



# The Neurontin Controversy: The Saga of Off-Label Drug Regulation Continues

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THE NEURONTIN CONTROVERSY:

THE SAGA OF OFF-LABEL DRUG REGULATION CONTINUES

Class of 2004

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April 27, 2004

Submitted in satisfaction of 3L written requirements and the requirements of the 2004 Food and Drug Law Course

## ABSTRACT

The regulation off-label drugs is a complicated and controversial area of the law. Regulators must protect patients' safety without interfering with physicians' practice of medicine or manufacturers' First Amendment rights. The recent Neurontin decisions, which apply the doctrine of false claims to prescription drug regulation, only adds additional complexity. This paper explores the federal government's attempts to regulate the promotion of off-label drugs. It discussed the advantages and disadvantages of off-label marketing, the current regulatory environment, and the implications of the Neurontin lawsuit.

## I. Introduction

On October 2, 2003, Philadelphia Assistant U.S. Attorney Virginia Gibson delivered a speech to the Pharmaceutical Compliance Forum noting the importance of the recent "Neurontin" decisions and signaling the government's new willingness to use the False Claims Act to restrict or even eliminate a manufacturer's ability to promote the off-label uses of its product.<sup>1</sup> This is not the first time the appropriateness and the legality of off-label drug promotion have been debated. Indeed, this gray area of the law, where a physician's duty to practice medicine to the best of his ability collides with the government's responsibility to monitor the nation's drug supply, has long perplexed policy makers, academic scholars, practitioners, and the regulated industry.

Off-label drug use refers to the very common practice of using a drug in a manner or for a reason not approved by the Food and Drug Administration (FDA). An off-label drug is not necessarily dangerous. In fact, for many diseases, it is the best or even the only course of treatment available. Pharmaceutical manufacturers, however, with certain minor exceptions, are not permitted to encourage off-label use of their product. Although this area of law has developed considerably over the last decade, several important issues

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<sup>1</sup> *Neurontin Ruling is Guide for DOJ Off-Label Promotion Cases - Prosecutor*, F-D-C REP. ("The Pink Sheet"), Oct. 13, 2003, at 15, 15 [hereinafter Pink Sheet].

remain unsettled. Are restrictions on off-label promotion good policy? Does government regulation promote patient safety or simply interfere with the legitimate practice of medicine? Are current laws constitutional? Adding to the confusion is the Neurontin case, which continues to be litigated in Massachusetts District Court and offers a novel theory for challenging the legality of off-label promotion. If successful, this case will dramatically alter the pharmaceutical industry's marketing practices and will provide the government with a new tool for its enforcement arsenal.

This paper discusses the government's historically muddled policy toward off-label drug promotion and current efforts to change that policy. Reluctant to interfere with a doctor's professional judgment, yet wary of drugs that have not been adequately tested for safety and effectiveness, Congress has long sent mixed signals regarding the legality of off-label drugs. The courts, in turn, have responded with decisions that mimic Congress' confused policy – some cases embrace the goal of protecting patients from off-label marketing while other cases dramatically curtail the FDA's authority. Although recent legislation has helped clarify which promotional practices are legal, the policy remains internally conflicted and the law remains susceptible to a constitutional challenge. Moreover, as seen in the Neurontin case, proponents of regulation have found new ways of using old laws to challenge pharmaceutical manufacturers' practices.

## II. Definition

An “off-label drugs” is simply a drug used for a condition or in a manner not appearing on the FDA approved label.<sup>2</sup> Indeed, almost every consumer is familiar with off-label medicines. The American Medical

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<sup>2</sup>James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 71 n.2, (1998). A recent FDA presentation defined off-label drugs as medicines “use[d] for indication[s], dosage form[s], population[s] or other use parameter[s] not mentioned in the approved labeling.” Janet Woodcock, *Lecture to Drug Information Association, A Shift in the Regulatory Approach*, (June 23, 1997), at <http://www.fda.gov/cder/present/diamontreal/regappr/sld001.htm>.

Association reported in 1995 that approximately half of all prescriptions were written for off-label uses.<sup>3</sup> Moreover, the General Accounting Office (GAO) has testified that 90 percent of cancer drug use, 80 percent of pediatric use, and 80-90 percent of drugs used to treat rare diseases are prescribed off-label.<sup>4</sup> Perhaps the best known example is aspirin. For years, physicians prescribed aspirin to reduce the risk of heart attacks.<sup>5</sup> However, the FDA did not approve such usage until 1998.<sup>6</sup> A less celebrated example is Fen-Phen.<sup>7</sup> Both fenfluramine (“Fen”) and phentermine (“Phen”) were approved by the FDA for weight loss.<sup>8</sup> However, doctors ignored fenfluramine’s labeling by having some patients use the medicine for more than a year when it was only labeled for duration of a “few weeks,” and by combining the two drugs even though neither label discussed using the drugs in tandem.<sup>9</sup> Many patients suffered heart valve damage as a result.<sup>10</sup> Most recently,<sup>11</sup> OxyContin, a powerful medication approved for moderate to severe chronic pain, generated considerable controversy, when it was prescribed for all types of discomfort.<sup>12</sup> Off-label drugs, therefore, come in a variety of forms. While some instances are widely accepted, and doctors could be accused of malpractice if they did not prescribe the drug,<sup>13</sup> others are dangerous and are not an appropriate part of medical care.

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<sup>3</sup>Veronica Henry, *Off-Label Prescribing: Legal Implications*, 20 J. LEGAL MED., 365, 365 (1999).

<sup>4</sup>*Final Report on the Activities of the House Comm. on Government and Oversight*, 104th Cong. 2d Sess. 104 H. REP. 874 (Section 2), (January 2, 1997) at 114.

<sup>5</sup>Jim Oliphant, *FDA’s New Drug War Industry Fights For Alternative Uses of Approved Products*, LEGAL TIMES, January 10, 2000 at 1.

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

<sup>7</sup>*See In re Diet Drugs (Phentermine, Fenfluramine, Dexfenfluramine)*, No. 99-20593, 2000 U.S. Dist. LEXIS 12275 (E.D. Pa. Aug. 28, 2000); *Elliot v. A.H. Robins Co. (In re N.Y. County Diet Drug Litig.)*, 691 N.Y.S.2d 501 (App. Div. 1999).

<sup>8</sup>Paul D. Rheingold & David B. Rheingold, *Offense or Defense? Managing the Off-Label Use Claim*, TRIAL, Mar. 2001, at 52.

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

<sup>10</sup>James O’Reilly and Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANN. HEALTH L. 295, 300 (2003).

<sup>11</sup>While Aspirin, Fen-Phen and Oxy-Contin are the examples cited most often in contemporary literature, older examples of off-label drugs include Retin-A, silicone, and collagen injections. Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 202 n.130 (citing Michael Unger, *More Bite Urged for Watchdog FDA*, NEWSDAY, Nov. 24, 1992 at 29).

<sup>12</sup>*See Note*, Mark A. Ford, *Another Use of OxyContin: The Case for Enhancing Liability for Off-Label Drug Marketing*, 83 B.U. L. REV. 429 (2003).

<sup>13</sup>Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, 399 (2002).

Indeed, Professor Salbu has identified three kinds of off-label activities – off-label use, off-label prescription, and off-label marketing.<sup>14</sup> Off-label use occurs when a consumer uses a drug in a manner inconsistent with its label.<sup>15</sup> Frequently, this entails changing the dosage amount or frequency, combining the drug with others, using the medicine to treat an unapproved condition, or giving the medicine to someone for whom it was not prescribed.<sup>16</sup> It is nearly impossible to monitor for off-label use and Congress has never attempted to outlaw its practice.<sup>17</sup>

Off-label prescription, in contrast, occurs when a doctor prescribes a drug in a manner inconsistent with its FDA approved label.<sup>18</sup> For example, a physician may prescribe a drug for a disease other than the ones listed on the label, in an unapproved dosage, for unapproved duration or in an unapproved combination with other medicines.<sup>19</sup> The doctor may also prescribe the drug to groups, such as children or pregnant women, for whom the FDA has not approved the drugs usage.<sup>20</sup> While it would be easier to enforce a ban on off-label prescription than it would be for off-label use, Congress has long deferred to a physician’s superior medical judgment to prescribe medicine.<sup>21</sup> Professor Salbu notes, “Numerous decisions support this approach, which emphasizes physician autonomy and discretion within an otherwise rigorous regulatory environment.”<sup>22</sup>

The final category, off-label promotion, will be the primary focus of this paper and *is* regulated by the FDA. Manufacturers cannot market their products “for purposes, to users, in dosages, or in combinations other than FDA-approved ones.”<sup>23</sup> While recent legislation has created certain exceptions to this blanket

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<sup>14</sup>Salbu, *supra* note 11, at 188.

<sup>15</sup>*Id.*

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

<sup>17</sup>*Id.*

<sup>18</sup>*Id.* at 189.

<sup>19</sup>*Id.*

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

<sup>21</sup>*Id.* at 189-190. *See also infra* notes 35-40 and accompanying text.

<sup>22</sup>*Id.* at 190 (citing *Rhone-Poulenc Rorer Pharms. Inc. v. Marion Merrell Dow Inc.*, 93 F.3d 511, 514 n.3 (8th Cir. 1996); *Weaver v. Reagen*, 886 F.2d 194, 198 (8th Cir. 1989); *United States v. Evers*, 453 F. Supp. 1141, 1149-50 (M.D. Ala. 1978), *aff’d*, 643 F.2d 1043 (5th Cir. 1981)).

<sup>23</sup>Salbu, *supra* note 11, at 191.

prohibition,<sup>24</sup> the promotion of drugs for off-label uses remains both highly regulated and controversial.

It must be stressed that there is no doubt as to the legality off-label *use* or *prescription*.<sup>25</sup> The only dispute concerns the appropriateness of prescription drug manufacturers *promoting* off-label aspects of their product. Attorneys Beck and Azari note that “[o]ff-label use is widespread in the medical community and often is essential to giving patients optimal medical care. . . . [M]edical ethics, FDA, and most courts recognize [recognize this fact].”<sup>26</sup> Moreover, the GAO reports that off-label use often represents “state-of-the-art” treatment,<sup>27</sup> and the FDA asserts that “good medical practice and patient interests require that physicians use commercially available drugs, devices, and biologics, according to their best knowledge and judgment.”<sup>28</sup> Thus, the term ‘off-label’ is merely a regulatory description of a drug; it is a legal status not a medical fact.<sup>29</sup>

Furthermore, one should be careful not to interpret the phrase “unapproved use” to mean “disapproved use.”<sup>30</sup> The FDA does not take a position on the safety of an off-label use; rather, the agency leaves that determination to the individual doctor as part of his or her practice of medicine. This position has been stated repeatedly. For example, in a 1972 pronouncement, the FDA declared that once a drug has left a manufacturer’s warehouse a “physician may, as part of the practice of medicine lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package

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<sup>24</sup>See Food and Drug Administration Modernization Act of 1997, Pub. L. No 105-115, 111 Stat. 2296 (codified at 21 U.S.C. §§ 360aaa *et seq.*); *infra* notes 135-69 and accompanying text.

<sup>25</sup>United States General Accounting Office, *Off-Label Drugs: Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies*, Pub. No. GAO/PEMD-91-14, 11 (1991) (“It is not the . . . [FDA’s] policy, intent, or bias to indicate that off-label uses are wrong, improper or even investigational”).

<sup>26</sup>Beck & Azari, *supra* note 2, at 72 *cited with approval in* *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 351 (2001).

<sup>27</sup>United States General Accounting Office, *supra* note 25, at 11.

<sup>28</sup>Beck & Azari, *supra* note 2, at 83 (quoting Food and Drug Admin., *Investigational Use of Marketed Products* (1989)).

<sup>29</sup>*Id.*

<sup>30</sup>Beck & Azari, *supra* note 2, at 84. This error is, nevertheless, a common one. For example, in *Proctor v. Davis*, 682 N.E.2d 1203, 1213 (Ill. App. 1997), the court described off-label use as “unauthorized” by the FDA, even though the agency lacks power to forbid off-label use.

insert.”<sup>31</sup> Ten years later, the FDA again stressed that off-label use is accepted medical practice, and FDA approved labeling should be used for informational purposes only.<sup>32</sup> Physicians have embraced this freedom, and off-label drug use has become an accepted method of treatment for many diseases.

### III. Regulatory History

In 1938 Congress passed the Food, Drug and Cosmetics Act<sup>33</sup> (FDCA) to replace the 1906 Food and Drugs Act.<sup>34</sup> In doing so, the members of the 75<sup>th</sup> Congress firmly established the federal government’s role in regulating the pharmaceutical industry and ensuring the safety of the nation’s prescription drug supply.

#### A. Practice of Medicine

During the debates leading to the FDCA’s passage, Congress made clear that while it intended to regulate production and distribution of prescription drugs, it did not wish to regulate the practice of medicine.<sup>35</sup> As the Third Circuit has observed:

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<sup>31</sup>Legal Status of Approved Labeling For Prescription Drugs; Prescribing For Uses Unapproved By The Food And Drug Administration: Notice of Proposed Rule Making, 37 Fed. Reg. 16,503, 16,503-04 (Aug. 15, 1972).

<sup>32</sup>Use of Approved Drugs for Unlabeled Indications, FDA DRUG BULLETIN, Apr. 1982, at 4

<sup>33</sup>Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 – 392).

<sup>34</sup>The first national statute regulating the general safety of prescription drugs was passed four years before the 1906 Act. The Biologics Act of 1902 was passed in response to the distribution of tetanus infected diphtheria antitoxin and required licensing of biological drugs sold in interstate commerce. Prior to the Biologics Act, Congress made several short-lived attempts to regulate specific sectors of the prescription drug market, such as the safety of smallpox vaccine, 2 Stat. 806 (1813), *repealed by* 3 Stat. 677 (1822) and imported drugs 9 Stat. 237 (1848). *See generally* Peter Barton Hutt and Richard A. Merrill, FOOD & DRUG LAW 7-9. (2d ed. 1991).

<sup>35</sup>For example, the Senate Report that accompanied the new law stated that “the bill is not intended as a medical practices act and will not interfere with the practice of the healing art.” S. REP. No. 361, 74th Cong., 1st Sess. 3 (1935).



New Uses for drugs are often discovered after FDA approves the package inserts that explain a drug's approved uses. Congress would have created havoc in the practice of medicine had it required physicians to follow the expensive and time-consuming procedure of obtaining FDA approval before putting drugs to new uses. Thus, Congress exempted the practice of medicine from the [FDCA] so as not to limit a physician's ability to treat his patients.<sup>36</sup>

However, this distinction – between the practice of medicine on one hand and the promotion of drugs on the other – has been a difficult one to maintain. As mentioned above,<sup>37</sup> federal regulations prohibit pharmaceutical manufacturers from encouraging off-label use of their products, but if physicians learn of and then utilize off-label uses, no law has been violated.<sup>38</sup> The problem is that the prescription drug industry and physicians work hand in hand to fight disease and minister to the sick.<sup>39</sup> In an era where most diseases are treated with prescription drugs,<sup>40</sup> it is difficult to regulate the pharmaceutical industry without interfering with a doctors' ability to treat their patients as they see best. As a result, the law seems to be in tension with itself. Off-label information must not be discussed, but physicians are free to use any information they learn.

## B. Labeling and Approval Requirements

The 1938 legislation required, *inter alia*, that manufacturers label their product with safety warnings and directions for use.<sup>41</sup> Over time, the FDA has come to understand this requirement as mandating that drug manufacturers label their product with a descriptions of all intended uses.<sup>42</sup> Thus, the agency has declared,

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<sup>37</sup> See *supra* notes 31 and 32 and accompanying text.

<sup>38</sup> The Supreme Court has observed that off-label usage is “an accepted and necessary corollary of the FDA’s mission to regulate in this area *without directly interfering with the practice of medicine.*” *Buckman Co. v. Plaintiffs’ Legal Committee*, 531 U.S. 341, 350 (2001) (emphasis added).

<sup>39</sup> Both sides, no doubt, have other motives as well.

<sup>40</sup> See Robin Toner, *Drawing up Plans to Pay for Pills for the Elderly*. NEW YORK TIMES, May 10, 1999, at A1.

<sup>41</sup> Federal Food Drug and Cosmetic Act, Ch 675, §502(f), 52 Stat. 1040, 1051 (1938).

<sup>42</sup> Final Guidance on Industry-Supported Scientific and Educational Articles, 62 Fed. Reg. 64,074, 64,075 (Dec. 3, 1997) (“The courts have agreed with the agency that section 502(f)(1) of the act requires information not only on how a product is to be used (e.g., dosage and administration), but also on *all the intended uses* of the product.”) (emphasis added). In support

“All drugs and devices must bear labeling with adequate directions for each intended use. If labeling for a drug or device fails to contain adequate directions for each intended use, the drug or device is deemed to be misbranded . . . and subject to seizure or other enforcement actions.”<sup>43</sup>

The FDCA defines labeling as “all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.”<sup>44</sup> This concept is understood broadly;<sup>45</sup> package inserts, brochures, and reprints of academic articles are all considered forms of labeling.<sup>46</sup> It is not necessary for a manufacturer to include this information with the shipment of the actual passage in order for it to be considered labeling.<sup>47</sup>

Amending the FDCA in 1962, Congress added requirements for manufacturers to not only show that their product is safe – as had previously been required – but also that it is effective for their intended use.<sup>48</sup> These amendments expanded the FDA’s power dramatically and “laid the foundation for the . . . issue of off-label promotion by specifying the type of clinical data that a manufacturer must submit for new drug approval and by requiring such information for each intended use.”<sup>49</sup> A manufacturer who wished to promote an already approved product for a new use could no longer rely on previous studies to show that the “new” drug is just as safe as the “old” one. Instead, the pharmaceutical company must prove that the product, already shown to be safe, is effective for the new treatment. As one commentator noted, the 1962 amendments “provide[]

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of this claim, the agency cites *Alberty Food Products v. United States*, where the Ninth Circuit held that a manufacturer misbrands a product when its label does not reflect the therapeutic uses suggested in newspaper advertisements. 185 F.2d 321 (9th Cir. 1950).

<sup>43</sup>Final Guidance on Industry-Supported Scientific and Educational Articles, *supra* n. 42 at 64,076.

<sup>44</sup>21 U.S.C. § 321(m) (2000).

<sup>45</sup>Elizabeth A. Weeks, *Is It Worth It Worth It? The New Policy on Dissemination of Information on Off-Label Drug Use Under the Food and Drug Administration Modernization Act of 1997*, 54 FOOD & DRUG L.J. 645, 647 (1999).

<sup>46</sup>Thomas A Hayes, *Drug Labeling and Promotion: Evolution and Application of Regulatory Policy*, 51 FOOD & DRUG L.J. 57, 61 (1996).

<sup>47</sup>*Kordel v. United States*, 335 U.S. 345, 350 (1948) (holding that a manufacturer who provides vendors with both the product and brochures can be found guilty of misbranding even though the product and “label” were shipped separately. “The fact that [the brochures] went in a different mail was wholly irrelevant.”)

<sup>48</sup>Pub. L. No. 87-781, §102(a)(1), 76 Stat. 780 (amending 21 U.S.C. §321(p)(1)) (“The term ‘new drug’ is amended by . . . inserting therein immediately after the words ‘to evaluate the safety’, the words ‘and effectiveness.’ . . .”)

<sup>49</sup>Weeks, *supra* note 45, at 654.

a solid basis for what the FDA describes as a seamless regulatory regime in which pharmaceutical products cannot be promoted or suggested for any use in the absence of labeling for that use approved by the FDA.”<sup>50</sup> In addition to expanding the number of criteria on which a drug will be reviewed, the 1962 Amendments also created a “substantial evidence” test.<sup>51</sup> This too expanded the FDA’s authority for the agency could now set standards for the type of clinical trials that a manufacturer must conduct and the quality of the data that a manufacturer must submit with a new drug application.<sup>52</sup>

The combination of the safety, labeling, and efficacy requirements have made the process of bringing a new drug to market an arduous one.<sup>53</sup> After completing animal testing, a manufacturer must complete an investigational new drug (IND) application in order to receive an exemption from the blanket prohibition against the introduction of unapproved drugs into interstate commerce.<sup>54</sup> Accompanying this application, the manufacturer must detail the general investigational plan, the design of human trials, and qualifications of the clinical investigators.<sup>55</sup>

Testing on human subjects is divided into three phases.<sup>56</sup> Phase I involves administering the new drug to a small number of healthy subjects in order to determine its toxicity and other metabolic functions.<sup>57</sup> Phase II offers the drug to a limited number of the anticipated patient population in order to determine efficacy, side effects, and risk.<sup>58</sup> Finally, Phase III trials are large-scale double blind studies of the drug’s efficacy and

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<sup>50</sup>Hayes, *supra* note 46, at 62.

<sup>51</sup>21 U.S.C. §355.

<sup>52</sup>Weeks, *supra* note 45, at 654.

<sup>53</sup>Compassionate use exceptions dramatically simplify the approval process for drugs intended for life-threatening illness with no other treatment. *See* 21 C.F.R. §§ 312.34, 312.36, 312.80 (2003).

<sup>54</sup>Weeks, *supra* note 45, at 654-55. *See also* 21 C.F.R. § 312 (2003). (detailing investigational new drug application requirements)

<sup>55</sup>Weeks, *supra* note 45, at 655.

<sup>56</sup>21 C.F.R. § 312.21.

<sup>57</sup>21 C.F.R. § 312.21(a).

<sup>58</sup>21 C.F.R. § 312.21(b).

safety in patients with the specified disease.<sup>59</sup> At this stage, investigators compare the drug to a placebo, information for the label is gathered, and benefits and risks are calculated from a statistically significant population.<sup>60</sup> During all three phases, of course, the clinical investigators must obtain informed consent from the test subjects.<sup>61</sup>

If the new drug successfully completes this process, the manufacturer will submit a “New Drug Application” (NDA).<sup>62</sup> The NDA includes detailed information about the components of the drug, chemical reactions, the result of clinical testing, a summary of risks and benefits, and proposed labeling.<sup>63</sup> Only then will the FDA consider approving the new drug for wide-scale distribution. This process has led one commentator to observe that “given the lengthy and expensive road to new drug approval, even for new uses of previously approved products, drug manufacturers face strong disincentives against seeking permission to market off-label uses of their product.”<sup>64</sup>

While time consuming and expensive,<sup>65</sup> this process has achieved its goal. The nation’s drug supply is both safe and effective. Off-label drug promotion presents difficulties because it deals with an area at the cusp of the law – the interaction between the regulated pharmaceutical industry and the unregulated<sup>66</sup> practice of medicine. While manufacturers must carefully follow detailed federal regulations for promoting off-label

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<sup>59</sup>21 C.F.R. § 312.21(c).

<sup>60</sup>See generally Weeks at 655 (describing the three phases)

<sup>61</sup>See 21 C.F.R. 50.20 and 50.25 (describing requirement for and elements of informed consent)

<sup>62</sup>See 21 C.F.R. 314

<sup>63</sup>21 C.F.R 314.50

<sup>64</sup>Weeks, *supra* note 45, at 655-56.

<sup>65</sup>A 1980 report from the House Committee on Science and Technology estimated that seven to thirteen years and 30 to 50 million dollars are needed in order to bring a drug from research to marketing approval. Weeks, *supra* note 45, at 655 (citing *Report of the Subcommittee on Science, Research and Technology of the House Committee on Science and Technology*, 96th Cong., 2d Sess. (1980)).

<sup>66</sup>This phrase is not to suggest that medicine is an unregulated industry. Indeed any physician who has had to contend with the Anti-Kickback Laws (42 U.S.C. § 1320a-7b), Stark Laws (42 U.S.C. § 1395nn), Medicare regulations, Medicaid regulations, state licensing requirements, and malpractice lawsuits is well aware that medicine is highly regulated. Rather, what is significant for the purposes of this paper is that Congress, by way of the FDCA, makes no attempt to regulate the daily practice of medicine – the dozens of decisions a doctor must make when evaluating, diagnosing, treating, and caring for a patient.

uses, the practice of medicine exception allows doctors to prescribe off-label uses as they see best.<sup>67</sup>

### III. The Policy Debate and the Legislative Response

#### A. Arguments Against Regulation

Congress has had a difficult time creating a coherent policy for off-label drugs because both the arguments in favor of regulation and those against are strong. Perhaps the best argument in favor of relaxing regulations is necessity. Many drugs have important off-label uses and government restrictions merely prevent needed medicine from reaching the sick. As the American Medical Association testified before Congress:

Prescribing FDA-approved drugs for off-label uses often is necessary for optimal patient care. For a product to have the most effective potential benefits, law and regulation . . . must follow, not precede, science. There are too many variations in clinical circumstances and too much time delay in regulations to allow the government to impede the physician's ability to practice in these regards when it is medically appropriate.<sup>68</sup>

Indeed, FDA's deference to the "practice of medicine" represents an intuitive understanding of this argument. The ultimate goal of the FDCA is to protect patients, and few patients will benefit if their physicians cannot prescribe medicine as they see best. Similarly, the FDA's policy of granting exceptions for life-threatening illnesses that have no cure reflects the agency's partial acceptance of a necessity argument.<sup>69</sup>

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<sup>67</sup>A doctor's off-label use of a product is "part of the 'practice of medicine' [and] does not require the submission of an Investigational New Drug Application . . . or review by an IRB [Institutional Review Board] unless such review is required by the institution in which the product will be used." Beck & Azari, *supra* note 2, at 83 (quoting Food and Drug Admin., *Investigational Use of Marketed Products* (1989)).

Moreover, this intuitive understanding is supported by empirical research. As discussed above,<sup>70</sup> the vast majority of cancer medications have important off-label uses. Also, children and patients with uncommon or “orphan diseases” rely on off-label drugs. In fact, among diseases afflicting fewer than 200,000 Americans, most are “totally without” FDA approved treatment,<sup>71</sup> and among drugs in general, “prescriptions for off-label uses . . . may account for more than 25% of the approximately 1.6 billion prescriptions written each year, with some recent estimates running as high as 60%.<sup>72</sup>

Thus, many opponents of FDA regulation argue that promoting off-label uses allows patients access to potentially life saving treatments. If doctors were not made aware of alternative uses to medicines the FDA has already approved, patients would have to go without adequate care. Since many doctors receive large amounts of information from pharmaceutical companies, placing restrictions on the dissemination of this information, it is argued, would only lead to sub-optimal patient care.<sup>73</sup>

Some respond to this argument by suggesting that doctors should augment their medical knowledge through careful study of the medical literature, rather than listening to drug companies promote their products. Senator Bill Frist, however, responds to these critics by noting that “if a conscientious doctor were to read two medical articles before retiring every night, he would have fallen 550 years behind in his reading at the end of the first year.”<sup>74</sup>

Related to the necessity argument, opponents of regulation contend that more information will aide doctors in treating patients. Once it is accepted that “off-label uses are desirable, it is difficult to maintain that doctors should be shielded from truthful information concerning how to use a product for an off-label use. Patients will benefit from having their doctors informed about off-label uses.”<sup>75</sup> Furthermore, rather than relying anecdotal evidence passed informally between colleagues, pharmaceutical manufacturers should be able to provide physicians with authoritative scientific information.<sup>76</sup> As one commentator argues, “the difference between a deadly poison and a useful medicine is the knowledge of how it should be used to treat a particular condition.”<sup>77</sup>

A third argument against regulation notes the time and expense needed for FDA approval of new uses of existing drugs.<sup>78</sup> If every use of a drug were subject to extensive FDA oversight, manufacturers would incur significant new research and development expenses.<sup>79</sup> Either the cost of the drug would increase significantly or manufacturers would simply not inform physicians of the full range of usefulness of the drug.<sup>80</sup> Neither outcome is desirable. Either patients who need medicine will suffer, or the cost of health in the United States, already among the highest in the industrialized world,<sup>81</sup> will grow even higher.

Next, opponents of greater regulation argue that the FDA could make better use of its limited resources by concentrating on the initial approval of prescription drugs. For example, former House Commerce Committee counsel Alan Slobodin has argued that the FDA unnecessarily spends resources on issues, like off-label drugs, which are tangential to its “core mission.”<sup>82</sup> The FDA, he contends, should focus on swift assessment of new drugs. This would hasten the pace of medical innovation – a benefit to both consumers and manufacturers – and would ultimately reduce the FDA’s overall costs.<sup>83</sup> Furthermore, these savings, might free government resources to be spent on other areas of public concern such as medical research or tax credits that encourage pharmaceutical innovation.<sup>84</sup>

A related argument maintains that the FDA is not capable of approving the multitude of off-label uses in the prescription drug marketplace. The agency neither has the financial resources nor the personnel to review each use. As Christopher writes, the FDA could not possibly “review drugs in its lengthy testing process at a pace equal to that at which physicians discover beneficial off-label uses.”<sup>85</sup>



Critics argue that less regulation will also lower costs for consumers. Professor Beales, for example, draws an analogy from state policies on advertising for prescription eyeglasses.<sup>86</sup> He notes that in a recent study, the average price of eyeglasses was approximately 20 percent higher in states that prohibited advertising than those with regulation.<sup>87</sup> Advertising led to increased sales, which in turn brought additional manufacturers into the market, led to competition, and lowered prices.<sup>88</sup> A study conducted in the 1970s found similar phenomenon in pharmaceutical marketing.<sup>89</sup>

Finally, opponents of regulation contend that the FDA's policies stifle innovation.<sup>90</sup> Research on new uses for existing medicines requires manufacturers to invest considerable resources, and the investment is risky because not all research will produce favorable results.<sup>91</sup> Moreover, even if a new use were to be discovered, the manufacturer may not recover enough money from new sales in order to justify the initial expenditure.<sup>92</sup> While the preceding cost benefit analysis is an inevitable result of a market economy, critics argue that the government should not add *additional* expense by ordering manufacturers to satisfy the FDA's numerous requirements.<sup>93</sup>

Furthermore, pharmaceutical manufacturers evaluate the benefits of additional research in the shadow of the remaining length of their patent. "Subjecting a new use to a lengthy approval process will decrease the amount of time the patent will cover the new use,"<sup>94</sup> which may influence whether the manufacturers decide to perform additional research to begin with.<sup>95</sup> In fact, one writer argues that the unpatented status of aspirin hindered the public education as to its cardiac benefits.<sup>96</sup> No one was willing to incur the research expense needed to prove that aspirin's "new" use was effective.<sup>97</sup> Thus, as one attorney notes, "as ... [with] many aspects of this industry, profit-making and scientific innovation are mutually advancing goals."<sup>98</sup>

## B. Arguments for Regulation

On the other side of the debate are supporters of government regulation. These critics note that an unregulated pharmaceutical industry has been responsible for many tragedies, and the modern regulatory scheme arose in response to the industry's malfeasance.<sup>99</sup> Any effort to circumvent these regulations, critics contend, will weaken consumer protections.<sup>100</sup> Indeed, the FDA has long argued that permitting manufacturers to promote off-label uses would "remove incentives to obtain definitive clinical study data, weaken the goal of evidence-based medicine, erode the drug efficacy requirements, and harm patients."<sup>101</sup>

Furthermore, critics argue, doctors are not as capable as the FDA at evaluating safety and efficacy. The very companies that stand to benefit from favorable result often finance research, and conflicts of interest are seldom disclosed.<sup>102</sup> Without the government's intervention, manufacturers would lack an incentive to conduct scientifically rigorous and statistically powerful research.<sup>103</sup> Moreover, good results, it is noted, generate favorable attention in the medical community even if the science does not reach the exacting standards set by the FDA.<sup>104</sup> In an area as complex and important as pharmaceutical research, the public should not have to trust a biased entity's assertions of safety. If there were ever a role for government, this is it.<sup>105</sup>

Many of these arguments were raised in 1997 when Congress debated amendments to the FDCA that would change the way off-label promotion is regulated.<sup>106</sup> Public Citizen, for example, asserted that the proposed law would provide "dangerously inadequate protection for the American public from the substantial risks of unknowingly being prescribed drugs for off-label uses."<sup>107</sup> Physicians also testified that drug companies emphasize positive results and omit information about side-effects, contraindications, adverse reactions and warnings.<sup>108</sup>

Supporters of regulation also argue that, in some instances, the *only* incentive for conducting further research comes from a desire to promote a drug's newly discovered use.<sup>109</sup> If there were no prohibitions on off-label marketing, there would be minimal research about the safety of off-label uses. While it is acknowledged that additional statutory requirements inhibit a pharmaceutical manufacturer's ability to recoup resources invested in research, this fact, critics contend, could be used against all forms of FDA regulation.<sup>110</sup> Society long ago decided that the benefit of pharmaceutical regulation outweighs the detriments. Consumers are rarely more vulnerable and less knowledgeable than when they seek medical care, and the government has a responsibility to protect this vulnerability.<sup>111</sup> While the pharmaceutical industry cannot be faulted for earning a profit, the FDA should do for consumers what they cannot do by themselves.

Next, critics contend that off-label drugs are essentially experimental medicines, and the patients who receive them are unwitting guinea pigs.<sup>112</sup> Patients who receive these drugs "become part of an uncontrolled experiment where no one is keeping track of ... who's helped and who's hurt."<sup>113</sup> Physician, insurance, and public interest organizations have all endorsed this view.<sup>114</sup> Manufacturers retort that off-label uses are promoted only if scientifically valid studies have proven the safety and efficacy of the new use.<sup>115</sup> Yet critics contend that without FDA's endorsement of this research, the results cannot be trusted and patients are exposed to medicine that differs very little from that which might be encountered in a phase III clinical trial.<sup>116</sup>

Supporters of increased regulation also argue that manufacturers abuse a regulatory loophole by only seeking FDA approval for uses that easily satisfy the agency's safety criteria.<sup>117</sup> Once the FDA has endorsed the product, the manufacturer then markets the drug to a far broader patient population than originally suggested.<sup>118</sup> Indeed, before passage of the 1997 reforms, the FDA expressed concern that if off-label marketing were allowed, manufacturers would seek approval for a "cheap, narrow indication and the next day begin selling the drug for multiple, broad, and profitable indications."<sup>119</sup>

Underlining these arguments is a belief that the market will not limit the promotion of drug to those uses that are safe and effective. This market failure, it is suggested, results from the conflicts of interest found throughout the pharmaceutical world.<sup>120</sup> Indeed, manufacturers, scientists, and physicians all face multiple and contradictory incentives.

Manufacturer's conflicts are perhaps the most obvious. As Professor Salbu explains, "If drug companies were in the business of protecting the public . . . [they] would spend their vast resources hiring personnel to achieve this end. . . . Drug companies, however, are in the business of selling pharmaceutical products for a profit, and the pressures to do this effectively can tempt companies to take imprudent risks with public health."<sup>121</sup> Government regulation, therefore, is needed to guard against these risks.

Although more objective than pharmaceutical manufacturers, scientists also display conflicts of interest.<sup>122</sup> Drug companies finance a considerable amount of scientific research<sup>123</sup> and scientists may feel pressure to arrive at favorable results.<sup>124</sup> Moreover, when experiments do produce legitimately favorable data, scientists often fail to disclose their financial ties to the manufacturer.<sup>125</sup> Finally, even without a financial stake in their sponsor's product, scientists who discover a new use may encourage physicians to prescribe the drug in what is technically still an off-label manner both to perform a public service and to enhance their own reputation.<sup>126</sup>

Doctors, who some argue will always protect patients from dangerous or useless drugs, face conflicts of their own. Pharmaceutical manufacturers frequently lobby physicians to prescribe their drug.<sup>127</sup> Tactics range from seminars in exotic locations to free lunches in the office.<sup>128</sup> While most physicians truly believe their professional judgment is not swayed, it is hard to believe that the drug industry would incur this expense if it did not have some effect on sales.

Additionally, doctors also face pressure to prescribe specific drugs from their patients.<sup>129</sup> Federal laws governing direct to consumer advertising have recently been relaxed,<sup>130</sup> and “today’s patients are bombarded by the efforts of pharmaceutical manufacturers to spur user demand.”<sup>131</sup> Patients increasingly come to the doctor believing they have a condition advertised on television and that the appropriate treatment is the advertised product.<sup>132</sup> Physicians, at times, report that they prescribe these medicines if the patient is persistent, even if the drug is not necessary.<sup>133</sup> The combined pressure of manufacturers and patients will, at times, overwhelm even the most conscientious of physicians and drugs that are either not needed or potentially harmful will be prescribed. Critics warn that relaxing off-label marketing restrictions will only exacerbate this problem.<sup>134</sup> Accordingly, doctors, like pharmaceutical manufacturers and scientists, should not be entrusted with the public’s health. Although no party in the pharmaceutical industry would deliberately cause harm, only the government can truly monitor all prescription drugs and filter out dangerous or ineffective uses.

### C. Compromise

As part of a broader overhaul of the Food and Drug administration,<sup>135</sup> and partly in response to the arguments discussed above, Congress passed the Food and Drug Administration Modernization Act of 1997 (FDAMA).<sup>136</sup> While not removing all restrictions on off-label marketing, the law does facilitate the distribution of information from the pharmaceutical industry to physicians. The FDAMA, which has been described as “the most important change in drug regulation in 20 years”<sup>137</sup> seeks to “balance the interests of physicians – and correspondingly of their patients – to obtain legitimate information about drug uses against FDA’s continued interest in ensuring that manufacturers continue to study drug effectiveness.”<sup>138</sup>

Significantly, the FDAMA *permits* manufacturers of an FDA approved drug to distribute information about new uses for that drug.<sup>139</sup> However, this information must be in one of two forms: an unabridged reprint of a peer-reviewed journal article or a reprint of a reference publication that experts in the field consider scientifically sound.<sup>140</sup> The peer-reviewed articles must be indexed in the “Index Medicus of the National Library of Medicine of the National Institutes of Health.”<sup>141</sup> The distribution must be accompanied by a disclosure statement that identifies the reprint as information regarding an unapproved use, notes that the manufacturer has sponsored the distribution, and identifies any author or consultant who has financial ties to the manufacturer.<sup>142</sup>

Manufacturers may only distribute information from journals that have a publicly stated policy of disclosing authors’ conflicts of interest.<sup>143</sup> Moreover, distributed material cannot be funded by, written at the request of, or influenced by the manufacturer.<sup>144</sup> The information distributed also cannot be false or misleading.<sup>145</sup> Under the new law, manufacturers can only distribute the information to health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, and government agencies.<sup>146</sup> Notably absent from this list are patients and consumer groups. The FDA must be informed of the intended distribution before it occurs and must be provided with a copy of both the article and clinical data regarding the safety and effectiveness of the new use.<sup>147</sup>

A manufacturer who chooses to take advantage of these new provisions must have received or be in the process of seeking supplemental FDA approval for the new use.<sup>148</sup> This last requirement, though, will be waived if a manufacturer can show that it would be economically prohibitive or unethical to conduct the studies needed for a supplemental application.<sup>149</sup> Every six months the manufacturer must inform the FDA of the articles that have been distributed and the recipients of the information.<sup>150</sup> The FDA may, in turn, order a manufacturer to halt distribution if the agency determines that the restrictions described above have not been complied with or the new use is not effective or creates a public health risk.<sup>151</sup>

The FDA announced the rules to implement this law approximately one year later.<sup>152</sup> As part of its mandate to ensure that promotional materials do not <sup>22</sup>pose a public health risk or contain false or misleading information, the agency placed additional restrictions on the types of articles or reference publications that manufacturers can distribute.<sup>153</sup> Letters to the editor, abstracts of publications, and “flagged reference material” contain little substantive discussion, the agency concluded, and therefore are not “scientifically

The FDAMA was a political compromise between those who favored greater restrictions on off-label marketing and those who hoped to facilitate its practice.<sup>163</sup> “As are most political compromises, the FDAMA is rather cumbersome.”<sup>164</sup> Indeed, some have wondered whether the new law is too burdensome and whether “anyone would ever run this gauntlet.”<sup>165</sup>

The statute, though, does balance two competing interests: the need to provide information to physicians and concerns that increased communication will threaten safety. For example, as discussed above, critics fear that off-label marketing will reduce a manufacturer’s incentive to conduct research on the safety and effectiveness of new uses.<sup>166</sup> The legislation responds to this concern by requiring the manufacturer to submit a supplemental application for the off-label use.<sup>167</sup> Moreover, even this compromise is tempered by an exception for studies that are economically infeasible or medically unethical. Likewise, the disclosure requirements address concerns that manufacturers are inherently biased, and the source requirements – distributed material can only be reprints from scientifically respected journals – address concerns that corporations will provide skewed or incomplete information. Finally as the ultimate safeguard, the FDA can order a manufacturer to cease distributing materials if the agency has doubts about the safety or effectiveness of the new use or if other provisions of the FDAMA have not been followed.<sup>168</sup>

By passing the FDAMA, Congress left in place the existing regulations for new drug approval and simply added a new layer of rules to govern off-label marketing.<sup>169</sup> The new law, combined with the practice of medicine exception discussed above, reflects a difficult policy choice between two views that both arguably have consumers’ best interests at heart. While the legislative branch has likely said its last word on this subject for some time, the courts have only begun to evaluate the current regulatory scheme.

#### IV. First Amendment Challenges

##### A. The Washington Legal Foundation Case



Two recent cases have important First Amendment implications for off-label drug regulation. The first, *Washington Legal Foundation v Friedman* resulted in five decisions addressing the merits of the case and over six years of litigation. Despite its complexity, the case essentially revolved around one question: Is it unconstitutional for the FDA to limit pharmaceutical manufacturers' ability to promote an off-label use of an otherwise legal product.

In 1994, the Washington Legal Foundation (WLF), a not-for-profit public interest group that “defends the rights of individuals and businesses to go about their affairs without undue influence from government regulators”<sup>170</sup> filed a lawsuit to challenge the FDA’s then “unformalized” policy of prohibiting pharmaceutical manufacturers from promoting off-label uses.<sup>171</sup> While the FDA had not yet produced final guidance documents on the subject,<sup>172</sup> the policy was evident from letters to manufacturers, speeches and articles authored by agency officials.<sup>173</sup>

WLF represented physicians (who were also members of the organization) who felt the FDA violated their First Amendment rights when it prohibited manufacturers from distribution information the doctors wished to receive. Notably, no manufacturers were named as plaintiffs,<sup>174</sup> and the FDA immediately challenged the case on standing and ripeness grounds.<sup>175</sup> The court, however, held that because WLF’s members

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<sup>170</sup>Washington Legal Foundation v. Friedman, 13. F. Supp. 2d 51, 54 (D.D.C. 1998) [hereinafter WLF II] (citing to Plaintiff’s complaint).

<sup>171</sup>Richard M. Cooper, *The WLF Case Thus Far: Not with a Bang, But a Whimper*, 55 FOOD & DRUG L.J. 477, 477. The suit was preceded by a 1993 citizen’s petition filed with the FDA challenging the agency’s policies on constitutional grounds. WLF I at 30. The petition was filed pursuant to 21 C.F.R. § 10.30 and can be found at <http://www.fda.gov/ohrms/dockets/dailys/01/May01/053001/cp00001.pdf>

<sup>172</sup>As of 1992, the agency did have formal policy on manufacturer support of continuing medical education (CME) See Draft Policy Statement on Industry-Supported Scientific and Educational Activities ACTION: Notice, 57 Fed. Reg. 56,412 (Nov. 27, 1992). CME is often linked with more formal means of promotion since manufacturers might use the “courses” to promote their product.

<sup>173</sup>Washington Legal Foundation v. Kessler, 880 F. Supp. 26, 28-29 (D.D.C. 1995) [hereinafter WLF I]. See also Cooper, *supra* note 177, at 477 n.2 (listing informal ways this policy was communicated).

<sup>174</sup>Cooper, *supra* note 177, at 477.

<sup>175</sup>See WLF I, *supra* note 173.

had standing,<sup>176</sup> the organization also had standing to represent them.<sup>177</sup> Moreover, the alleged “collective effect of the FDA’s conduct [was] . . . to discourage manufacturers from disseminating information they would otherwise have chosen to distribute” and accordingly the issue was ripe for judicial review.<sup>178</sup>

In response to this decision, the FDA released final guidance documents detailing agency policy regarding (1) manufacturer distribution via “enduring materials” of information concerning off-label uses<sup>179</sup> and (2) continuing medical education seminars and symposia.<sup>180</sup> “Enduring materials” are reprints of articles published in medical journals, scientific journals, or medical textbooks.<sup>181</sup> These guidance documents were viewed by all parties as superseding the FDA’s prior unwritten policy and they became the “central focus” of the lawsuit.<sup>182</sup>

Following the discovery process, both parties moved for summary judgment, and in July 1998 Judge Royce

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<sup>176</sup>The court cited *Virigna Pharmacy Bd. v. Virginia Consumer Council*, 425 U.S. 748 (1975) for the notion that when a willing speaker exists, both the listener and speaker have a First Amendment right to the speech.

<sup>177</sup>WLF I, *supra* note 173, at 31 (citing *Hunt v. Washington State Apple Advertising Comm’n*, 432 U.S. 333 (1977) (holding that an organization has “representational” standing to sue on behalf of its members provided that there is an injury-in-fact to at least one of the members)).

<sup>178</sup>WLF I, *supra* note 173, at 35-36. The court based its decision on numerous warning letters sent to pharmaceutical companies and comments from Commissioner David Kessler that he “would urge all members of the pharmaceutical industry to take a long hard look at their promotional practices. I do not expect companies to wait until this guidance document becomes final to put their advertising and promotional houses in order.” *Id.* Also, WLF alleged that the FDA Director of Policy Development wrote, “Although this document was published as a draft policy statement with an invitation to submit comments, it reflects actual agency policy. It tells you how the agency makes decisions from day to day in determining whether activities are subject to regulation and are potentially illegal under the Food, Drug and Cosmetic Act.” *Id.*

<sup>179</sup>Advertising and Promotion; Guidances, 61 Fed. Reg. 52,800 (Oct. 8, 1996). The guidance document states that distributed articles must focus primarily on approved uses and can not be “written, edited, excerpted, or published specifically for, or at the request of” a drug manufacturer. *Id.* at 52,800 – 801. The text also may not solely focus on the manufacturer’s product and the manufacturer may not edit, comment on, or influence the text of the article. *Id.* Finally, the manufacturer may not “refer to or otherwise promote. . . information in the reference text that is not consistent with the approved labeling for the product.” *Id.* An exception was allowed for articles written by or influenced by the manufacturer if “the reference text results in a balanced presentation of the subject matter.” *Id.* An exception was also granted for articles provided to a physician after a direct inquiry. *Id.* For a more detailed summary, see WLF II, *supra* note 170, at 58.

<sup>180</sup>Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074 (Dec. 3, 1997). The document attempted to distinguish between situations in which the CME was independent from the influence of the manufacturer, and therefore not subject to regulation, and situations where the manufacturer does exert influence. *Id.* at 64095. For a more detailed summary see WLF II, *supra* note 170, at 57.

<sup>181</sup>WLF II, *supra* note 170 at 54.

<sup>182</sup>Cooper, *supra* note 171, at 479.

Lamberth ruled for WLF on the merits.<sup>183</sup> While the FDA had argued that it was merely regulating conduct, the court found that the case concerned the promotion of off-label uses and that promotion is speech.<sup>184</sup> Judge Lamberth did, however, grant the FDA’s contention that the regulated speech was commercial speech rather than pure speech.<sup>185</sup> The regulations, therefore, were only subject to intermediate scrutiny as outlined by *Central Hudson Gas and Electric Corp. v. Public Service Comm’n of New York*<sup>186</sup> and did not face a more rigorous strict scrutiny test.

This last finding – that the speech was commercial - while preliminary in nature, was extremely significant. As the Supreme Court has explained, “The Constitution accords less protection to commercial speech than to other constitutionally safeguarded forms of express.”<sup>187</sup> Moreover, the answer was also not readily apparent. The district court noted that the question was “not an easy one, as the communications present one of those complex mixtures of commercial and non-commercial elements.”<sup>188</sup> Indeed, the manufacturers hoped to “communicate . . . the speech of others – the work product of scientists, physicians, and other academics”<sup>189</sup> and *scientific information* is given full constitutional protection.<sup>190</sup>

Central Hudson outlines a four-part test for evaluating whether restrictions placed on commercial speech are unconstitutional: 1) the commercial speech “must concern lawful activity and not be misleading;” 2) the government’s interest in regulating the speech must be “substantial;” 3) the restrictions must directly advance the government’s interest; and 4) the regulations must be no “more extensive than is necessary” to

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<sup>183</sup> See WLF II *supra* note 170.

<sup>184</sup> *Id.* at 59. (“This court is hard pressed to believe that the agency is seriously contending that ‘promotion’ of an activity is conduct and not speech, or that ‘promotion’ is entitled to no First Amendment protection.”) The government, of course, has far greater latitude to regulate conduct than it does to regulate speech.

<sup>185</sup> *Id.* at 62-65.

<sup>186</sup> 447 U.S. 557 (1980).

<sup>187</sup> *Bolger v. Youngs Drug Products Corp.*, 463 U.S. 60, 64-65 (1983).

<sup>188</sup> WLF II, *supra* note 170, at 62.

<sup>189</sup> WLF II, *supra* note, at 62 (citing *First National Bank of Boston v. Bellotti*, 435 U.S. 765, 784 (1978) (holding that speech does not lose First Amendment protection merely because it was uttered by a corporation)). It was thought that the Supreme Court might clarify this issue further in *Nike v. Kasky*, 156 L. Ed. 2d 580, 123 S. Ct. 2554 (2003), but the Court dismissed the case on procedural grounds.

<sup>190</sup> See A. Elizabeth Blackwell & James M. Beck, *Drug Manufacturers First Amend Right to Advertise and Promote Their Products for Off-Label Use: Avoiding a Pyrrhic Victory*, 58 FOOD & DRUG L.J. 439, 446 (2003).

accomplish the government's objective.<sup>191</sup>

Applying the first prong, the court found that the speech was neither unlawful nor misleading.<sup>192</sup> While the FDA had argued that drugs must be considered misbranded and therefore illegal if they are promoted for off-label use, Judge Lamberth rejected this argument as tautological.<sup>193</sup> The proper question, he explained, is “not whether the speech violates a law or regulation, but whether the conduct that the speech promotes violates the law”<sup>194</sup> Since off-label prescription and off-label use are both lawful, the government could not make use of this prong. The court similarly dismissed the FDA's contention that the promotions would be misleading: “In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.”<sup>195</sup> Thus, while manufacturer's claims on labels or promotional materials are subject to FDA regulatory authority, conclusions reached by scientists in peer-review journals are not misleading simply because the FDA has not approved them.<sup>196</sup> “The FDA is not a peer review mechanism for the scientific community.”<sup>197</sup>

Next, the court had little difficulty determining that the government's interest was substantial. Few things are more important, Judge Lamberth wrote, than “ensuring that when a citizen takes a prescription drug, that individual has absolute assurance that the product is safe and effective for the condition for which his physician has prescribed it.”<sup>198</sup> He further noted that the Supreme Court has consistently held that the government has a substantial interest in protecting the health and safety of its citizens.<sup>199</sup> The court also acknowledged that the government has an interest in providing manufacturers with an incentive to receive

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<sup>191</sup>Central Hudson, 447 U.S. at 564-66.

<sup>192</sup>WLF II, *supra* note 170, at 69.

<sup>193</sup>*Id.* at 66.

<sup>194</sup>*Id.* (citing 44 Liquormart v. Rhode Island, 517 U.S. 484, 497 n.7).

<sup>195</sup>*Id.* at 67.

<sup>196</sup>*Id.*

<sup>197</sup>*Id.* (quoting Lars Noah & Barbara A. Noah, *Liberating Commercial Speech: Product Labeling Controls and the First Amendment*, 47 FLA. L. REV. 63, 96 (1995)).

<sup>198</sup>WLF II, *supra* note 170, at 69.

<sup>199</sup>*Id.*

approval for previously unsanctioned uses, but rejected the FDA’s claim that there is a substantial government interest in ensuring that unbiased information is disseminated to physicians.<sup>200</sup>

Similarly, the FDA satisfied the third prong of the *Central Hudson* test; the agency’s policy directly advanced the substantial government interest.<sup>201</sup> The FDA’s regulations limiting a manufacturer’s ability to promote off-label uses, encourage the manufacturer to seek supplemental approval of newly discovered uses. “[O]ne of the few mechanisms available to FDA to compel manufacturer behavior is to constrain their marketing options.”<sup>202</sup> Thus, if a manufacturer is proscribed from distributing enduring materials that discuss an off-label use of the manufacturer’s product, “that proscription provides a strong incentive to get the use on-label.”<sup>203</sup>

Nevertheless, the court deemed the regulations unconstitutional because they were more extensive than necessary.<sup>204</sup> While the FDA did not need to prove that it employed the least restrictive means possible, at it would have had to under strict scrutiny, the agency’s regulations could not burden “substantially more speech than necessary.”<sup>205</sup> Requiring “full, complete, and unambiguous disclosure by the manufacturer” would accomplish the agency’s goals without unduly burdening commercial speech.<sup>206</sup> The disclosure would alert physicians to the off-label status of the promoted use while still allowing the manufacturer could communicate its message. Moreover, the FDA’s goal of ensuring compliance with the overall regulatory structure would not be hindered. “There still are enormous differences between the permitted marketing of on-label as opposed to off-label uses.”<sup>207</sup> For instance, manufacturers may not distribute internally-produced marketing

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<sup>200</sup> *Id.* at 69 – 71. The court rejected the FDA’s second contention because of its paternalistic assumption that the medical community needs to be protected from truthful commercial information. *Id.* at 69-70. The Supreme Court has noted that “the First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good.” *44 Liquormart*, 517 U.S. at 503.

<sup>201</sup> *WLF II*, *supra* note 170 at 71.

<sup>202</sup> *Id.* at 72

<sup>203</sup> *Id.*

<sup>204</sup> *Id.*

<sup>205</sup> *Id.* (quoting *United States v. Edge Broadcasting Co.*, 509 U.S. 418, 430 (1993)).

<sup>206</sup> *Id.* at 73

<sup>207</sup> *Id.*

literature to physicians in order to promote off-label uses. Pharmaceutical companies also many not engage in direct-to-consumer advertising to increase demand for off-label uses.<sup>208</sup> Finally, the FDA approval is an important indication of safety and effectiveness. Physicians will take notice of this endorsement – or the lack there of – and manufacturers will seek it.<sup>209</sup>

The FDA’s policy of restricting off-label promotion was therefore held unconstitutional<sup>210</sup> and the court used its injunctive power to specify the realm of manufacturer activity protected by the First Amendment.<sup>211</sup> Under the terms of the injunction, the FDA could not “in any way prohibit, restrict, sanction, or otherwise seek to limit any pharmaceutical . . . manufacturer:

from disseminating . . . [to] medical professionals any articles concerning prescription drugs . . . published in a bona fide peer-reviewed professional journal, regardless of whether such article includes a significant or exclusive focus on uses of drugs . . . other than those approved by FDA. . . .<sup>212</sup>

Similarly, the FDA could not prohibit manufacturers from dissemination articles from reference textbooks regardless of whether the article dealt with an off-label use.<sup>213</sup> Finally the FDA was ordered not to prevent manufacturers from suggesting content or speakers to independent CME providers, regardless of whether the content or speaker would address off-label uses.<sup>214</sup>

Judge Lamberth did, however, add one note of caution at the end of his opinion. Nothing in the injunction, he wrote, should be construed to limit the FDA’s ability to enforce laws and regulations prohibiting the distribution of false or misleading material.<sup>215</sup> Moreover, the FDA is free to insist that manufacturers disclose their financial interest in the subject of the distributed material and that fact that the FDA has not approved the discussed uses.<sup>216</sup>

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<sup>208</sup> *Id.*

<sup>209</sup> *Id.*

<sup>210</sup> *Id.* at 74

<sup>211</sup> Cooper, *supra* note 171, at 479.

The injunction, however, did not end the case. One year later a third WLF decision was announced in which Judge Lamberth made clear that his earlier injunction also applied to the newly passed FDAMA.<sup>217</sup> Although the FDAMA “altered to some extent” the FDA’s policies on off-label uses, the constitutional analysis remained the same and the new law was held unconstitutional.<sup>218</sup>

The stage was thus set for an appeal to the Circuit Court of Appeals. In a decision that has been described as unclear<sup>219</sup> and confusing,<sup>220</sup> the Circuit Court dismissed the FDA’s appeal and vacated the district court’s decisions and injunctions “insofar as they declare the FDAMA . . . unconstitutional.”<sup>221</sup> Curiously, the court did not reach the merits of the case. Rather, as a result of the government’s clarification of its position during oral arguments, the court found that “the dispute between the parties . . . disappeared before our eyes.” The case thus no longer presented a controversy to be resolved and was dismissed.

The court based its reasoning on the FDA’s declaration that the FDAMA “established nothing more than a ‘safe harbor’ ensuring that certain forms of conduct would not be used against manufacturers in misbranding and ‘intended use’ enforcement actions based on pre-existing legislative authority.”<sup>222</sup> In other words, the agency declared that the new law did not authorize it to restrict speech, but merely created an exception to the off-label restrictions *already found* in the FDCA for certain types of marketing. Since the FDAMA did not restrict speech, there was no need to apply the intermediate scrutiny found in the *Hudson* test or, for that matter, to determine whether the speech at issue was commercial (regulation of which requires intermediate scrutiny) or scientific (necessitating strict scrutiny.)

While this interpretation of the FDAMA was ambiguous in the FDA’s brief, the agency stated “definitively” during oral arguments that Act did not regulate speech.<sup>223</sup> In fact, when the court noted that one section specifically prohibited “the dissemination of information in violation of section 360aaa”<sup>224</sup> [(which describes the manner in which a manufacturer may legally disseminate off-label information) and thus, on its face, seemed to restrict speech, the counsel for the agency responded that the provision simply declares that “a manufacturer who disregards section 360aaa’s conditions cannot avail itself of the FDAMA safe harbor, and might be liable in some fashion if it breached an agreement with the Secretary pursuant to that section.”<sup>225</sup> Thus, as the court explained, “were a pharmaceutical company to send out reprints of an article devoted to its drug’s off-label uses to thousands of physicians tomorrow, the government agreed – indeed stipulated – that the agency would draw no independent prosecutorial authority from FDAMA to buttress any enforcement proceedings.”<sup>226</sup>



Upon learning the FDA's position, counsel for WLF stated that his client no longer had a constitutional objection to the FDAMA.<sup>227</sup> Since both parties agreed that the statute did not violate the First Amendment, the court dismissed the case.<sup>228</sup> The court was clear that "the government has announced here nothing less than an official interpretation of the FDAMA which the agency may not change unless it proves a reasoned explanation for doing so."<sup>229</sup>

These rulings produced a flurry of scholarship<sup>230</sup> and some confusion within the pharmaceutical industry.<sup>231</sup>

Much of the confusion can be traced to the court's cryptic final footnote:

"In disposing of the case in this manner, we certainly do not criticize the reasoning or conclusions of the district court. As we have made clear, we do not reach the merits of the district court's First Amendment holdings and part of its injunction still stands."<sup>232</sup>

Thus, although the circuit court vacated the injunctions and dismissed the case, it appeared to approve of the lower court's constitutional analysis.<sup>233</sup>

Shortly after the Circuit Court decision, the FDA clarified in a *Federal Register* notice its policy on off-label drug promotion.<sup>234</sup> The agency affirmed the safe harbor theory<sup>235</sup> and concluded that it may "proceed, in the context of case-by-case enforcement, to determine from a manufacturer's written materials and activities how it intends that its products be used."<sup>236</sup> If a drug manufacturer intends to promote an unapproved use and fails to comply with the safe-harbor requirements, the FDA will bring, the agency declared, a misbranding case.

Predictably, the issue once again found its way to Judge Lamberth's court room. This time the WLF brought a motion to confirm and enforce district court's earlier injunction.<sup>237</sup> The foundation argued that the FDA's latest iteration of policy was exactly what the court had earlier prohibited and should be banned.<sup>238</sup> Although the Circuit Court had vacated parts of the injunction, WLF argued that a portion of the injunction "still stands."<sup>239</sup>

The district court rejected this motion. Washington Legal Foundation had not claimed that the FDA's notice violated the First Amendment. It also did not argue that the agency's notice contradicted its official interpretation of the FDAMA as announced during oral arguments before Circuit Court.<sup>240</sup> Therefore, the court concluded that the motion was premised on whatever force was left in its earlier injunction, and "quite simply . . . [there was] none."<sup>241</sup> The injunction was based entirely on constitutional law and the Court of Appeals vacated the injunction "insofar as [it] declare[s] the FDAMA . . . unconstitutional."<sup>242</sup> Accordingly, the injunction had been "wholly vacated"<sup>243</sup> and the FDA's notice could not violate something that no longer existed.

Thus, the legality of off-label regulation remains uncertain. While it seems clear that a manufacturer is safe while operating within the FDAMA's safe harbor, it is possible that promotional activities occurring in waters beyond the harbor may be protected by the First Amendment as well. Indeed, Judge Lamberth concluded his decision by acknowledging the unsatisfactory outcome of this case:

Today, the Court adds another order to this case's voluminous file; yet the order will do little to resolve the issues that lies at the heart of this dispute: whether the FDA violates the First Amendment by penalizing drug manufacturers for sending scientific literature to physicians regarding off-label use. After six years' worth of briefs, motions, opinions, Congressional acts, and more opinions, the issue remains 100% unresolved, and the country's drug manufacturers are still without clear guidance as to their permissible conduct. To say that the FDA's . . . Notice finally clarifies the situation is a farce; the Notice specifically invites a constitutional challenge to each and every one of its enforcement actions. That is no way to establish policy on an issue that both sides argue is of – quite literally – life and death proportions<sup>244</sup>

## B. The Western States Case

The ultimate outcome in this policy debate remains unclear, and attempts to predict the future are almost always foolhardy. Nevertheless, it should be noted that many scholars have turned to the Supreme Court's recent *Western States*<sup>245</sup> decision for guidance. This case, which was decided after the *Washington Legal Foundation* series, dealt with the constitutionality of a different section of the FDAMA. Section 503A regulates the practice of pharmacy compounding. This practice "involves a pharmacist making a variation from an approved drug, based on a doctor's prescription, to meet the individual needs of a patient."<sup>246</sup> For example, a pharmacist might substitute an inactive ingredient if a patient is allergic to a component of the standard mixture or might prepare a sweeter version of a particularly bitter drug for a young child.<sup>247</sup> Any change in a drug, however, "even in the inactive ingredients, can affect its safety and efficacy."<sup>248</sup>

Compounding thus presents a similar regulatory challenge as off-label drugs. On one hand, there is considerable value in this practice and Congress during the FDAMA debates was loathe to ban it outright. On the other hand, the FDA expressed concern that unqualified approval could become a loophole in which pharmacies could mass produce unapproved drugs and act as de facto manufacturers.<sup>249</sup> Finally, industry noted that pre-market approval of special compounds is not feasible since it would be prohibitively costly and time-consuming for the FDA to approve each variation of a drug.<sup>250</sup>

The legislation that emerged took a middle position. Section 503A restricts a pharmacist's ability to advertise its ability to compound a specific drug, but does not prohibit a pharmacist's ability to advertise this practice generally.<sup>251</sup> More specifically, the Act exempts compounded drugs from the FDA's usual drug approval requirements so long as the pharmacy complies with the advertising restrictions.<sup>252</sup>

The compounding provisions of the FDAMA were challenged by a group of pharmacies specializing in compounding drugs on First Amendment grounds, and the Supreme Court ruled that the restrictions violated the Constitution's guarantee of free speech.<sup>253</sup> Since both parties agreed that the advertising restricted by Section 503A was commercial speech, Justice O'Connor, writing for the majority, concluded that the provisions would be analyzed under the *Central Hudson* framework.<sup>254</sup> Several commentators suggest that the Court's quick acceptance of the commercial speech framework reveals an emerging judicial consensus that restrictions on pharmaceutical advertising will be evaluated as prohibitions on commercial rather than scientific speech.<sup>255</sup>

Both parties agreed that the speech regulations did not satisfy the first prong of the *Central Hudson* test.<sup>256</sup> The advertisements at issue did not concern unlawful activity and could not be called misleading.<sup>257</sup> Instead, the dispute centered on the remaining three prongs: was there a substantial government interest, did the regulations advance this interest, were the regulations no more extensive than necessary. On the first prong, the Court accepted the government's assertion that it had a substantial interest in "preserving the effectiveness and integrity of the FDCA's new drug approval process and the protection of the public health that it provides."<sup>258</sup> This is significant because the FDA made a similar argument during the *WLF* cases.<sup>259</sup> The Court quickly passed the requirement that the regulation directly advance the government's interest, simply stating, "Assuming it is true that drugs cannot be marketed on a large scale without advertising, the FDAMA's prohibition on advertising compounded drugs might indeed 'directly advance' the government's interest."<sup>260</sup> Indeed, this reasoning resembles Judge Lamberth's ruling that one of the few mechanisms available to the government for influencing a manufacturer's behavior is to restrict its marketing options.<sup>261</sup> Instead, Justice O'Connor spent the most time on *Central Hudson*'s holding that the government's restrictions must be no more extensive than is necessary to serve its interests. She found, as Judge Lamberth did in *Washington Legal Foundation*, that the government could achieve its objective using less drastic means that prohibiting advertisements.<sup>262</sup>

In dicta that will likely guide future courts as they <sup>35</sup>consider the constitutionality of restrictions on off-label drug promotion, Justice O'Connor rejected the dissent's argument that the FDAMA's advertising ban was motivated by a desire to protect patients who do not need a compounded (and possibly dangerous) drug but might convince their doctors to prescribe them anyway.<sup>263</sup> The government does not, she explained, have an

Similarly, the majority rejected the argument that the government has an interest in banning the advertising of compounded drugs because patients might misunderstand the risks assumed in taking the medicine. Since the government did not contend that the advertisements were misleading, it could not logically argue that patients might be deceived or given the wrong impression.<sup>267</sup> Finally, Justice O'Connor noted that the amount of beneficial speech prohibited by Section 503A further supports the Court's decision to hold the new law unconstitutional.<sup>268</sup> The advertising restrictions "would affect pharmacists other than those interested in producing drugs on a large scale. It would prevent pharmacists with no interest in mass-producing medications, but who serve clients with special needs [such as patients in a children's hospital] from telling doctors . . . about . . . alternative drugs available through compounding."<sup>269</sup> Likewise, prohibitions against off-label drug advertising affect not only those manufacturers who hope to manipulate the system,<sup>270</sup> but also those manufacturers who legitimately discover a new use for an existing product and wish to share this information with physicians and their patients.

*Western States* and *Washington Legal Foundation* indicate that prohibitions against advertising off-label uses have a high constitutional hurdle to clear. While certainly the speech protected in the FDAMA safe harbor is protected, First Amendment rights to commercial speech may extend further. Future decisions will have to clarify this ambiguity.

Interestingly, the one post *WLF* and *Western States* decision to address off-label promotion found the FDAMA's provisions to be constitutional. In February 2003, the government brought a nineteen-count indictment against Ross Caputo and his business associates in United States District Court for the Northern District of Illinois.<sup>271</sup> The indictment charged the directors of the AbTox corporation with selling a misbranded medical device<sup>272</sup> when it promoted the off-label uses of its sterilizer.<sup>273</sup> Like earlier cases, Judge Ruben Castillo conducted a *Central Hudson* analysis and determined that speech did not concern an unlawful activity and was not misleading.<sup>274</sup> Moreover, noting that *Western States* identified maintaining the effectiveness and integrity of the new drug approval process as a substantial government interest, the court held that there was such an interest and the speech prohibitions directly advanced the government's objective.<sup>275</sup>

Yet in a departure from the holding of the D.C. District Court (and arguably the reasoning of the U.S. Supreme Court) Judge Castillo ruled that the regulations satisfied the final prong of the *Central Hudson* test – they were *not* more broad than necessary to advance the government’s interest.<sup>276</sup> Explaining his reasoning in just one paragraph, Judge Castillo noted that the “Defendants’ First Amendment challenge strikes at the every heart of the FDA’s ability to proscribe manufacturer promotion of off-label uses.” The court was “unable to identify a less burdensome alternative that would advance the government’s substantial interest.”<sup>277</sup> Judge Lamberth’s disclosure alternative was not mentioned.

It remains to be seen whether this case is an anomaly or represents an alternative method of analysis for off-label drugs. The different result could perhaps be explained by the fact that Judge Castillo was considering a small constitutional issue within the larger context of a criminal trial, while Judge Lamberth had the luxury of pondering the legality of the FDAMA in a case brought to explore the reaches of the First Amendment. Indeed, the *Caputo* case also dealt with mail fraud, wire fraud, conspiracy, and criminal violations of the Food, Drug, and Cosmetic Act.<sup>278</sup>

Given the attention that the *Washington Legal Foundation* cases generated and the similar reasoning found in *Western States*, a manufacturer willing to challenge the constitutionality of the FDAMA, would likely find itself in a favorable position. Judge Castillo’s decision will probably have little influence outside the Northern District of Illinois.

## V. The Neurontin Decisions

### A. The False Claims Act

The Neurontin controversy illustrates many of the principles discussed in the sections above. First unsealed in 1999 but originally filed in 1996, the case illustrates the latest attempt to regulate off-label drug use. The case arose under the False Claim Act (FCA). This law, which Congress originally passed to combat Civil War profiteering, has grown considerably in both scope and significance in recent years. It provides that any person who:

(1) knowingly presents or causes to be presented to an officer or employee of the United States Government a false or a fraud claim for payment or approval; [or who]  
(2) knowingly makes, uses, or causes to be made or used, a false record or statement to get a false or fraudulent claim paid or approved by the Government. . .  
is liable to the United States Government for a civil penalty . . . , plus three times the amount of damages which the government sustains because of the act of that person. . . .<sup>279</sup>

Although the legislative history focused on fraud committed by military contractors,<sup>280</sup> the FCA has emerged as the “federal government’s primary weapon to combat waste, fraud, and abuse”<sup>281</sup>

Much of the law’s success can be attributed to its unique enforcement mechanisms. A private party (referred to as a relator) who learns of fraud against the government through non-public sources is authorized to act a “de facto attorney general” and bring a legal action on the government’s behalf.<sup>282</sup> These suits, which are known as *qui tam* actions,<sup>283</sup> offer the relator strong incentives to identify and prosecute fraud; for each violation of the False Claims Act, a successful relator will collect a large percentage of the civil penalty and treble damages owed to the government.<sup>284</sup> The *qui tam* provisions therefore “offset inadequate law enforcement resources and encouraged ‘a rogue to catch a rogue’ by inducing informers ‘to betray [their] coconspirators.’”<sup>285</sup> Indeed, the False Claims Act’s success in deterring fraud on the federal government is well accepted and documented.<sup>286</sup> Those who would defraud the government are forced to consider the severe consequences of their actions and the real possibility of being caught.<sup>287</sup>

## B. The Complaint

The relator in the Neurontin case was David Franklin, a former “medical liaison” for Parke-Davis, a prescription drug manufacturer. Franklin alleged he was part of an “elaborate and clandestine” effort to promote the off-label uses of Neurontin.<sup>288</sup> The complaint, based on Franklin’s five months with the company,<sup>289</sup> alleged that his former employer engaged in a campaign of false and misleading statements that led the federal government to needlessly purchase Neurontin for Medicaid beneficiaries.

By way of background, Medicaid can generally only be used for “covered outpatient drugs.”<sup>290</sup> This term is defined to exclude drugs “used for a medical indication which is not a medically accepted indication.”<sup>291</sup> Medically accepted indications encompass uses which are approved under the Federal Food Drug and Cosmetic Act or are listed in statutorily specified drug compendia.<sup>292</sup> Thus, as the district court explained, “unless a particular off-label use for a drug is included in one of the identified drug compendia, a prescription for the off-label use of that drug is not eligible for reimbursement under Medicaid.”<sup>293</sup> On behalf of the United States government, Franklin, therefore, charged Parke-Davis with causing pharmacists, doctors, and patients to request and receive reimbursement for uses of Neurontin not covered by the Medicaid program.<sup>294</sup>



In 1994, the FDA approved Neurontin as an “adjunctive treatment” for epilepsy.<sup>295</sup> As such, Neurontin was not labeled for use by itself; instead, it was envisioned as an “add-on drug in the event that a primary anti-epilepsy drug was not successful.”<sup>296</sup> The medicine was approved for adults and in dosages of 900 to 1800mg/d.<sup>297</sup> In his amended complaint, Franklin observed that while the market for the approved use of Neurontin was limited, “the market for the others uses of Neurontin contemplated by Parke-Davis – pain management, psychiatric disorders, anxiety, and depression – was huge.”<sup>298</sup> Parke-Davis’ desire to enter this broader market, the complaint argued, led it to illegally promote Neurontin’s many off-label uses.<sup>299</sup>

Franklin described a “publication strategy” in which Parke-Davis allegedly used and then surpassed the limited leeway it had to promote off-label uses of Neurontin.<sup>300</sup> There were several reasons, Franklin explained, to engage in this legally questionable campaign. First, Parke-Davis concluded that it would “be uneconomical to assume the expense and time necessary to conduct clinical trials to prove that Neurontin was safe and effective” for off-label uses.<sup>301</sup> Indeed, even if the research were successful, and the off-label uses were shown to be safe and effective, Parke-Davis’ patent would soon expire and generic manufacturers would “reap much of the reward of proving Neurontin could be safely used for other indications.”<sup>302</sup> By promoting off-label drugs surreptitiously, Parke-Davis expanded its product’s market without the expense usually associated with such an endeavor. Moreover, Franklin noted, the publications strategy had an additional advance – it could be launched immediately.<sup>303</sup> There was “no need to wait for the results of scientifically conducted clinical trials to determine if Neurontin was actually effective in the treatment of these conditions.”<sup>304</sup>

Franklin identified several components of Parke-Davis’ strategy. First, the company sought to take advantage of a pre-FDAMA regulation that permitted manufacturers to distribute publications describing off-label uses of already approved drugs so long as the publications were produced by third parties.<sup>305</sup> Parke-Davis created “events and programs that would allow special Parke-Davis employees and independent contractors under Parke-Davis’ control to promote off-label usage under circumstances that would allow the company to plausibly deny that it had solicited off-label usage.”<sup>306</sup> For example, the company allegedly “hired non-physician technical writers to create articles<sup>40</sup> for medical journals and the paid actual specialists to be the articles’ authors.”<sup>307</sup>

This ghost writing scheme was elaborate. Parke-Davis allegedly had complete control over the content of dozens of articles. It worked with hired technical writers to conceive the article idea, fabricate ideas, and

These medical liaisons were supposed to provide “balanced scientific information to doctors” but, in fact, were charged with aggressively soliciting requests for off-label information from physicians.<sup>316</sup> Liaisons were allegedly trained to provide “non-scientific, anecdotal information designed to convince physicians that off-label usage of Neurontin were safe and effective.”<sup>317</sup> In essence, the medical liaisons functioned as a “surrogate sales force who had the liberty to solicit physicians regarding off-label uses.”<sup>318</sup>

Franklin further claimed that Parke-Davis knew that it was inappropriate to use medical liaisons in this capacity. Before receiving his job offer, the company asked Franklin whether he had difficulty working in gray areas or bending rules, and during a training session, he was warned that “under no circumstances should any information about off-label uses be put in writing.”<sup>319</sup>

To support his allegations, Franklin recorded conversations he had with Parke-Davis executives. For example, in a May 1996 teleconference, John Ford, a marketing executive in the company’s New Jersey headquarters instructed the medical liaisons that in order to remain profitable, Neurontin had to be marketed for monotherapy (it had only been approved as an adjunctive therapy), pain, bipolar disease and other psychiatric disorders.<sup>320</sup> Each of these uses were off-label. In other conversation, “Ford was even blunter”:

I want you out there every day selling Neurontin... We all know Neurontin is not growing [as an] adjunctive therapy, beside that is not where the money is. Pain management, now that’s money. Monotherapy, that’s money. We don’t want to share these patients with everyone, we want them on Neurontin only. We want their who drug budget, not a quarter, not half, the whole thing... We can’t wait for them to ask, we need to get out there and tell them up front... That’s [why] we need to be holding their hand whispering in their ear Neurontin for pain, Neurontin for monotherapy, Neurontin for everything... I don’t want to see a single patient coming off Neurontin until they have been up to at least 4800mg/day. I don’t want to hear that safety crap either; have you tried Neurontin? Every one of you should take one just to see there is nothing; it’s a great drug.<sup>321</sup>

Tying these allegation in to the False Claims Act, Franklin observes that a “key aspect of this selling was misrepresentation.” First, the status of the medical liaisons was misrepresented. Medical liaisons were introduced as specialists in the specific use they were pressing at a particular meeting.<sup>322</sup> Thus, medical liaisons could be experts in anti-epileptic drugs during a morning session and an expert in cardiac medication in the afternoon.<sup>323</sup> “Sales personnel were instructed to introduce medical liaisons as scientific employees who were given momentary leave of their academic duties to make an individual presentation to the physician; the fact that the liaisons were part of the Parke-Davis’ standard marketing detail was intentionally hidden.”<sup>324</sup> The information conveyed to the physicians was equally false. “Extensive misrepresentations” were made regarding the scientific evidence for various off-label uses.<sup>325</sup> Depending on the use promoted, medical liaisons fabricated studies, exaggerated results, de-emphasized adverse effects of the drug, exaggerated the value of anecdotal evidence, and misrepresented Parke-Davis’ role in creating and sponsoring the distributed publications.<sup>326</sup>

Concluding his allegations, Franklin observed that “one-quarter to one-third of all Neurontin prescriptions in the United States were paid for by the Medicaid program.”<sup>327</sup> Because off-label uses are not eligible for reimbursement, he argued, “submission of a claim for reimbursement constitutes a false claim for the purposes of [the False Claims Act.]”<sup>328</sup> While, it is the pharmacist who physically submits the false claim, a person who knowingly causes such a claim to be filed is equally liable under the law.<sup>329</sup> “Parke-Davis knew that off-label prescriptions for Neurontin were ineligible for Medicaid reimbursement and that its activities would, in fact, cause numerous ineligible prescriptions to be submitted to Medicaid.”<sup>330</sup>

### C. Two Decisions

While the case has not yet settled or reached a conclusion, Judge Patti Saris of the United States District Court for the District of Massachusetts has ruled on Parke-Davis' motion to dismiss<sup>331</sup> and motion for summary judgment.<sup>332</sup> Both motions were denied.

In her decision denying the motion to dismiss, Judge Saris quickly rejected Parke-Davis' argument that Franklin did not plead with the specificity required by Federal Rule of Civil Procedure 9(b).<sup>333</sup> A more difficult question was Parke-Davis' contention that Franklin failed to state valid claim.

The pharmaceutical manufacturer argued that a relator "cannot use the FCA as an end-run around the enforcement provisions of the FDCA by creating a cause of action for money damages."<sup>334</sup> In a ruling significant for not only the parties in this case but the pharmaceutical industry as a whole, the court rejected this line of reasoning. While Judge Saris acknowledged that the FDCA does not provide the government with a civil damage remedy to enforce the ban on off-label promotion,<sup>335</sup> she held that this omission does not "preclude [an] FCA claim where the manufacturer has knowingly caused a false statement to be made to get a false claim paid or approved by the government."<sup>336</sup> Furthermore, although there is not an FCA cause of action each time a federal law or regulation is violated, the Act does create liability when "failure to abide by a rule or regulation amounts to a material misrepresentation[] made to obtain a government benefit."<sup>337</sup>

Parke-Davis next argued that the promotion of off-label uses does not constitute a false statement or fraudulent conduct as required by the act.<sup>338</sup> This contention was also rejected.<sup>339</sup> While simply distributing a scientific article might not rise to the level of an actionable offense, Franklin alleged “more than a mere technical violation” of the off-label regulations.<sup>340</sup> “The gravamen of Relator’s claim is that Parke-Davis engaged in an unlawful course of fraudulent conduct including knowingly making false statements to doctors that caused them to submit claims that were not eligible for payment by the government under Medicaid.”<sup>341</sup> Thus, the alleged FCA violations arose not from the unlawful marketing activity itself, but from the manufacturer’s attempt to cause others to defraud the government.<sup>342</sup>

Next Parke-Davis argued that the illegal actions of doctors and pharmacists were an “intervening force” breaking the causal connection between its own actions and the fraud on the government.<sup>343</sup> This idea was summarily rejected as a matter of black letter law.<sup>344</sup> Such an argument would only be sustained if the intervening force was unforeseeable, and “participation of doctors and pharmacists in the submission of false claims was not only foreseeable, it was an intended consequence of the alleged scheme of fraud.”<sup>345</sup>

Concluding her opinion,<sup>346</sup> Judge Saris seemed to recognize the significance of the case before her and to signal her receptiveness to Franklin’s basic premise:

To be sure, Relator’s theory of liability takes the parties into territory that is not well-charted by the existing decisional law. Nevertheless, the statutory language – which must provide the touchstone for the Court’s analysis – supports Relator’s somewhat expansive claim. . . . Moreover, the terms of the FCA must be read liberally in accordance with their remedial purpose.<sup>347</sup>

In her order denying Parke-Davis' motion for summary judgment Judge Saris discussed and elaborated on similar themes. First, Parke-Davis argued that it could not be held liable because it did not make a false statement.<sup>348</sup> Under the company's interpretation of the FCA, "an FCA plaintiff must prove a false statement that led to a false claim."<sup>349</sup> The court, however, rejected the idea that the FCA contains a "double-falsehood requirement."<sup>350</sup> Examining the text of the statute,<sup>351</sup> Judge Saris concluded that in order for §§3729(a)(1) and (a)(2) to have different meaning, as canons of statutory interpretation require, only (a)(2) can be logically read as containing a double-falsehood requirement.<sup>352</sup> While §3729(a)(2) imposes liability on any person who "knowingly makes, uses, or causes to be made or used *a false record or statement* to get a *false or fraudulent claim* paid or approved by the government" §3729(a)(1) merely creates liability when a defendant "knowingly presents, or causes, to be presented . . . *a false or fraudulent claim.*"<sup>353</sup> Since Franklin did not limit his claims to §3729(a)(2) he did not need to prove that Parke-Davis lied to physicians about Neurontin's off-label efficacy or safety.<sup>354</sup> There is sufficient evidence to hold a manufacturer liable if it is proven that the company simply induced physicians or pharmacists to file false claims with truthful statements.<sup>355</sup>

Note that this section of the opinion clarified an ambiguous passage of the court’s earlier opinion and underscored the influence this case may have on industry practice. In her earlier decision, Judge Saris noted in dicta that “A much closer question would be presented if the allegations involved only the unlawful – yet truthful – promotion of off-label uses to physicians who provide services to patients who are covered by Medicaid *without any fraudulent representation by the manufacturer.*”<sup>356</sup> In dismissing Parke-Davis’ motion for summary judgment, however, Judge Saris wrote: “With the benefit of a more fulsome factual record, it is now apparent that the ‘much closer question’ can no longer be ducked. Under §3729(a)(1), the only issue is whether Parke-Davis ‘caused to be presented’ a false claim, and §3729 does not require that the ‘cause’ be fraudulent or otherwise independently unlawful.”<sup>357</sup> This ruling is significant. A manufacturer need not lie or deceive in order to incur liability. Simply encouraging physicians or pharmacists to recommend drugs in an off-label manner could make a drug company susceptible to a False Claims cause of action.

In its motion for summary judgment, Parke-Davis withdrew its earlier statement that the company “does not dispute that an off-label prescription submitted for reimbursement by Medicaid is a false claim within the meaning of the FCA.”<sup>358</sup> As discussed above, the Medicaid program will only pay for “covered outpatient drugs” and this term excludes drugs prescribed for off-label purposes.<sup>359</sup> Parke-Davis argued, however, that “forty-two states permit reimbursement for off-label, non-compensum drug prescriptions. . . . [T]herefore claims for Medicaid reimbursement for off-label Neurontin prescriptions in those states were not false claims.”<sup>360</sup> In support of this conclusion, the company cited 42 U.S.C. § 1396r-8(d)(1)(B) which it contends allows states to decide for themselves whether they wish to cover off-label drugs.<sup>361</sup> This statute states that “a state *may* exclude or otherwise restrict coverage of a covered outpatient drug if – (i) the prescribed use is not for a medically accepted indication.”<sup>362</sup> Since this provision uses the word “may,” the company argued, states need not and most do not exclude coverage. Franklin, however, disputed Parke-Davis’ conclusion that 42 states will reimburse for Neurontin.<sup>363</sup> Moreover, he argued that §1396r-8 only encompasses “*covered* outpatient drugs” and, as noted earlier, this phrase excludes off-label uses.<sup>364</sup>

While acknowledging that Franklin’s interpretation of §1396r-8 rendered it superfluous and thus less desirable, Judge Saris ultimately concluded that “it is not clear which side gets the better of the statutory-tail-chases-cat debate” and reserved judgment until the government submits an amicus brief stating its “understanding of the extent to which the Medicaid statute empowers states to provide coverage of off-label, non-compensum prescriptions.”<sup>365</sup> The court was able to avoid the issue because Parke-Davis had acknowledged that eight states do not offer reimbursement for off-label prescriptions and in those states submitting a request for payment constitutes a false claim.<sup>366</sup> Thus, “at best Parke-Davis’ argument goes to the amount of damages and does not provide a basis for summary judgment of liability under the FCA.”<sup>367</sup>

#### D. Implications



The significance of this case has not gone unnoticed. In an October 2003 speech, Assistant U.S. Attorney Virginia Gibson commented that prosecutors across the country are monitoring the case and have found the opinion “instructive.”<sup>368</sup> She further noted that the opinion sanctions lawsuits against manufacturers who use “truthful” off-label promotion but nevertheless violate the law.<sup>369</sup> Gibson outlined the types of evidence the Department of Justice would consider when determining whether to prosecute a manufacturer for off-label promotion.<sup>370</sup> For example, “we would look at a situation where . . . there was a very small market for the approved use . . . but there was a very large sales force. That would prompt us to look further.”<sup>371</sup> Other factors that would attract attention from DOJ officials included “financial incentives for off-label use only; failure to identify the company’s funding for research for articles that it presents . . . [and] health consequences from off-label uses that are not disclosed.”<sup>372</sup> Finally, Ms. Gibson affirmed that prosecutors will “look at the role of the manufacturer in the prescribing activity at all levels – whether there were inducements, whether there were false statements.”<sup>373</sup> Indeed, the Boston U.S. attorney’s office has filed a statement of interest with the court and is negotiating a settlement with Parke-Davis.<sup>374</sup>

At the same conference, Paul Kalb, a Washington DC attorney told participants that he believes FCA cases involving off-label promotion will increase.<sup>375</sup> Since the FCA, unlike the FDCA, creates a private right of action, there will be countless potential whistleblowers available to bring suit.<sup>376</sup> Indeed, other attorneys have reached similar conclusions: “This is going to be the seminal case for off-label False Claims Act litigation” a former Justice Department lawyer commented.<sup>377</sup> “The Neurontin case is a wake-up call to the manufacturer community to take a hard look at how their compliance and training is set up.”<sup>378</sup>

## VI. Conclusion

Promotion of off-label drugs presents a policy conundrum for the courts, the FDA, and Congress. As with most regulation of the prescription drug industry, policy makers must walk a fine line between protecting the public's interest in safe and effective medicine and allowing the sick access to the medicine they need. This balancing is only more difficult in the area of off-label promotion. The drug has been approved by the FDA; it is on the market; doctors are free to prescribe it; and there is usually some evidence that the new use is safe and effective. Nevertheless, for very legitimate reasons, the FDA restricts manufacturers' ability to inform physicians and the public of their products' off-label capabilities.

The FDA is no doubt correct that the pharmaceutical industry needs a reason to seek the government's endorsement of newly discovered uses. The approval process is long, cumbersome, and expensive, and manufacturers are operating in the shadow of their product's looming patent expiration. Few would voluntarily endure this process if they were not rewarded with the ability to promote their product to a new set of patients. Yet, the Agency's regulations seem to clash with First Amendment values for the government is restricting the distribution of information. If a product is sold legally, and if manufacturers are not lying or deceiving, why should there be limitations on communicating with physicians? It is perhaps this collision of values that has kept the legal status of off-label drugs nebulous. Indeed, the FDA, the courts, and Congress seem unable to decide whether to frown upon or approve of off-label promotion and many questions remain. The constitutionality of regulations restricting off-label promotion has not been decided definitively. While Congress, no doubt, has created a safe harbor for manufacturers, are activities outside this small area also protected by the Constitution? If a manufacturer distributed a sales brochure rather than a scientific article, it would surely violate the FDAMA, but perhaps this activity is protected by the First Amendment.

The Neurontin lawsuit only exacerbates an already complicated area of the law. If Franklin is successful, private whistleblowers will be able to trump whatever balance Congress created in the FDCA and FDAMA. Manufacturers who wish to promote off-label uses of their products will either have to risk a false claims lawsuit or simply stop promoting off-label drugs altogether. Surely this is not a desirable outcome. It is not economically feasible to seek approval<sup>49</sup> for all uses of drugs, and physicians need more information to treat their patients, not less.

Drugs used for cancer treatment illustrates this point. As discussed above,<sup>379</sup> most oncologists rely on off-label drugs to treat their patients. Often the off-label drug offers the only hope of saving a life. Few could

Perhaps Neurontin is a bad case from which to evaluate the debate over off-label promotion. At least in the early stages of the lawsuit, it appears that Parke-Davis went well past what it legally can do (as well as what it morally should do) in order to sell its product. There is no reason to believe that other companies would act as aggressively if restrictions on off-label promotion were relaxed.

On the other hand, perhaps this case illustrates precisely why FDA regulation is needed. Companies respond to natural pressures from the marketplace by trying to sell more goods. Indeed, in most industries, increased sales is a sure sign of success. Perhaps, therefore, the pharmaceutical industry – and the public – needs government regulation to check a manufacturer's ability to promote a product that it believes is life-saving but may be deadly.

Commentators have struggled with these problems and have arrived at a variety of conclusions. Some argue that we ought to simplify the approval process so that it will be less burdensome to manufacturers.<sup>381</sup> Others have suggested that tort law or anti-trust law will protect patients and the government need not specifically regulate off-label promotion.<sup>382</sup> While it is true that these areas of the law offer an important avenue of compensation and restrict truly outrageous behavior, these commentators ignore what seems to be the lesson of the Neurontin and Washington Legal Foundation lawsuits – there should be a comprehensive policy of off-label promotion that balances society's multitude of interests.

This balancing is a task for Congress and not private litigants. While I do not dispute the need for compensation when injuries occur, only a legislative body can weigh the many competing interests. Although it is no doubt difficult, and it will surely be impossible to please all parties, Congress ought to develop a comprehensive policy that balances the right to communicate and the need for information with legitimate concerns about patient safety. This policy should not be set by *qui tam* lawsuits, tort cases, or even constitutional challenges. Rather, it should be created by the government itself.