup> *Id.* at 63,384–85.



data and information within the health care community, and the statutory requirements that prohibit companies from promoting products for unapproved uses.”<sup>46</sup>

In 1998, the Washington Legal Foundation (“WLF”), a nonprofit public interest law and policy center, sought to enjoin the FDA from enforcing the policies put in place by the two guidance documents.<sup>47</sup> As relief, the WLF sought a declaratory judgment “that the FDA policies expressed in the Guidance Documents violate the rights of its members under the First Amendment of the Constitution.”<sup>48</sup> Specifically, the WLF alleged that the use of journal articles to promote off-label uses of FDA-approved pharmaceuticals qualified as protected free speech.<sup>49</sup>

In *Washington Legal Foundation v. Friedman*,<sup>50</sup> the United States District Court for the District of Columbia held that the Guidance Documents were an unconstitutional restriction of commercial speech.<sup>51</sup> The court applied the three-factor test set forth in *Bolger v. Youngs Drug Products Corp.*<sup>52</sup> for determining whether speech qualifies as “commercial speech.”<sup>53</sup> *Bolger* established that the First Amendment affords a lesser degree of protection to commercial speech because such speech does “no more than propose a commercial transaction.”<sup>54</sup> The three factors are: (1) whether the speech was an advertisement; (2) whether the speech referred to a specific product; and (3) whether there was an economic motivation in conducting the speech.<sup>55</sup>

In *Bolger*, Youngs Drug Products Corporation attempted to mail the general public unsolicited advertisements containing information about its products, along with information regarding venereal disease and family planning.<sup>56</sup> The government sought to enforce a federal statute that prohibited companies from mailing unsolicited

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<sup>46</sup> Advertising and Promotion; Guidances, 61 Fed. Reg. 52,800 (Oct. 8, 1996).

<sup>47</sup> Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 54 (D.D.C. 1998), *amended by* 36 F. Supp. 2d 16 (D.D.C. 1999), *appeal dismissed & vacated in part sub nom.* Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

<sup>48</sup> *Id.*

<sup>49</sup> *See id.* at 59.

<sup>50</sup> 13 F. Supp. 2d 51, 54 (D.D.C. 1998), *amended by* 36 F. Supp. 2d 16 (D.D.C. 1999), *appeal dismissed & vacated in part sub nom.* Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

<sup>51</sup> *See id.* at 72–74.

<sup>52</sup> 463 U.S. 60 (1983).

<sup>53</sup> Wash. Legal Found., 13 F. Supp. 2d at 64.

<sup>54</sup> *Id.* at 66 (quoting Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc., 425 U.S. 748, 762 (1976)) (internal quotation marks omitted).

<sup>55</sup> *See id.* at 66–67 (noting that all three factors must be present for speech to be “commercial”).

<sup>56</sup> *See id.* at 62.

contraceptive advertisements.<sup>57</sup> The Court held that the pamphlets were advertisements,<sup>58</sup> that the pamphlets made reference to the specific contraceptive product, and that Youngs had an economic motivation for mailing the pamphlets.<sup>59</sup> Separately, each factor would have been insufficient to constitute commercial speech.<sup>60</sup> All together, however, the factors supported the Court's conclusion that despite the informational nature of the pamphlets, the communication constituted commercial speech.<sup>61</sup>

Applying these factors in *Washington Legal Foundation*, the district court held that the dissemination of journal articles qualified as an advertisement despite the fact that the manufacturer was communicating the words of others.<sup>62</sup> While the court acknowledged that "[s]cientific and academic speech reside at the core of the First Amendment,"<sup>63</sup> the court clarified that directing attention to favorable information also qualifies as an advertisement.<sup>64</sup> Since the journal article advertisements referred to a particular product and the manufacturer had a clear economic motive to disseminate them, the communication qualified as commercial speech.<sup>65</sup> The court then turned to the question whether the manufacturer's commercial speech was constitutionally protected under the First Amendment.<sup>66</sup>

Whether commercial speech is entitled to First Amendment protection is determined using the test set forth in *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*.<sup>67</sup> In *Central Hudson*, a gas and electricity company challenged a ban on advertisements promoting the use of electricity in New York.<sup>68</sup> The Supreme Court used the following four-part analysis to determine whether the ban on commercial speech was constitutional:

At the outset, we must determine whether the expression is protected by the First Amendment. For commercial speech to come within that provision, it at least must concern lawful activity and not be misleading. Next, we ask whether the asserted governmental interest is substantial. If both inquiries

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<sup>57</sup> See *id.* at 63.

<sup>58</sup> *Id.* at 66 (quoting *Va. State Bd. of Pharmacy*, 425 U.S. at 762).

<sup>59</sup> See *id.* at 66–67.

<sup>60</sup> *Id.*

<sup>61</sup> *Id.* at 67.

<sup>62</sup> *Id.* at 62–63.

<sup>63</sup> *Id.* at 62.

<sup>64</sup> See *id.* at 63.

<sup>65</sup> See *id.* at 63–65.

<sup>66</sup> *Id.* at 65.

<sup>67</sup> 447 U.S. 557 (1980).

<sup>68</sup> See *id.* at 560.

yield positive answers, we must determine whether the regulation directly advances the governmental interest asserted, and whether it is not more extensive than is necessary to serve that interest.<sup>69</sup>

Thus, in certain situations, the government can restrict commercial speech consistent with the First Amendment.

Applying the four prongs of the *Central Hudson* test in *Washington Legal Foundation*, the district court first held that the commercial speech was “neither unlawful nor inherently misleading” because prescribing drugs for off-label purposes was not illegal.<sup>70</sup> The court reasoned that since the journal articles were describing the benefits of off-label uses without pharmaceutical involvement, they were not deceptive or coercive speech; nor were they inherently misleading.<sup>71</sup> Second, the court held that, in addition to the government’s substantial interest in protecting the “health and safety of its citizens,”<sup>72</sup> the FDA also had a substantial interest in incentivizing manufacturers to “get off-label uses on-label”<sup>73</sup> by applying for supplemental new drug applications.<sup>74</sup> The district court further held that the Guidance Documents’ restrictions directly advanced this substantial interest by controlling labeling, marketing, and advertising efforts of off-label uses in order to incentivize manufacturers to seek further approval.<sup>75</sup>

Examining the fourth prong of the *Central Hudson* test, however, the court found that the Guidance Documents were an unconstitutional restriction on commercial speech because they used overly restrictive means to satisfy the FDA’s purposes.<sup>76</sup> The court reasoned that the “full, complete, and unambiguous disclosure by the manufacturer” of off-label uses served as a less-burdensome alternative that would address the FDA’s concerns more effectively than the measures contained in the Guidance Documents.<sup>77</sup> The court noted that disclosure would inform physicians of the potential for misleading bias, and that the narrow scope of the communication

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<sup>69</sup> *Id.* at 566.

<sup>70</sup> *Wash. Legal Found.*, 13 F. Supp. 2d at 65–66.

<sup>71</sup> *See id.* at 67–68.

<sup>72</sup> *Id.* at 69.

<sup>73</sup> *Id.* at 70.

<sup>74</sup> *See id.* at 71. However, the court rejected the proposition that the government had a substantial interest in ensuring that physicians can make informed prescription choices based on accurate and unbiased information, since the fear that physicians might misuse the information, without more, was deemed unsupported. *Id.* at 69–70.

<sup>75</sup> *Id.* at 72.

<sup>76</sup> *See id.* at 72–74.

<sup>77</sup> *Id.* at 73.

through journal articles still provides manufacturers incentives to get FDA approval for off-label uses in order to use alternative marketing efforts.<sup>78</sup> The court also noted that physicians are reluctant to prescribe drugs without FDA approval, and that off-label uses are the most effective treatment for many conditions.<sup>79</sup>

In 1997, the FDA passed section 401 of the Food and Drug Administration Modernization Act (“FDAMA”),<sup>80</sup> which explicitly created a safe harbor from the prohibition on marketing off-label use for journal articles.<sup>81</sup> Although the bill was signed into law on November 21, 1997, it did not go into effect until a year after its enactment,<sup>82</sup> and therefore did not apply to *Washington Legal Foundation*.<sup>83</sup> The FDAMA required that manufacturers label articles as promoting off-label use if: (1) the information related to a use unapproved by the FDA; (2) the manufacturer paid to disseminate the information; or (3) the authors had a significant financial interest in the manufacturer.<sup>84</sup> In addition, the manufacturer was required to include a bibliography of other relevant scientific publications.<sup>85</sup> Manufacturers were required to submit medical journal articles to the FDA before distributing them, and had to agree to file a supplemental new drug application expanding FDA approval for the drug to its off-label use within three years of the journal’s initial dissemination by the manufacturer.<sup>86</sup> The FDAMA, however, included a sunset provision that caused the law and any regulations promulgating it to expire on September 30, 2006.<sup>87</sup> Since Congress failed to renew the Act, the law regarding off-label use reverted to the prior framework that prohibited any promotion for strictly unapproved uses.<sup>88</sup>

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<sup>78</sup> *See id.*

<sup>79</sup> *See id.*

<sup>80</sup> Pub. L. No. 105-115, § 401, 111 Stat. 2295, 2356–65 (1997) (codified as amended at 21 U.S.C. § 360aaa (2006)) (repealed 2006).

<sup>81</sup> Bruce Patsner, *Promotion of Off-Label Uses of Prescription Medical Products: FDA’s Proposed New Guidance*, HEALTH L. PERSP., June 2008, at 1, 3, available at [http://www.law.uh.edu/healthlaw/perspectives/2008/\(BP\)%20off%20label.pdf](http://www.law.uh.edu/healthlaw/perspectives/2008/(BP)%20off%20label.pdf).

<sup>82</sup> FDAMA § 401(d), 111 Stat. at 2364 (1997).

<sup>83</sup> *See Wash. Legal Found.*, 13 F. Supp. 2d at 58.

<sup>84</sup> 21 U.S.C. § 360aaa(b)(6)(A)(i)–(iii) (repealed 2006).

<sup>85</sup> *Id.* § 360aaa(b)(6)(B).

<sup>86</sup> *See* Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 21 C.F.R. § 99 (2009).

<sup>87</sup> *See* FDAMA § 401(e), 111 Stat. at 2364; Press Release, U.S. Food & Drug Admin., FDA Proposes Guidance for Dissemination of Information on Unapproved Uses of Medical Products (Feb. 15, 2008), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116859.htm>.

<sup>88</sup> Patsner, *supra* note 81, at 1, 3.

## III. THE CURRENT GUIDANCE

The FDA attempted to fill the regulatory twilight left in the wake of the FDAMA's sunset provision with a new draft guidance document. A copy of an internal draft reached the Congressional Committee on Oversight and Government Reform, leading the Committee's Chairman Henry Waxman to write an appeal to Dr. Andrew C. von Eschenbach, Commissioner of the FDA.<sup>89</sup> The letter noted that "[t]he draft guidance . . . would, in effect, allow drug and device companies to short-circuit FDA review and approval by sponsoring drug trials that are carefully constructed to deliver positive results and then using the results to influence prescribing patterns."<sup>90</sup> Congressman Waxman went on to state that "[t]he draft guidelines appear to be an effort by [the] FDA to displace Congress and establish by administrative fiat a new system for use of journal articles that lacks the safeguards set by Congress . . . permit[ing] far more dissemination of articles on unapproved uses than was sanctioned under [the] FDAMA."<sup>91</sup> In his reply, Dr. von Eschenbach noted that the proper time to comment on the draft guidance would be after the draft guidance completed internal review and was subjected to public comment through the Federal Register.<sup>92</sup>

On February 15, 2008, the FDA published the draft guidelines in the Federal Register, accepting public comment until April 15, 2008 as a Level 1 guidance document. The rule was finalized on January 13, 2009.<sup>93</sup> According to the Guidance, drug manufacturers should only reprint scientific or medical journal articles that are published in peer-reviewed journals with an editorial board of experts, and that require all involved parties to disclose conflicts of interest.<sup>94</sup> Journal articles promoting off-label uses should not originate in a special supplement or journal funded by the manufacturer, and should not be primarily distributed by the manufacturer.<sup>95</sup> The articles should not be

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<sup>89</sup> Letter from Henry A. Waxman, Chairman, Comm. on Oversight & Gov't Reform to Andrew C. von Eschenbach, Commissioner, M.D., Comm'r, U.S. Food & Drug Admin. (Nov. 30, 2007), available at [http://online.wsj.com/public/resources/documents/waxmanletter\\_113007.pdf](http://online.wsj.com/public/resources/documents/waxmanletter_113007.pdf).

<sup>90</sup> *Id.* at 1.

<sup>91</sup> *Id.* at 5-6.

<sup>92</sup> See Letter from Stephen R. Mason, Acting Assistant Comm'r for Legislation, U.S. Food & Drug Admin. to Henry A. Waxman, Chairman, Comm. on Oversight & Gov't Reform (Dec. 21, 2007).

<sup>93</sup> 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; Availability, 74 Fed. Reg. 1694 (Jan. 13, 2009).

<sup>94</sup> GOOD REPRINT PRACTICES, *supra* note 19, at 4.

<sup>95</sup> *Id.*

written, edited, excerpted, or published by the manufacturer, and must be distributed in their entirety without markings or characterizations from the manufacturer.<sup>96</sup> The information in the articles should not be false or misleading and cannot pose a “significant risk to the public health.”<sup>97</sup> In addition, the article should be accompanied by a “comprehensive bibliography of publications discussing adequate and well-controlled clinical studies” published about the use, as well as copies of any articles that specifically call its veracity into question.<sup>98</sup> The article should not accompany the product, and should be distributed separately from promotional materials.<sup>99</sup> Finally, the article should include a statement disclosing the following: (1) that the use has not been approved by the FDA; (2) the manufacturer’s interest in the drug; (3) any author known to have a financial relationship with the manufacturer; (4) any person known to have provided funding for the study; and (5) any significant risks known by the manufacturer that are not discussed in the journal article.<sup>100</sup>

Several significant concerns were raised in the notice-and-comment proceedings for the now-finalized draft guidance. The American Medical Association, for instance, expressed concern that the current system of peer-review for medical journals would be incapable of identifying inaccurate and unbiased articles, citing several industry practices that complicate their vetting processes.<sup>101</sup> Furthermore, the Illinois and Oregon attorneys general noted that three elements present in the FDAMA’s prior legislation were omitted in the Draft Guidance.<sup>102</sup> These omissions would significantly reduce the ability of both the FDA and state attorneys to limit deceptive practices.<sup>103</sup> In particular, the attorneys general noted that the Draft Guidance eliminates requirements that:

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<sup>96</sup> *Id.* at 4–5.

<sup>97</sup> *Id.* at 5.

<sup>98</sup> *Id.* at 5–6.

<sup>99</sup> *Id.* at 6.

<sup>100</sup> *Id.*

<sup>101</sup> See Letter from Michael D. Maves, Executive Vice President & CEO, Am. Med. Ass’n., to Div. of Dockets Mgmt., Food & Drug Admin. (Apr. 15, 2008), available at <http://www.regulations.gov/fdmspublic/ContentViewer?objectId=0900006480509aea&disposition=attachment&contentType=pdf> (submitting comments on the Draft Guidance that discussed the AMA’s concerns about the peer-review process as a safeguard against industry manipulation).

<sup>102</sup> See Letter from Lisa Madigan, Illinois Attorney General and Hardy Myers, Oregon Attorney General, to Div. of Dockets Mgmt., Food & Drug Admin. 1–2 (Apr. 21, 2008), available at <http://www.regulations.gov/fdmspublic/ContentViewer?objectId=0900006480518fe6&disposition=attachment&contentType=pdf> (commenting on the Draft Guidance and urging the FDA to adopt additional safeguards to prevent manufacturers from using the loophole to avoid the approval process).

<sup>103</sup> *Id.* at 1.

1) Drug manufacturers must have filed an application for FDA approval of the new use of the drug before that off-label use can be discussed in medical literature to be distributed to health professionals; 2) Medical literature must be submitted to the FDA for review before the information is distributed to medical professionals; and 3) Drug manufacturers must biannually prepare and submit a list of all the articles and references on the new use that were disseminated to health professionals, and a list of the categories of providers that received the literature pertaining to the new use.<sup>104</sup>

The final guidance document responded to some of these concerns. In particular, the FDA noted that, due to the sunset of section 401 of the FDAMA, mandatory review practices were outside the agency's purview.<sup>105</sup> In an attempt to respond to concerns that pharmaceutical companies would use journal articles to indefinitely promote off-label uses without applying for new FDA approval, the FDA also added a section to the finalized Guidance encouraging manufacturers to seek FDA approval for new uses of FDA-approved drugs.<sup>106</sup>

It is important to note that the timing of the guidance document's finalization was likely influenced by the political climate. In a public letter dated September 17, 2008, Democratic Congressman Henry A. Waxman accused FDA Commissioner von Eschenbach of prioritizing pharmaceutical industry desires over consumer interests.<sup>107</sup> According to the letter, the FDA, in anticipation of the changing administration, planned to push through a number of measures highly favorable to drug companies "in record time."<sup>108</sup> Furthermore, the FDA timed the publication of the final version of the Guidance during President Bush's last week in office, creating the appearance that it was passing a midnight regulation.<sup>109</sup>

Midnight regulations describe the "systematic tendency across time and across parties to increase regulatory volumes during the

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<sup>104</sup> *Id.* at 1–2.

<sup>105</sup> 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; Availability, 74 Fed. Reg. 1694 (notice Jan. 13, 2009) ("The sunset of [Section 401] eliminated the authority of FDA to require submission of articles for the agency's review before dissemination . . .").

<sup>106</sup> See *id.*

<sup>107</sup> See Letter from Henry A. Waxman, Chairman, Comm. on Oversight & Gov't Reform, to Andrew C. von Eschenbach, Comm'r, U.S. Food & Drug Admin. (Sept. 17, 2008), available at <http://www.pharmalive.com/News/download.cfm?articleid=572507&attachmentid=83365>.

<sup>108</sup> See *id.* at 2.

<sup>109</sup> See Lisa Richwine, *FDA Lets Drugmakers Advise Doctors on Unapproved Uses*, REUTERS, Jan. 12, 2009, <http://www.reuters.com/article/domesticNews/idUSTRE50C0QK20090113>.

waning days of an administration.”<sup>110</sup> During midnight periods, agency accountability to the public is largely absent, since administrations attempt to either postpone their actions until after elections in order to avoid political fallout, or hurry to implement the administration’s agenda before the change of administration in the next political term.<sup>111</sup> Avoiding public accountability runs counter to one purpose of the notice-and-comment procedure.

Generally, agencies do not devote resources to issuing non-legislative rules as midnight regulations. Since non-legislative rules such as guidance documents are intended to create general policies rather than binding law, the value of rushing legislation through is diminished. Moreover, since non-legislative rules are not intended to create practically binding norms, administrations generally have less reason to be concerned about political fallout stemming from guidance documents.<sup>112</sup> Thus, under the Clinton administration, only one interpretive rule and one policy statement were issued between November 5, 2000 and the end of his administration.<sup>113</sup> Since the APA generally requires agencies to follow the same procedures for promulgation and revocation of regulations, most interpretive rules or policy statements can be revoked relatively easily by publishing notice of revocation in the Federal Register.<sup>114</sup> However, since the FDA uses the more extensive notice-and-comment procedure for its guidance documents, that might impose a greater burden on the subsequent administration.<sup>115</sup> In light of the history of midnight regulations, the FDA’s decision to release the Guidance so close to the end of the Bush Administration seems to be a break from tradition, warranting closer scrutiny into the true nature of the Guidance.

#### IV. SHOULD THE GUIDANCE BE A LEGISLATIVE RULE?

The FDA promulgated a functionally binding legislative rule in the guise of a non-binding guidance document. Upon first impression, the

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<sup>110</sup> Jason M. Loring & Liam R. Roth, *After Midnight: The Durability of the “Midnight” Regulations Passed by the Two Previous Outgoing Administrations*, 40 WAKE FOREST L. REV. 1441, 1442 (2005) (quoting Jay Cochran, III, *The Cinderella Constraint: Why Regulations Increase Significantly During Post-Election Quarters* 15 (Mar. 8, 2001) (unpublished working paper), available at [http://mercatus.org/sites/default/files/publication/The\\_Cinderella\\_Constraint\(1\).pdf](http://mercatus.org/sites/default/files/publication/The_Cinderella_Constraint(1).pdf)) (internal quotation marks omitted).

<sup>111</sup> See *id.* at 1446–47.

<sup>112</sup> Jack M. Beermann, *Presidential Power in Transitions*, 83 B.U. L. REV. 947, 969 (2003).

<sup>113</sup> See *id.* at 967.

<sup>114</sup> See *id.* at 994.

<sup>115</sup> See *id.*



FDA's Guidance resembles a guidance document. In addition to explicitly referring to itself as such, the header notes that:

This guidance document represents the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You may use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, please contact the appropriate FDA staff.<sup>116</sup>

In recent years, agencies are increasingly issuing guidance documents "in lieu of engaging in the more costly, *and binding*, informal rulemaking process . . . ."<sup>117</sup> Professor Robert Anthony has observed that agencies improperly use guidance documents to impose practically binding rules on the regulated or benefited public.<sup>118</sup> The misuse of guidance documents by federal agencies, in particular, has drawn attention from Congress, corporations, and academics as a backdoor method of creating binding norms without following the proper procedures.<sup>119</sup> The misuse of informal rulemaking instruments, such as guidance documents, to create practically binding norms makes it necessary to inquire whether regulating the dissemination of journal articles by manufacturers should have been issued as a binding legislative rule, a non-binding policy statement or guidance document, or as a congressionally authorized statute.

In *Community Nutrition Institute v. Young*,<sup>120</sup> the court addressed the language necessary to make a regulation legally and practically binding. In *Community Nutrition*, a regulation purported by the FDA to be a policy statement limiting the amount of "'poisonous or deleterious substances' in food" was challenged due to the legally binding effect of the regulation.<sup>121</sup> Although the FDA claimed the regulation's action levels were not binding, the use of mandatory,

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<sup>116</sup> GOOD REPRINT PRACTICES, *supra* note 19.

<sup>117</sup> Gwendolyn McKee, *Judicial Review of Agency Guidance Documents: Rethinking the Finality Doctrine*, 60 ADMIN. L. REV. 371, 372 (2008) (emphasis added).

<sup>118</sup> See Anthony, *Bind the Public*, *supra* note 26, at 1315 (arguing that agency guidance, to the extent it goes beyond interpreting the regulatory language, should not bind the public).

<sup>119</sup> See Christopher E. Wilson, Comment, *Not Good Enough For Government Work: How OMB's Good Guidance Practices May Unintentionally Complicate Administrative Law*, 59 ADMIN. L. REV. 177, 181 (2007) (noting that, despite guidance producing some positive effects, its misuse has been a major cause for concern).

<sup>120</sup> 818 F.2d 943 (D.C. Cir. 1987) (per curiam).

<sup>121</sup> *Id.* at 945 (citation omitted).

definitive language in the text gave the regulation binding force.<sup>122</sup> Since the purported policy statement did not go through notice-and-comment procedures, the court held that the FDA violated APA procedural requirements and invalidated the regulation.<sup>123</sup>

Legislative rules are distinguishable from non-legislative rules, such as interpretive rules and policy statements, because they bind, or attempt to bind, the affected public.<sup>124</sup> Legislative rules include rules that purport to be legally binding, as well as rules that have the practical effect of binding the public.<sup>125</sup> Robert Anthony explains that non-legislative rules are practically binding to the affected public “if the agency treats it the same way it treats a legislative rule—that is, as dispositive of the issues that it addresses—or leads the affected public to believe it will treat the document that way.”<sup>126</sup> In contrast, interpretive rules merely seek to interpret existing law rather than create new law, and policy statements create general statements of policy or procedure that are neither binding nor interpretive.<sup>127</sup>

The FDA’s finalized Guidance regarding manufacturer distribution of journal articles recognized that the lapsed FDAMA had created a safe harbor rather than an interpretation of the limitations on drug marketing in the FDCA.<sup>128</sup> In doing so, the FDA accepted that Congress banned the promotion of off-label drug usage through the FDCA, but then created a legislative exception to that rule that mirrored the FDAMA’s provision. So rather than interpreting an existing rule, the FDA sought to amend the existing rule to provide a safe harbor. And while the Guidance uses clear language disclaiming any intent to be legally binding,<sup>129</sup> a number of factors indicate that the practical effect of the rule will be to create a practically binding norm.

According to the Government Accountability Office (“GAO”), the FDA issued 117 regulatory letters for “violative promotions of prescription drugs” between 2003 and 2007.<sup>130</sup> Of these regulatory letters, 42 were in response to off-label promotional efforts.<sup>131</sup> Half of

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<sup>122</sup> See *id.* at 947.

<sup>123</sup> *Id.* at 948–49.

<sup>124</sup> See Anthony, *Bind the Public*, *supra* note 26, at 1314.

<sup>125</sup> See *id.* at 1327 (noting that when agencies issue rules and claim they are nonlegislative, courts must still determine whether the rules are binding).

<sup>126</sup> *Id.* at 1328.

<sup>127</sup> See Robert A. Anthony, “Interpretive” Rules, “Legislative” Rules and “Spurious” Rules: *Lifting the Smog*, 8 ADMIN. L.J. AM. U. 1, 7, 11 (1994) [hereinafter Anthony, *Lifting the Smog*].

<sup>128</sup> See GOOD REPRINT PRACTICES, *supra* note 19.

<sup>129</sup> *Id.*

<sup>130</sup> GAO REPORT, *supra* note 11, at 3.

<sup>131</sup> *Id.* at 6.

the letters pertaining to off-label promotions addressed materials specifically targeted at physicians that would be governed under the auspices of the new Guidance.<sup>132</sup> FDA officials with the Division of Drug Marketing, Advertising, and Communications (“DDMAC”) informed the GAO that drug companies had complied with the letters, so the FDA did not pursue enforcement action through the Department of Justice.<sup>133</sup> During this time period, drug companies could challenge the FDA’s regulatory letter and negotiate to avoid taking corrective measures by petition.<sup>134</sup> While DDMAC officials noted that drug companies would occasionally engage in extensive discussions challenging agency assessments, between 2003 and 2007, the FDA did not reverse any of its decisions requiring drug companies to cease disseminating violative off-label promotions.<sup>135</sup> Thus, while the FDA’s judgments were non-binding in name, they had a practically binding effect on drug companies.

Tens of thousands of promotional materials are submitted to the FDA for review every year.<sup>136</sup> The DDMAC informed the GAO that they received more materials than the agency could review.<sup>137</sup> Since the FDA is overburdened, it exercises its discretion in pursuing claims against only a fraction of materials it actually reviews.<sup>138</sup> Under the new Guidance, the FDA is purportedly not legally bound to follow its guidelines since the document uses discretionary language instead of mandatory language. However, if prior enforcement history is any indication, the manufacturers should expect to be *practically* bound by the guidelines and therefore subject to a legislative rule. According to DDMAC officials and the GAO’s analysis, drug companies generally comply with the actions requested in FDA regulatory letters.<sup>139</sup> Furthermore, every time a drug company contested an FDA determination during the five-year period covered in the GAO report, the FDA upheld its regulatory decision.<sup>140</sup>

The FDA may be tempted to argue that since both Level 1 guidance documents and legislative rules go through substantially similar notice-and-comment procedures, the distinction between the two is moot. The Good Guidance Practices adopted by the FDA that require notice-and-comment proceedings for Level 1 guidance

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<sup>132</sup> *Id.* at 20.

<sup>133</sup> *See id.* at 6.

<sup>134</sup> *See id.* at 22.

<sup>135</sup> *Id.*

<sup>136</sup> *See id.* at 17 fig.1.

<sup>137</sup> *Id.* at 16.

<sup>138</sup> *Id.* at 5.

<sup>139</sup> *Id.* at 6.

<sup>140</sup> *See id.* at 22.

documents are non-binding;<sup>141</sup> so as long as the FDA can present an appropriate justification for deviating from the guidance, the rule is merely subject to APA procedures. And since both the APA and Level 1 guidance documents are subject to almost identical notice-and-comment procedures,<sup>142</sup> the Guidance essentially satisfied the requirements for legislative rulemaking under the APA.

While the Guidance assiduously complied with the procedural formalities necessary to create binding law, it failed to provide proper notice to the public of its practically binding intent. Issuing notice prior to rulemaking serves a signaling purpose to the public. A private party examining a Level 1 guidance document replete with non-binding language is more likely to overlook or disregard the document, and trust the agency to utilize its discretion.<sup>143</sup> That same party, however, might take a binding legislative rule more seriously.<sup>144</sup> Because of its failure to issue notice of its intent to create a binding rule, the FDA denied the public the opportunity to knowingly participate in notice-and-comment procedures for the creation of a binding, legislative rule. As Robert Anthony explains, regulations that purport to be policy statements but are practically treated as binding by the agency should be invalidated as an attempt to circumvent the legislative rulemaking procedures.<sup>145</sup> Here, when it issued the final Guidance as a midnight regulation mere days before a change of administration, the FDA attempted to minimize the political accountability of decision makers.<sup>146</sup> And by issuing its rule under the guise of a discretionary policy, the FDA attempted to downplay the potential impact of the Guidance, which was intended to be both substantive and binding.<sup>147</sup> Because the FDA has failed to satisfy the informal rulemaking procedures required under the APA for binding legislative rules, the Guidance should be invalidated.

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<sup>141</sup> See Good Guidance Practices, 21 C.F.R. § 10.115(d) (2009).

<sup>142</sup> See discussion *supra* p. 536–37 (discussing public scrutiny requirements for Level 1 guidance documents).

<sup>143</sup> See Hunnicutt, *supra* note 23, at 181

<sup>144</sup> *Id.*

<sup>145</sup> See Anthony, *Lifting the Smog*, *supra* note 127, at 10 (classifying such regulations as “spurious rules,” and asserting that, while these rules are technically policy statements, they should not be exempt from APA requirements for legislative rulemaking).

<sup>146</sup> See *supra* notes 110–11 and accompanying text (discussing the general absence of agency accountability during “midnight” periods).

<sup>147</sup> See discussion *supra* Section III (noting that despite disclaimers of intent, the Guidance will create a legally binding norm).

## V. PROPOSAL FOR A LEGISLATIVE RULE

As a result of the procedural problems in the formulation of the current Guidance, the FDA should issue a revised legislative rule through notice and comment that not only clearly indicates its binding nature, but also grants the public a chance to provide the FDA with informed input about the rule. The FDA should use this opportunity to reintroduce previously abandoned limitations on drug companies to ensure that physicians have information that will promote the safest medical treatment for their patients' conditions. The new rule should reinstate the terms of the 1996 Guidance Documents, paired with the FDAMA constraints.<sup>148</sup> In particular, manufacturers should be required to file a supplemental new drug application for the new use prior to disseminating journal articles primarily promoting an off-label use, and manufacturers should be limited to distributing journal articles that primarily address FDA approved uses of the drug.<sup>149</sup>

The purpose of the FDA approval process is to ensure that drugs are not approved unless they are "safe and effective."<sup>150</sup> Due to numerous precautions taken in the approval process, however, the FDA delays the availability of a host of potentially life-saving treatments.<sup>151</sup> Allowing physicians to issue drugs for off-label use helps to reduce the potential loss of life by granting physicians greater freedom over the treatment process.<sup>152</sup> However, the current Guidance provides a backdoor that allows manufacturers to market pharmaceutical drugs for new off-label uses and circumvent the FDA approval process entirely.<sup>153</sup> As Dr. Aaron S. Kesselheim asks, "[i]f a drug company can go directly to the physician with its published trials without having to go through the FDA first, why would it ever go before the FDA?"<sup>154</sup> Reinstating the requirement from the lapsed FDAMA<sup>155</sup> that manufacturers must first submit a supplemental new drug application for a given off-label use before distributing journal

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<sup>148</sup> Advertising and Promotion; Guidances; Republication, 61 Fed. Reg. 52,800 (Oct. 8, 1996); Food and Drug Administration Modernization Act, 21 U.S.C. § 360aaa (repealed 2006).

<sup>149</sup> Advertising and Promotion; Guidances; Republication, 61 Fed. Reg. at 52,801; 21 U.S.C. § 360aaa-3.

<sup>150</sup> Jonathan H. Adler, *More Sorry than Safe: Assessing the Precautionary Principle and the Proposed International Biosafety Protocol*, 35 TEX. INT'L L.J. 173, 195 (2000).

<sup>151</sup> *Id.* at 195. For instance, during the nine-and-a-half-month review process for Misoprostol, a drug that prevents gastric ulcers, the drug could have saved as many as 8,000 to 15,000 lives. *Id.* at 196.

<sup>152</sup> See Stafford, *supra* note 10.

<sup>153</sup> See Mike Mitka, *Critics Say FDA's Off-Label Guidance Allows Marketing Disguised as Science*, 299 JAMA 1759, 1759 (2008).

<sup>154</sup> *Id.* at 1760.

<sup>155</sup> 21 U.S.C. § 360aaa-3 (repealed 2006).

articles to physicians that primarily focus on that use would still give physicians access to potentially life-saving information, while ensuring that drug companies do not have the unrestrained ability to market their drugs for any use supported by a mere scintilla of evidence.

However, requiring manufacturers to apply for the expansion of supplemental drug applications is not enough to properly protect patients. Manufacturers would still be incentivized to apply for drugs under narrow uses supported by copious amounts of research in order to receive the drug's initial certification, and then attempt to drastically extend the scope of the drug's use by filing applications for new uses of the drug. Supplemental new drug applications can take even longer to approve than the initial application for FDA approval,<sup>156</sup> so manufacturers could extensively market off-label uses while awaiting the FDA's response. Therefore, the FDA should also restrict manufacturers awaiting approval through the supplemental process to distributing articles that deal primarily with the drug's already approved purpose. Physicians would still be able to read articles detailing off-label uses of drugs in medical journals or through conversations with their peers.

Admittedly, the court in *Washington Legal Foundation* found the 1996 Guidance Documents unconstitutional, holding the limitations on article distribution to be overly restrictive in light of the alternatives.<sup>157</sup> The court viewed full disclosure of any conflicts of interest as a sufficient and less burdensome alternative for advancing the FDA's interests.<sup>158</sup> In making this determination, the court relied on estimations that off-label use only accounted for a small proportion of drug use.<sup>159</sup> However, recent case law and research studies suggest that restrictions previously deemed unconstitutional might pass constitutional muster.<sup>160</sup>

Four years after *Washington Legal Foundation*, the Supreme Court in *Thompson v. Western States Medical Center*<sup>161</sup> applied a commercial-speech analysis to the FDAMA's prohibition on unlawful

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<sup>156</sup> See Katherine A. Helm, Note, *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, 134 (2007).

<sup>157</sup> *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 73 (D.D.C. 1998), amended by 36 F. Supp. 2d 16 (D.D.C. 1999), appeal dismissed & vacated in part *sub nom.* *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

<sup>158</sup> *Id.* at 73.

<sup>159</sup> See *id.* at 56 (citing a study that found that off-label use of the sixty-four most frequently prescribed drugs constituted only 4.7% of the use of patented drugs and 2.0% of the use of non-patented drugs).

<sup>160</sup> See *infra* pp. 553–57.

<sup>161</sup> 535 U.S. 357 (2002).

or misleading advertising.<sup>162</sup> *Thompson* addressed the validity of a blanket restriction on the advertising or promotion of compounded drugs by pharmacies, pharmacists, or physicians.<sup>163</sup> Once again, the Court's decision hinged on the final prong of the *Central Hudson* test—whether the government could achieve its interests in a less restrictive manner.<sup>164</sup> And once again, the Court held that the government failed to meet the necessary standard, noting that “there is no hint that the Government even considered” alternatives to an outright ban on commercial speech by the affected parties.<sup>165</sup>

Although the Court in *Thompson* established that prohibiting manufacturers from informing physicians of off-label use is unconstitutional in some cases,<sup>166</sup> the 1996 Guidance Documents allowed manufacturers to disseminate journal articles promoting off-label use, as long as the article focused primarily on the drug's approved use.<sup>167</sup> *Thompson* involved a blanket prohibition preventing drug companies from advertising compounded drugs under any circumstances, preventing drug companies from large-scale marketing of compounded drugs in any context.<sup>168</sup> In comparison, the 1996 Guidance Documents merely regulated the context of off-label drug use. Moreover, since *Washington Legal Foundation*, less restrictive guidelines, such as those set forth in the FDAMA, have proven ineffective at serving the government's substantial interest in ensuring manufacturers seek approval for off-label drug uses. In fact, courts have consistently found that “constraining the marketing options of manufacturers is one of the ‘few mechanisms available’ to the FDA to ensure that manufacturers will not seek approval only for certain limited uses of drugs, then promote that same drug for off-label uses . . . .”<sup>169</sup> Manufacturers have incentives to use the safe harbor

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<sup>162</sup> *Id.* at 368 (noting that the *Central Hudson* commercial speech analysis provides an “adequate basis for decision”).

<sup>163</sup> *See id.* at 360. The restriction at issue was in section 127(a) of the FDAMA. *See* 21 U.S.C. § 353a(c) (2000).

<sup>164</sup> *See Thompson*, 535 U.S. at 371–73 (discussing less restrictive alternatives to the blanket prohibition on advertising of compounded drugs).

<sup>165</sup> *Id.* at 373.

<sup>166</sup> *See United States v. Caputo*, 517 F.3d 935, 939 (7th Cir. 2008) (citing *Thompson*, 535 U.S. 357), *cert. denied*, 129 S. Ct. 94 (2008).

<sup>167</sup> *See Advertising and Promotion; Guidances; Republication*, 61 Fed. Reg. 52,800 (Oct. 8, 1996).

<sup>168</sup> *Thompson*, 535 U.S. at 371.

<sup>169</sup> *United States v. Caronia*, 576 F. Supp. 2d 385, 401 (E.D.N.Y. 2008); *see also United States v. Caputo*, 288 F. Supp. 2d 912, 921 (N.D. Ill. 2003) (noting that “one of the few mechanisms available to the FDA to compel manufacturer behavior is to constrain their marketing options; i.e. control the labeling, advertising, and marketing” (quoting *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 72 (D.D.C. 1998), *amended by* 36 F. Supp. 2d 16 (D.D.C. 1999), *appeal dismissed & vacated in part sub nom. Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000))).

created by the Guidance to sidestep the costly and time-consuming FDA-approval process in order to extend the life cycle of generic drugs or to increase revenues.<sup>170</sup> While there may be a compelling interest in making physicians aware of potentially life-saving treatments involving off-label drugs, physicians should be more than capable of discovering and communicating potential treatments to patients and other physicians without the involvement of manufacturers, especially since the current Guidelines call for the distribution of studies conducted independent of the manufacturer. Since alternative constraints have failed to adequately stem the growing tide of unapproved off-label uses of pharmaceuticals, the Guidance Documents, while previously deemed unconstitutional for lack of fit, may now provide the least restrictive method of limiting commercial speech by the manufacturers.

Recent Congressional investigations and scientific studies demonstrate that, even under the more restrictive guidelines established in section 401 of the FDAMA, off-label uses of pharmaceutical drugs made up a substantial proportion of overall drug sales. Under the more relaxed standard set forth in the finalized Guidance, the growth of off-label drug use is likely to continue. In a 2006 study evaluating the off-label prescription of 160 common drugs, off-label drug use accounted for 21% of all prescriptions.<sup>171</sup> The percentages are significantly higher for anticonvulsants (74%), antipsychotics (60%), and antibiotics (41%).<sup>172</sup> Making matters worse, in 73% of off-label uses, the application of the drug to the disease was shown to have little to no scientific support.<sup>173</sup> The results of this study demonstrate a significant change from the 4.7% rate of off-label use cited in *Washington Legal Foundation*.<sup>174</sup> Dr. David Wilkes, a professor of medicine at the University of California Davis, notes that “[physicians] are prescribing these drugs (off label) that are often very, very expensive—it’s rarely a generic drug, it’s always some sort of trade name drug that has been marketed.”<sup>175</sup> Even in cases where the FDA takes regulatory action against drug manufacturers for serious promotional violations, advertisements promoting off-label uses of pharmaceutical drugs may persist in the marketplace for over a year after identification. The FDA takes an

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<sup>170</sup> See Stafford *supra* note 10 at 1427–28.

<sup>171</sup> *Id.* at 1427.

<sup>172</sup> *Id.* (citing David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021 (2006)).

<sup>173</sup> *Id.*

<sup>174</sup> 13 F. Supp. 2d at 56.

<sup>175</sup> Sharon Kirkey, *Off-Label Drug Use Can Have Painful Consequences*, VANCOUVER SUN, Jan. 2, 2009, at B3.



average of seven months to initiate regulatory action against a manufacturer, and the manufacturer takes an average of four months to reply to the FDA's demand.<sup>176</sup> Moreover, these regulatory actions are not always sufficient to prevent repeat violations. For eleven out of forty-two drugs cited by the FDA for improper off-label promotional efforts, the products had received prior citations for improper off-label use.<sup>177</sup>

Possibly of greater concern, a national survey conducted of over one thousand physicians between November 2007 and August 2008 indicated that many physicians are unfamiliar with the FDA-approved uses of the drugs they are prescribing.<sup>178</sup> While 95% of physicians claimed they "generally know the FDA-labeled indications of medications they prescribe" and 79% of physicians cited FDA approval as an important factor guiding their prescribing habits, 41% of the physicians surveyed erroneously believed that some off-label uses were approved despite lacking or uncertain evidence supporting them.<sup>179</sup> The study indicated that primary care physicians as a group were only able to correctly identify the FDA-approved uses of the drugs they personally prescribed for a specified indication 42% of the time.<sup>180</sup> And, with one notable exception, physicians who prescribed drugs to patients for off-label purposes were more likely to believe the use was FDA-approved than their counterparts who chose not to prescribe the drug for the off-label use.<sup>181</sup>

The FDA does not seek to regulate physician prescription practices. However, these statistics raise serious questions as to the efficacy of the FDA's limits on off-label marketing. While these pervasive problems in off-label identification do not necessarily mean that the journal articles disseminated by manufacturers are inherently misleading or that they are the only factor contributing to off-label prescribing practices, it does suggest that physicians are receiving the wrong message from some source.<sup>182</sup>

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<sup>176</sup> GAO REPORT, *supra* note 11, at 6.

<sup>177</sup> *Id.* at 23.

<sup>178</sup> See Donna T. Chen et al., *U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base For Commonly Prescribed Drugs: Results of a National Survey*, 18 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1094, 1096 (2009) (noting that only fifty-five percent of all physicians surveyed knew the FDA approval status of the commonly used drug-indication pairs examined).

<sup>179</sup> *Id.* at 1099.

<sup>180</sup> *Id.* at 1097.

<sup>181</sup> *Id.* at 1097 tbl.2 (displaying that for twenty-one of the twenty-two drugs surveyed, physicians prescribing a drug for a given off-label use were more likely to believe the drug was FDA-approved for that purpose; the only exception was trazodone, which is used off label to treat insomnia).

<sup>182</sup> See, e.g., Posting of Jim Edwards to BNET, *Pfizer's West Side Story: How "The Sharks" Sold Bextra Off-Label*, <http://industry.bnet.com/pharma/10004061/pfizers-west-side>

Similarly, recent investigations into the peer-review process may raise questions regarding the accuracy and bias of journal articles disseminated by manufacturers to promote off-label use. Problems inherent in the peer-review process challenge the commonly held notion that journal publications “accurately represent[] the state of knowledge about sponsors’ products.”<sup>183</sup> In addition, some scientists have been slow to comply with journal requirements mandating the disclosure of relevant financial interests as a prerequisite for journal publication, and journal editors are often hard-pressed to detect and punish violators.<sup>184</sup> Jerome Kassirer, the editor of the *New England Journal of Medicine* from 1991 to 1999,<sup>185</sup> admitted that the hierarchy within medical journals means that:

[s]ome [journals], particularly those journals with robust full-time editorial staffs and venerable reputations, have the toughest peer-review standards. Others, mostly those staffed by editors whose day job is running a department or division, may not have the expertise to deal with the crush of new manuscripts. Their journals often receive papers rejected from the top tier of journals: it is fair to say that there is often a reason why these papers were rejected; yet they often end up published in a peer-reviewed journal and could be distributed by drug representatives.<sup>186</sup>

Kassirer goes on to explain that at some lower-tier journals, the peer-review process consists solely of two reviewers checking off “accept” or “reject.” If both reviewers accept, the article is published.

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-story-how-the-sharks-sold-bextra-off-label/ (Sept. 3, 2009) (noting that Pfizer marketing teams engaging in illicit off-label marketing campaigns for the drug Bextra referred to their teams by aggressive names such as “The Sharks” or “The Highlanders,” and incorporated practices such as providing physicians reprints of articles with the page citing approved drug uses flipped to the back so physicians would first see the information regarding off-label uses).

<sup>183</sup> Bruce M. Psaty & Wayne Ray, *FDA Guidance on Off-Label Promotion and the State of the Literature from Sponsors*, 299 JAMA 1949, 1949 (2008) (discussing the misrepresentations regarding drug safety and efficacy that can result from drug company sponsors’ common practice of declining to publish studies with unfavorable results and the FDA’s lack of oversight over study design).

<sup>184</sup> See THOMAS O. MCGARITY & WENDY E. WAGNER, BENDING SCIENCE: HOW SPECIAL INTERESTS CORRUPT PUBLIC HEALTH RESEARCH 77 (2008).

<sup>185</sup> See Laura Johannes, *Medical Journal Ousts Editor, Ending Battle*, WALL ST. J., July 27, 1999, at 1 (describing how the departure of the *New England Journal of Medicine*’s longtime editor would likely result in the journal pursuing more financially lucrative ventures).

<sup>186</sup> Posting of Jerome Kassirer to Health Affairs Blog, *Fantasy at FDA: Protecting the Public from Drug Company Reprints*, <http://healthaffairs.org/blog/2008/04/23/fantasy-at-fda-protecting-the-public-from-drug-company-reprints/> (Apr. 23, 2008, 14:40 EST).

If both reject, the article is declined. In the event of a tie, a third reviewer casts the deciding vote.<sup>187</sup>

Surviving a journal's peer-review process does not necessarily add credence to an article's claims. In fact, it may even be a hindrance. In a recent study, scientists demonstrated that the "Winner's Curse," an auction theory where the winning bidder tends to overpay, may apply to journal publications.<sup>188</sup> As the authority of journals is judged, at least in part, by selectivity, articles tend to gravitate to research that shows positive results, with negative or contradictory data merely discussed among colleagues or at conferences.<sup>189</sup> Applying the Winner's Curse theory to the article selection process, journals that select articles are likely to have overestimated the importance or efficacy of information contained in the selected article.<sup>190</sup> The Winner's Curse theory in turn would motivate prospective authors to devote more time to developing research showcasing outliers that produce positive results, as opposed to negative or equivocal findings, due to the publish-or-perish imperative. This bias in publications might help explain an overabundance of extreme or spectacular results: upon evaluating forty-nine of the most-cited papers in highly visible journals between 1990 and 2004, a quarter of the reported randomized trials and five of the six reported non-randomized studies were contradicted or identified as exaggerated by 2005.<sup>191</sup>

When the court in *Washington Legal Foundation* held that the Guidance Documents were overly burdensome, the court relied heavily on financial disclosure and the peer-review process in determining that the potential for manufacturers to mislead the public was negligible.<sup>192</sup> Studies since *Washington Legal Foundation*, however, have demonstrated that these protections are not enough.

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<sup>187</sup> *Id.*

<sup>188</sup> See Neal S. Young et al., *Why Current Publication Practices May Distort Science*, 5 PUB. LIBR. SCI. MED. 1418, 1418–19 (2008), available at <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0050201>.

<sup>189</sup> See *id.* at 1419 (noting that "in a recent paper, it was shown that while almost all trials with 'positive' results on antidepressants had been published, trials with 'negative' results submitted to the U.S. Food and Drug Administration, with few exceptions, remained either unpublished or were published with the results presented so they would appear 'positive'"); see also Benedict Carey, *Researchers Find Bias in Drug Trial Reporting*, N.Y. TIMES, Jan. 17, 2008, at A20 (noting that while thirty-seven of thirty-eight positive antidepressant trials were published in journals, only fourteen out of thirty-six trials with failed or unconvincing results made it into journals).

<sup>190</sup> Young et al., *supra* note 188, at 1418.

<sup>191</sup> *Id.* at 1418–19.

<sup>192</sup> See *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998) (writing that conclusions reached by academics and presented in scholarly peer-reviewed journals or textbooks are not "untruthful" merely because the FDA has not yet evaluated the claim), *amended by* 36 F. Supp. 2d 16 (D.D.C. 1999), *appeal dismissed & vacated in part sub nom. Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

In the decade since *Washington Legal Foundation* was decided, off-label use of pharmaceuticals has increased exponentially despite the application of the FDAMA.<sup>193</sup> The FDA's slow reaction to violations and the medical community's substantial difficulty disclosing inherent biases in research<sup>194</sup> establish that restricting drug-manufacturer marketing to the distribution of journal articles dealing primarily with approved uses of drugs is a necessary step towards safeguarding the public from taking unwarranted risks with off-label drugs.

### CONCLUSION

Off-label uses of pharmaceutical drugs can save lives, and providing physicians with the resources to make informed decisions about treatment plans should be encouraged.<sup>195</sup> However, the FDA is also charged with ensuring that pharmaceuticals are approved and properly labeled.<sup>196</sup> Both Congress and the FDA implemented rules to allow for the dissemination of medical journal articles while encouraging the manufacturers to apply for FDA approval, first with the 1996 Guidance Documents, followed by section 401 of the FDAMA, and finally through the current Guidance. While the court in *Washington Legal Foundation v. Friedman* held that the 1996 Guidance Documents violated the First Amendment by infringing upon the manufacturers' freedom to engage in commercial speech,<sup>197</sup> the court did not advocate an outright ban on the practice of promoting off-label uses of FDA approved drugs.<sup>198</sup>

While Congress implemented section 401 of the FDAMA to provide a safe harbor from the ban on off-label marketing by manufacturers, the sunset provision expired on September 30, 2006, leading the FDA to initiate notice-and-comment procedures to reinstate many of the FDAMA's provisions as a guidance document. The resulting Guidance should not have been issued as a Level 1 guidance document. It will likely be practically binding, and thus, is functionally a legislative rule rather than a non-legislative policy statement. Although the FDA sought public feedback on the

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<sup>193</sup> See *supra* notes 171–73 and accompanying text.

<sup>194</sup> See discussion *supra* pp. 555–56.

<sup>195</sup> Posting of Jerome Kassirer to Health Affairs Blog, *Fantasy at FDA: Protecting the Public from Drug Company Reprints*, <http://healthaffairs.org/blog/2008/04/23/fantasy-at-fda-protecting-the-public-from-drug-company-reprints/> (Apr. 23, 2008, 14:40 EST).

<sup>196</sup> Cf. Food, Drug, and Cosmetic Act, 21 U.S.C. § 355 (2006) (setting forth the approval process for new drugs); *id.* § 352(a) (outlining proper labeling requirements for drugs to avoid being designated misbranded).

<sup>197</sup> 13 F. Supp. 2d at 73.

<sup>198</sup> *Id.* at 72.

regulation through notice-and-comment proceedings, the public was not made aware of the Guidance's true nature, and the rule is therefore in violation of the APA's informal rulemaking requirements. The FDA should either have issued its Guidance as a legislative rule as defined by the APA, or waited for Congress to issue a new law authorizing agency action. The current Guidance should therefore be invalidated.

In the future, the FDA should pursue a legislative rule that governs manufacturer dissemination of journal articles promoting off-label use by limiting the safe harbor to only allow articles that primarily focus on the drug's authorized use. The rule should also require drug manufacturers to apply for supplemental drug applications for any secondary off-label uses mentioned in a journal article. Even with these measures in place, the rule would not preclude physicians from independently seeking out journal articles detailing off-label drug uses. As a result, patients may still receive sub-optimal or harmful treatment, such as that received by the Neurontin patients that suffered from suicidal tendencies as a result of an off-label use that had little to no scientific support.<sup>199</sup> What the measures would do, however, is help ensure that pharmaceutical companies do not actively market off-label uses that have not been subject to review and approval by the FDA. This in turn helps ensure that physicians have access to updated and unbiased research to guide their decisions in prescribing medication for off-label use, which could go a long way toward preventing the harms caused by the overprescription of Neurontin for off-label uses based on drug manufacturer marketing efforts.

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<sup>199</sup> See *supra* notes 15–18 and accompanying text.

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