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# Verify, Then Trust: How to Legalize Off-Label Drug Marketing

Fazal Khan, M.D., J.D.\* & Justin Holloway, J.D.\*\*

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\* Associate Professor of Law, University of Georgia School of Law.

\*\* J.D. 2012, University of Georgia School of Law.

## I. INTRODUCTION

The Food and Drug Administration (FDA) only allows drugs in the marketplace after pharmaceutical companies prove that they are both “safe” and “effective.”<sup>1</sup> Once the FDA approves a drug, doctors can legally prescribe the drug in any manner they choose. The FDA does not regulate the practice of medicine, and “physicians are free to prescribe ‘any legally marketed device’ for uses other than those approved by the FDA.”<sup>2</sup> Physicians have this freedom under the premise that it allows them “to provide the best-available treatments when the FDA approval process does not keep pace with medical advancements or when rare diseases do not affect enough patients to economically justify manufacturers’ seeking FDA approval for new uses to treat these diseases.”<sup>3</sup> In fact, doctors often prescribe drugs for medical indications other than the FDA tested and approved uses in a practice known as “off-label” drug use.<sup>4</sup>

To maximize profits, major pharmaceutical companies (“pharma”) primarily rely on two disparate business practices—innovation and marketing.<sup>5</sup> Obviously, discovering additional uses for pre-existing drugs can result in an expanded market and increased profits for these products. However, it is illegal for pharma to actively market these “off-label” uses without securing FDA approval for these additional indications. Pharma, however, can conduct research outside of the FDA regulatory process to discover additional uses for a specific drug. In turn, these studies on alternative uses might persuade doctors to prescribe the drug in an off-label manner, but only if doctors become aware that such off-label uses are medically indicated.<sup>6</sup> How this off-label usage information reaches doctors is a contentious legal point.<sup>7</sup> There is a fine line “between drug companies providing information about possible off-label uses and drug companies promoting use in a manner not sanctioned by the [FDA].”<sup>8</sup>

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1. 21 C.F.R. § 310.301 (2006); see George S. Craft, Jr., *Promoting Off-Label in Pursuit of Profit: An Examination of a Fraudulent Business Model*, 8 HOUS. J. HEALTH L. & POL’Y 103, 104 (2007).

2. Craft, *supra* note 1, at 105 (citing 21 U.S.C. § 396 (2006 & Supp. 2010)).

3. *Id.*

4. See Anique Gonzalez, *Drug Companies and “Off-Label” Marketing*, GEN. COUNSEL CONSULTING, <http://bit.ly/RgGaLK> (last visited Oct. 22, 2012).

5. Craft, *supra* note 1, at 104. In this article, when the authors use the term “pharma,” they are referring to multi-national pharmaceutical companies that principally rely on patented drugs, as opposed to generic drugs, for their profits.

6. See Craft, *supra* note 1, at 108-09.

7. See *id.* at 105-06.

8. Gonzalez, *supra* note 4.

Belying pharma's claims that drugs cost so much because of research and development (R&D) expenses, over the past decade, drug manufacturers have spent approximately twice as much on marketing existing drugs than on R&D for new drugs.<sup>9</sup> In 2002, before the Department of Justice (DOJ) began actively investigating the prevalence of off-label marketing,<sup>10</sup> the ten largest pharmaceutical companies spent 31 percent of their revenues on marketing.<sup>11</sup> Comparatively, these same ten companies spent only 14 percent on R&D.<sup>12</sup> Given these statistics, it comes as no surprise that a 2001 study revealed that doctors prescribed drugs in an off-label manner 21 percent of the time.<sup>13</sup> However, the truly alarming fact associated with this finding is that 73 percent of these off-label drug usages had little or no scientific support.<sup>14</sup> In other words, the vast majority of off-label prescriptions imposed unnecessary medical risks on patients and unnecessary financial costs on payors (*i.e.*, patients, private insurers, self-insured employers, Medicare, and Medicaid).

A major reason for the high prevalence of off-label usage is the rigorous clinical testing imposed by the FDA for a new drug application (NDA). In its role as "market gatekeeper," the FDA will reject an NDA if: (1) the accompanying submitted reports "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof";<sup>15</sup> (2) "the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions";<sup>16</sup> or (3) "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."<sup>17</sup> In other words, the FDA will not accept a NDA unless there is substantial evidence that regulators could fairly and responsibly conclude that the

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9. Craft, *supra* note 1, at 104.

10. In the latter part of the decade, pharmaceutical giants Pfizer and Eli Lilly & Co. settled civil and criminal lawsuits in excess of \$1.4 billion each, and smaller companies settled suits for hundreds of millions of dollars. See Melly Alazraki, *Pfizer Pays a Record \$2.3 Billion to Settle Criminal Charges*, DAILYFINANCE.COM (Sept. 2, 2009, 3:00 PM), <http://aol.it/4WMzB>.

11. Craft, *supra* note 1, at 104.

12. *Id.* at 104-05.

13. David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1023 (2006), available at <http://bit.ly/RR413E>.

14. *Id.*

15. 21 U.S.C. § 355(d) (2006 & Supp. 2011).

16. *Id.*

17. *Id.*

drug will have the effect it purports to have under the conditions of use prescribed or recommended in its proposed labeling.<sup>18</sup>

Given the costly and time-consuming process for obtaining FDA approval for off-label uses, coupled with the flexibility in the practice of “medical arts,” pharma has limited incentive to submit market-approved products for additional FDA testing. In fact, if an approved drug has a large off-label market, there is a significant financial risk for drug manufacturers in seeking FDA validation for these uses. If the clinical trials reveal negative safety or efficacy data, the already established off-label market for the drug would cease to exist. Consequently, there is a substantial gap in reliable scientific data supporting the safety and efficacy of drugs used in an off-label manner.<sup>19</sup>

As a result of the decreased safety and efficacy in off-label prescribing, the FDA, DOJ, and the Office of Inspector General of the U.S. Department of Health and Human Services (OIG) have pursued stringent investigations of pharma.<sup>20</sup> These three bodies have prosecuted manufacturers guilty of illegal off-label promotion as violations of the Food, Drug, and Cosmetic Act of 1938 (FDCA) and the federal False Claims Act (FCA).<sup>21</sup> Investigations in the past five years have led to payouts by Pfizer and Eli Lilly, two titans in the industry, of \$2.3 billion and \$1.42 billion, respectively.<sup>22</sup> Moreover, since 2004, “Pfizer, Eli Lilly & Co., Bristol-Myers Squibb Co., and four other drug companies have paid a total of \$7 billion in fines and penalties.”<sup>23</sup> However, at the same time, from 2001 to 2008, Pfizer made \$16.8 billion in revenue from selling the medicines it was fined for, and Eli Lilly made \$36 billion in revenue from off-label prescribing of a single drug between 2000 and 2008.<sup>24</sup> Emphasizing not just the profitability but prevalence of off-label sales, in 2002, Pfizer earned \$2.27 billion from sales of a drug Neurontin, of which \$2.12 billion (approximately 94 percent of overall sales for the drug) came from off-label use.<sup>25</sup> While these fines may seem staggering in isolation, their deterrent effect pales in comparison with the huge financial profits stemming from off-label marketing. As an amoral

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18. Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL’Y L. & ETHICS 717, 730-31 (2005).

19. *Id.* at 731.

20. Craft, *supra* note 1, at 105.

21. *See id.* at 107-08, 112-15; *see also* John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL’Y L. & ETHICS 299, 308-14 (2010).

22. Alazraki, *supra* note 10.

23. David Evans, *Pfizer Broke the Law by Promoting Drugs for Unapproved Uses*, Bloomberg (Nov. 9, 2009, 12:01 AM), <http://bloom.bg/1y6tDl>.

24. *Id.*

25. *Id.*

economic actor, pharma could conclude that such fines are a “cost of doing business” and not substantially change their illegal business practices.<sup>26</sup>

This article will discuss the current state of off-label medicine, relevant legislation in the area, and a proposal designed to capture the benefits of off-label medicine while limiting its dangers when practiced perniciously. Part II will discuss the regulations in place governing off-label promotion and will detail the practice of ghostwriting and its associated concerns. Part III will analyze the costs and benefits of off-label marketing and practice of medicine, and will utilize a case study to demonstrate the predicament of drug manufacturers. Part IV will set forth a proposal to use the newly created Patient-Centered Outcomes Research Institute to generate unbiased research on off-label uses, which, in turn, would create a safe harbor for drug companies to widely disseminate studies generated through this process to the medical community. Finally, Part V will present concluding thoughts on the overarching policy considerations driving the need for legislative reform.

## II. OFF-LABEL MARKETING: A TALE OF REGULATORY FAILURE

The FDA serves as the gatekeeper when it comes to ensuring that drug manufacturers abide by federal regulations and properly submit their drugs for testing. Although the FDA does not have the authority to prevent medical practitioners from prescribing previously approved drugs for off-label purposes, it has statutory authority over pharma’s marketing of such drugs and uses this authority to prevent manufacturers from engaging in illegal off-label promotion.<sup>27</sup>

The FDA draws its statutory authority to regulate the sale and marketing of drugs in the U.S. via the FDCA.<sup>28</sup> The FDCA bestows substantial authority upon the FDA to determine the safety and efficacy of all “new” (including approved drugs that are being marketed for an unapproved use) drugs prior to marketing and to regulate a new drug’s proposed labeling to ensure that it is not false or misleading.<sup>29</sup> “Labeling” is a term of art that encompasses more than simply the external label on a bottle; it is defined under the FDCA to include all tangible material that accompanies a drug.<sup>30</sup> Specifically, labeling

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26. *Id.*

27. Eisenberg, *supra* note 18, at 733.

28. Osborn, *supra* note 21, at 308 (citing 21 U.S.C. §§ 301-99 (2006)).

29. *Id.*

30. *Id.*; see also Richard C. Ascroft, *The Impact of the Washington Legal Foundation Cases on Pharmaceutical Manufacturer Practices in the United States*, 34 IND. L. REV. 95, 100 (2000).

“includes the product’s package insert and promotional materials, including the detailing brochures used by the manufacturer to promote sales of the product”;<sup>31</sup> thus, this broad language allows the FDA to control the marketing and promotion of new drugs.

Investigations surrounding off-label promotion have relied on two theories under the FDCA. The first theory contends that off-label promotion constitutes misbranding, meaning that the product contains inadequate directions for the unapproved use or that the manufacturer has supplied “false or misleading” information concerning the product.<sup>32</sup> The second theory rests on a separate conception of misbranding, maintaining that “it constitutes the introduction of an unapproved new drug into interstate commerce.”<sup>33</sup>

A. *Legal Implications of FDA’s Broad Definition of “Labeling”*

Regarding the first theory pertaining to false or misleading information, the FDCA specifies that the drug’s labeling may not suggest that it be used for any new condition that has not been approved by the FDA. The FDA’s expansive reading of the term “labeling” includes nearly any item or information a drugmaker presents regarding a product, even materials that do not accompany the drug, such as promotions and advertisements.<sup>34</sup> Thus, the FDCA’s “prohibition of false or misleading labeling is transformed by the [FDA] into an effective prohibition on any advertisement, promotional message, or discussion that is not ‘consistent with’ the approved product labeling . . . regardless of whether it is truthful or accurately reflects good medical practice.”<sup>35</sup>

Advocates of liberal off-label usage argue that, to the extent the rule prohibits dissemination of information that is medically valid, it is illogical and harmful to the public interest.<sup>36</sup> Their contention is that the primary rationale for off-label medicine is to allow new treatments to be used therapeutically well before the exhaustive FDA approval process would allow. Therefore, by imposing this particular limitation, the FDA is frustrating the potential benefits of off-label medicine.

However, this deregulatory position ignores the risks of relaxing current limitations on off-label marketing and credulously accepts the

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31. Ascroft, *supra* note 30, at 100.

32. Craft, *supra* note 1, at 107 (quoting Jack Cinquegrana & Diana K. Lloyd, *Shifting Perspective on Off-Label Promotion*, PHARMEXEC.COM (Jan. 1, 2006), <http://bit.ly/QNxcUg>).

33. *Id.* at 108.

34. Osborn, *supra* note 21, at 308 (citing 21 C.F.R. § 202.1 (2012)).

35. *Id.* at 308-09.

36. *See infra* Part III (discussing the commonly identified benefits of off-label medicine).

“truthful” nature of studies funded by pharma. As discussed below, pharma has become quite adept at manipulating the information marketplace. One tactic instituted by pharma is the inclusion of contractual gag clauses to prevent clinical investigators from publishing unfavorable results that would negatively affect the financial interests of the pharmaceutical company.<sup>37</sup> Merck used this tactic to suppress negative safety data on Vioxx, a blockbuster anti-inflammatory drug that it later pulled from the market because of increased risks of heart attack and strokes associated with long-term use of this product.<sup>38</sup> Another troubling strategy used is “ghostwriting,” where professional writers are paid to create scientific publications and, in turn, researchers or doctors with impressive credentials are paid to attach their name and legitimacy to such articles.<sup>39</sup> Without checking these abuses, there will remain a valid suspicion that dissemination of “truthful” off-label findings can harm patients and the practice of medicine.

*B. Liability for Introducing Products into Interstate Commerce*

The second theory under the FDCA providing for the FDA’s regulatory powers is that the FDCA also makes it a crime to introduce an unapproved new drug into interstate commerce.<sup>40</sup> As previously mentioned, it is sometimes irrelevant that the drug has already received approval for marketing and distribution by the FDA because a drug is considered “new” when it is promoted for uses that have not been FDA approved.<sup>41</sup>

The term “new” takes on an extended meaning—limiting the range of marketing and promotional activities of drug manufacturers—as a result of the FDA’s differentiation between “intended” and “unintended” uses. “A manufacturer’s intended use includes all uses objectively intended by the drug manufacturer based upon statements made in labeling, in advertisements, or in written or oral statements by company representatives, and if the FDA-approved labeling does not cover each ‘intended use’ then a drug [] is deemed misbranded.”<sup>42</sup> Thus, although FDAMA allows drug manufacturers to distribute information on off-label uses within strict limitations, the FDCA effectively counters this

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37. See Robert Steinbrook, *Gag Clauses in Clinical-Trial Agreements*, 352 NEW ENG. J. MED. 2160, 2160 (2005) (“Sponsors with a financial interest in the outcome of clinical research can suppress negative results.”).

38. *Id.*

39. *Id.*

40. Craft, *supra* note 1, at 108.

41. *Id.*

42. Osborn, *supra* note 21, at 309.

permission by requiring that each so-called intended use be FDA-approved; otherwise, the company has violated the law by introducing a “misbranded” product into interstate commerce.

*C. Liability under the False Claims Act*

In addition to liability under the FDCA, a pharmaceutical company may also find itself in violation of the federal False Claims Act (FCA). The FCA makes it unlawful to “knowingly present[], or cause[] to be presented, a false or fraudulent claim for payment or approval” by the government.<sup>43</sup> The pharmaceutical industry contends that the application of the FCA to off-label promotion is convoluted because it requires several links to ultimately find the drug manufacturers liable. This is a fair claim given the chain of liability: (1) drug companies publish and disseminate off-label information through peer-reviewed articles, medical journals, and other qualified reference publications that alert medical practitioners and pharmacists of the new, alternative uses of the already FDA-approved drugs; (2) the drug companies then sell the products to wholesale distributors; (3) the wholesale distributors in turn sell to pharmacies and other providers; and (4) these other providers in turn file claims with the government (*e.g.*, Medicare and Medicaid).<sup>44</sup> The essence of this legal charge is that pharma promotional activities cause false claims to be submitted to the government for medically unnecessary off-label uses.<sup>45</sup> The theory of liability is somewhat strained because it is not the drug manufacturer’s direct actions that subject it to liability. Rather, the manufacturers’ liability is contributory because pharmacies and providers file claims with the government, which ultimately makes the manufacturers’ off-label promotion illegal under the FCA.

*D. The Qui Tam Suit and its Effect on FCA Liability*

Another cornerstone of the FCA is the availability of a qui tam suit, or whistleblower provisions, which allows individuals who are aware of

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43. See 31 U.S.C. §§ 3729-33 (2006).

44. 31 U.S.C. § 3729 (a)(1)(A) (2006).

45. Craft, *supra* note 1, at 113 (“These claims are based on the theory that manufacturers promote off-label uses of drugs, knowing that physicians will prescribe such uses to Medicaid patients and that these patients will seek reimbursement for these off-label prescriptions from Medicaid [and Medicare].”); see also Gonzalez, *supra* note 4 (explaining how insurance companies, which ordinarily will only cover “medically necessary” prescriptions and not “experimental” medications, are now contesting the off-label prescriptions that they were forced to cover and alleging that they lost billions of dollars as a result).

fraud against the government to file suit on the government's behalf and receive a portion of the recovered funds.<sup>46</sup> "Whistleblowers can file suit under the FCA for fraud resulting from off-label promotion due to [the] negative effects it has on state and federally funded programs such as Medicaid, which may prohibit reimbursement for off-label prescriptions."<sup>47</sup> To entice employees to blow the whistle on their employer's former or current wrongdoing, those coming forth with information stand to collect as much as 30 percent of any settlement the company makes with the government.<sup>48</sup>

The pertinent time in determining liability under the FCA is the date in which the off-label speech occurs.<sup>49</sup> As with liability under the FDCA, the truth or medical accuracy of the information asserted and promoted is irrelevant under the FCA. Moreover, even if a pharmaceutical company intends to seek FDA approval for the drug's use, and the use later becomes FDA approved, the relevant inquiry focuses only on whether the information was ever marketed off-label.<sup>50</sup> In addition to this fairness critique, from a utilitarian perspective, drug manufacturers can argue that current FDCA and FCA limitations on off-label promotion are too restrictive and inhibit unhealthy patients from receiving beneficial, potentially life-saving medicines solely because they have not passed the lengthy and arguably inefficient FDA approval process.

A separate fairness argument for drug manufacturers is that whistleblowers are over-incentivized. Whistleblowers, as mentioned, play an integral part in federal regulation and enforcement under the FCA. However, by allowing them to recover up to 30 percent of fines incurred by the pharmaceutical companies, it is plausible that some people in a position to blow the whistle might attempt to game the system. For example, David Franklin, a former employee of Parke-Davis (later purchased by Pfizer), acted as a whistleblower when he sued on behalf of taxpayers to recover money the government paid for drugs illegally promoted off-label.<sup>51</sup> The problematic aspect of this narrative is

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46. Craft, *supra* note 1, at 113.

47. *Id.* at 113; *see also* Evans, *supra* note 23 (shedding light on how a former Pfizer employee was instrumental in bringing the illegality of the company's off-label promotion to the government's attention and mentioning how the employee collected \$24.6 million under the FCA for blowing the whistle on his former employer).

48. Evans, *supra* note 23.

49. Osborn, *supra* note 21, at 310.

50. *Id.*; *see also* United States *ex rel.* Franklin v. Parke-Davis, 147 F. Supp. 2d 39, 51-52 (D. Mass. 2001) (ruling that, in general, a violation of the FDCA for off-label promotion is sufficient to establish liability under the FCA, regardless of whether the underlying promotional statements were false or medically inaccurate).

51. Evans, *supra* note 23.

that Franklin holds a Ph.D. in microbiology from the University of Rhode Island, and, before taking a job with Parke-Davis, he was a pediatric researcher at Harvard University's Dana-Farber Cancer Institute.<sup>52</sup> Franklin is also married to a lawyer.<sup>53</sup> Given his background in science and medicine, and his spouse's legal acumen, one can question why he agreed to perform tasks that *a priori* he should have reasonably known were illegal. Thus, it is quite plausible that similarly situated and informed corporate insiders are motivated to further illegal promotion schemes, rather than resist them, given the potential to recover millions of dollars—even if they are essentially blowing the whistle on their own actions.

*E. Liability under the FCA Pursuant to the Anti-Kickback Statute*

One additional theory of liability under the FCA involves claims made pursuant to the Anti-Kickback Statute (AKS), which “prohibits payments in any form, direct or indirect, made purposefully to induce or reward the referral or generation of federal health care business.”<sup>54</sup> No private right of action exists under the AKS, which is why the FCA has served as the necessary vehicle for whistleblowers to bring fraud claims for AKS violations.<sup>55</sup> Allowing whistleblower actions via the FCA for violations of the AKS is an integral part of federal regulation because it helps reduce two violations at once: (1) it helps cut down on the propensity of inducements and rewards being paid to doctors for referrals involving federal health care business, while (2) alerting the proper authorities of illegal off-label promotions.

*F. The Washington Legal Foundation Cases and FDAMA*

Although several mechanisms exist for the FDA to regulate off-label promotion and marketing, their power to do so was constitutionally limited by the Washington Legal Foundation (WLF) cases in the 1990s.<sup>56</sup> The WLF challenged the FDA's restrictions on distribution of off-label information by manufacturers on First Amendment freedom of speech grounds.<sup>57</sup> The WLF decisions allow manufacturers to disseminate scientific publications concerning the off-label use of their products to

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52. *Id.*

53. *Id.*

54. Craft, *supra* note 1, at 113; *see also* Stephanie Greene, *False Claims Act Liability for Off-Label Promotion of Pharmaceutical Products*, 110 PENN ST. L. REV. 41, 56 (2005) (citing 42 U.S.C. § 1320a-7b (2000)).

55. Greene, *supra* note 54, at 56-57.

56. Osborn, *supra* note 21, at 311.

57. Ascroft, *supra* note 30, at 103.

physicians or other medical professionals, regardless of whether such articles include a significant or exclusive focus on uses of drugs or medical devices other than those approved by the FDA.<sup>58</sup> Moreover, manufacturers can have open involvement with continuing medical education (CME) seminars that discuss off-label uses by providing financial support and by suggesting the content or the speakers for the event.<sup>59</sup>

In response to the WLF cases, Congress passed the Food and Drug Administration Modernization Act (FDAMA) in 1997. Before the passage of the FDAMA, the FDA strongly opposed the dissemination of off-label information of any kind by a drug manufacturer.<sup>60</sup> Section 401 of FDAMA included the first provision to allow pharmaceutical companies to disseminate off-label information under certain circumstances.<sup>61</sup>

FDAMA allowed drug companies to disseminate off-label information only to health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, and governmental agencies.<sup>62</sup> Manufacturers were only allowed to circulate authorized information contained in either unabridged peer-review journals or certain qualified reference publications.<sup>63</sup> If manufacturers decided to disseminate off-label information, they were required to prominently affix alongside the information a disclaimer alerting readers that, if applicable, other drugs were approved for this use and that the information contains a drug or device that is not FDA approved.<sup>64</sup> Notably, pharmaceutical companies could only disseminate such information if they were actively seeking approval by the FDA for the new use by means of a supplemental new drug application (sNDA) or if such approval would be cost-prohibitive or unethical.<sup>65</sup> Thus, while FDAMA opened the door slightly to drug manufacturers, it placed

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58. See *id.* at 104-05; see also Green, *supra* note 54, at 52.

59. Green, *supra* note 54, at 52-53.

60. Ascroft, *supra* note 30, at 101.

61. *Id.* at 102.

62. *Id.*; see also Food and Drug Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

63. Ascroft, *supra* note 30, at 102.

64. *Id.*

65. *Id.*; see also Tim Mackey & Bryan A. Liang, *Off-Label Promotion Reform: A Legislative Proposal Addressing Vulnerable Patient Drug Access and Limiting Inappropriate Pharmaceutical Marketing*, 45 U. MICH. J. L. REFORM 1, 8 (2011) (discussing how the court upheld FDAMA's sNDA requirement in the second WLF case, quantifying it as a safe harbor provision that did not prohibit protected speech or certain conduct "but merely ensured manufacturers that enforcement action[s] would not be taken if they conformed [with] certain requirements").

significant limitations on the exchange of off-label information and allowed the FDA substantial room to regulate and investigate possible violations.

FDAMA attempted to provide clarity in FDA regulation and enforcement of off-label marketing. The regulatory waters were muddled, however, by the WLF cases, and this ambiguity was exacerbated by FDAMA's expiration on September 30, 2006.<sup>66</sup> The current state of flux provides even more reason for simplified, enforceable legislation in this arena.

*G. Ghostwriting: A Form of False-Advertising?*

The WLF decisions effectively permit some marketing of drugs for unapproved uses without the risk and expense of the trials required for FDA approval.<sup>67</sup> Drug companies subsequently took advantage of this opening by practicing the scientifically and ethically troubling practice of "ghostwriting."<sup>68</sup> Ghostwriting is the process by which a pharmaceutical company contracts with or hires a medical education and communications company (MECC) to draft articles about new uses for FDA-approved drugs or medical devices.<sup>69</sup> The company itself or the MECC it contracts with will then work with prominent physicians and scientists and pay the academic to sign his or her name as the author to increase the likelihood that the article will be published in important medical journals.<sup>70</sup> Thus, when the article appears in the press, the doctor appears as the author, while the contributions of the ghostwriter and the pharmaceutical company remain hidden.<sup>71</sup>

Medical literature on off-label medicine can have benefits because it makes physicians, especially in rural areas, aware of contemporary medical techniques and newfound uses for previously approved drugs. However, these benefits only occur if the information is accurate. The concern about ghostwriting "is that doctors might change their prescribing habits after reading certain articles, unaware they were commissioned by a drug company."<sup>72</sup> Ghostwritten articles always

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66. Mackey & Liang, *supra* note 65, at 8.

67. Eisenberg, *supra* note 18, at 733-34.

68. *Id.*

69. See generally Natasha Singer, *Medical Papers by Ghostwriters Pushed Therapy*, N.Y. TIMES, Aug. 5, 2009, at A1.

70. See *id.*; see also STAFF OF S. COMM. ON FIN., 111TH CONG., GHOSTWRITING IN MEDICAL LITERATURE (2010), available at <http://1.usa.gov/XagUKU> (written by Sen. Charles E. Grassley).

71. Barton Moffatt & Carl Elliott, *Ghost Marketing: Pharmaceutical Companies and Ghostwritten Journal Articles*, 50 PERSP. IN BIOLOGY & MED. 18, 19 (2007).

72. Singer, *supra* note 69.

contain undisclosed conflicts of interests, making it impossible for a doctor to know whether an article is legitimate.<sup>73</sup> Given their financial incentives, it is not surprising that “a ghostwriter of original research will package the message of the research paper so that it fits into the marketing plan for the drug.”<sup>74</sup> Thus, surreptitiously affixing the names of well-regarded scientists and doctors to these articles enhances the legitimacy of these articles’ favorable conclusions.<sup>75</sup>

Exemplifying the potential harm caused by ghostwriting is Wyeth’s (a pharmaceutical company later acquired by Pfizer) push for two of its hormone drugs to be used to protect against aging skin, heart disease, and dementia.<sup>76</sup> Ghostwritten articles emphasizing the benefits of the two hormones were published in medical journals from 1998 to 2005.<sup>77</sup> However, in 2002, a federal study on hormone therapy demonstrated that menopausal women taking certain hormones had an increased risk of invasive breast cancer, heart disease, and stroke.<sup>78</sup>

Heads of these MECCs vow that the companies “will not participate in the publication of any material in which it does not have complete confidence in the scientific validity of the content, based upon the best available data.”<sup>79</sup> Nevertheless, this example shows explicitly how medical research can take swift and dangerous turns, and further why participating in the required FDA testing is so important to ensure public safety.

Lurking within many of these ghostwritten articles is a Faustian bargain. Pharmaceutical companies directly pay MECCs to draft articles that include research—whether or not substantiated—supporting the drug’s use for off-label purposes. In the worst-case scenario, the academics that sign off on the draft as being scientifically accurate do not even perform research or review the adequacy of findings. They are merely selling their established credibility and putative integrity for monetary gain. Thus, these articles are not only biased in favor of the drug manufacturers, but their existence can undermine faith in actual high-quality studies because, intrinsically, there is no transparency in these arrangements.

When questioned about the credibility of their findings, pharmaceutical companies will often deny their affiliated academics the

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73. Moffatt & Elliott, *supra* note 71, at 24.

74. *Id.* at 22.

75. STAFF OF S. COMM. ON FIN., *supra* note 70, at 2.

76. See Singer, *supra* note 69.

77. See *id.*

78. See *id.*

79. See *id.*

opportunity to review raw data.<sup>80</sup> This situation occurred with Proctor & Gamble (P&G) and Aubrey Blumsohn, a senior lecturer in the Bone Metabolism Unit at Sheffield University.<sup>81</sup> In 2002, Blumsohn contracted with P&G to perform research and speak on the company's behalf about new uses for drugs.<sup>82</sup> However, when Blumsohn finally became convinced that P&G had intentionally skewed their data to make it look as if a drug was performing better than it really had, P&G refused to share the raw data with him.<sup>83</sup> This instance reveals that the research-driven data that pharma gives to MECCs and academics might not only be selectively cherry-picked, but could also be falsified.

The prevalence of ghostwriting exacerbates the problem. One study published in the *Journal of the American Medical Association (JAMA)* concluded that ghostwriting was evident in 11 percent of published articles appearing in six leading medical journals.<sup>84</sup> More specifically, a study solely focusing on medical literature devoted to the Pfizer's drug, Zolof, found that, in three years, approximately 57 percent (55 of 96) of all published articles on the drug in peer-reviewed medical journals were written by a MECC that Pfizer hired to manage publications on Zolof.<sup>85</sup>

Due to this lack of transparency, inherent conflict of interest, problems with credibility and falsification, and its ubiquity, the practice of ghostwriting is a fraud on journals, their readers, and patients. Pharma has mastered the secrecy of the process and has repeatedly breached respected medical journals' safeguards to publish these ghostwritten articles. Readers, very often doctors, are thus deceived into believing flawed or falsified studies as credible basis for medical decision-making. In turn, ghostwriting affects patients because doctors put these unsubstantiated treatments into practice, which can be either unbeneficial or possibly dangerous to the patient.

#### *H. Unethical and Aggressive Courting of Physicians*

Ghostwritten articles are simply one component of an integrated strategy to promote off-label usage. Pharma's multi-pronged approach includes the following tactics: (1) instructing sales representatives to initiate discussions with doctors during sales calls regarding off-label uses; (2) using medical liaisons working in conjunction with sales representatives when the medical community believes the liaisons are

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80. See Moffatt & Elliott, *supra* note 71, at 21.

81. See *id.*

82. See *id.* at 21-22.

83. See *id.* at 21.

84. See Moffatt & Elliott, *supra* note 71, at 22.

85. See *id.* at 22-23.

individuals hired to provide scientific knowledge rather than sell a manufacturer's drug; (3) paying doctors to allow its sales representatives to participate in discussions with patients regarding treatment options; (4) paying doctors to travel to lavish locations to attend consultant or advisory meetings that exclusively discuss off-label uses of the company's drugs; (5) hosting teleconferences where the company pays doctors to instruct other doctors about newly discovered off-label uses; and (6) hosting CME seminars that are intended to give the appearance of providing independent medical education regarding off-label uses.<sup>86</sup>

These tactics represent potentially multiple AKS violations. Further, although the WLF decisions decided that hosting CME seminars are within a manufacturer's rights, the above practices are clearly aimed to increase the market for their drugs in an ethically questionable manner. Given drug manufacturers' aggressive tactics to expand the market for their drugs without applying for supplemental FDA-approval, it is obvious why the FDA and DOJ are adamant about investigating these companies for illegally circumventing the system. As former Associate Attorney General Robert McCallum highlighted, the stakes are the following:

It is of paramount importance that the DOJ use every legal tool at its disposal to assure the health and safety of the consumer of America's health care system, and to pursue companies and individuals that steal from the taxpayers and inflict suffering on patients and families.<sup>87</sup>

### *I. Gag Clauses and Data Transparency*

Gag clauses are a means for pharmaceutical companies, as sponsors of clinical research with a financial interest in the outcome, to suppress negative test results. As Robert Steinbrook notes, gag clauses frequently appear in clinical-trial agreements and serve to "prevent investigators from examining the data independently" or from publishing the results "without first obtaining the consent of the sponsor."<sup>88</sup> Negative results are thus routinely underreported or unreported altogether.

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86. See Craft, *supra* note 1, at 115-16 (referencing Sentencing Mem. of the United States, United States v. Warner-Lambert Co., Criminal No. 04-10150 RGS (D. Mass. 2004)).

87. Press Release, U.S. Dep't of Justice, Warner-Lambert to Pay \$430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion (May 13, 2004), available at <http://1.usa.gov/NtwuuH>.

88. Robert Steinbrook, *Gag Clauses in Clinical-Trial Agreements*, 352 NEW ENG. J. MED. 2160, 2160 (2005).

Pharma's control over the clinical-trial process results in a lack of transparency and, consequently, an unsafe environment for American consumers. Pharma retains this control due to the monetary support they provide academic institutions, unaffiliated medical centers, and private contract research organizations (CROs). As a result, these research bodies are forced to compete with each other over pharma-sponsored clinical-trial agreements. One could argue that academic institutions have reputational interests and institutional values that can countervail this pressure to accept gag clauses. However, for-profit CROs do not have these same constraints. In fact, over the last decade, CROs have dramatically increased their share of the clinical research at the expense of academic institutions because of their malleability to pharma's needs.<sup>89</sup> Thus, this race to the bottom in the clinical testing marketplace enables pharma to insist on gag clauses in research contracts.

Over a decade ago, the International Committee of Medical Journal Editors (ICMJE) "began to require that the responsible author of a study state in writing that he or she accepted full responsibility for the conduct of the trial, had access to the data, and controlled the decision to publish."<sup>90</sup> However, the ICMJE only represents a handful of medical journals and is not in a position to establish industry-wide guidelines. Such lack of influence is demonstrated by a Duke University study, which revealed that academic institutions routinely engaged in industry-sponsored research that failed to adhere to ICMJE guidelines.<sup>91</sup> Although several researchers and regulatory bodies propose the need for standard contract provisions for industry-sponsored research, such provisions are frequently absent from clinical-trial agreements because of the ongoing competition for research sponsorship.

The argument against gag clauses continues to gain traction since the avoidable Vioxx fiasco and the trial-related disclosure of internal emails of pharmaceutical giant Merck. These documents demonstrate that Merck knew years before it pulled Vioxx off the shelves that the drug had increased risks of heart disease and stroke as compared to its industry competitors: aspirin and naproxen.<sup>92</sup> Although Vioxx was not

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89. Fazal Khan, *The Human Factor: Globalizing Ethical Standards in Drug Trials Through Market Exclusion*, 57 DEPAUL L. REV. 877, 894 (2007) (Observing that, "as the size of the drug market dramatically expanded . . . pharmaceutical companies became impatient with academic centers, and by the late 1990s the monetary flow from drug companies to academic centers had greatly receded.").

90. See Steinbrook, *supra* note 88, at 2160.

91. *Id.*

92. See Anna Wilde Mathews & Barbara Martinez, *Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage*, WALL ST. J., Nov. 1, 2004, at A1; Dani Veracity, *Leaked Documents Show Merck Knew of Vioxx Dangers, Yet Hid Them for Years*, NATURALNEWS.COM (Aug. 6, 2005), <http://bit.ly/TxNoPN>; E. Huff, *Merck Sat on*

taken off the market until September 2004, reports indicate that Merck knew of the life-threatening side effects as early as 1996.<sup>93</sup> Merck conducted tests during which they intentionally excluded participants with an increased risk of heart disease because they did not want to risk the chance of profuse negative results.<sup>94</sup>

The company's research directors also explained the profound negative side effects of Vioxx to Merck's executive management. In March 2000, Merck's research chief, Edward Scolnick, wrote in an email his belief that test results unmistakably affirmed that heart problems associated with Vioxx were "clearly there" and that it was a "shame."<sup>95</sup> Merck's indiscretions affecting public safety went even further, as they consistently threatened and sued academic researchers who questioned the safety of Vioxx during public lectures.<sup>96</sup> These actions demonstrate that not only is pharma willing to cease sponsoring academic institutions who insist on publishing the truth, but companies are willing to risk the health of the nation as they intentionally mislead American doctors and patients about the safety of their products.

Progress against gag clauses may be forthcoming as concern mounts about public safety, distrust of the pharmaceutical industry spreads, and advocacy within the medical community for greater openness in conducting and reporting clinical trials increases.<sup>97</sup> Senators Chris Dodd and Chuck Grassley confronted this challenge head on and attempted to pass legislation including the Fair Access to Clinical Trials (FACT) Act of 2007 and the Food and Drug Administration Safety Act of 2007 (FDASA).<sup>98</sup>

The FACT Act sought to amend the Public Health Service Act and was premised on increased transparency of the entire industry and greater accountability in health research and development.<sup>99</sup> It sought to ensure that both the scientific community and the public have access to basic

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*Data Showing Vioxx Risks for Years Before Pulling Drug*, NATURALNEWS.COM (Jan. 15, 2010), <http://bit.ly/4Qn4cJ>.

93. Veracity, *supra* note 92.

94. *Id.* (uncovering one email from a Vice President stating that "the possibility of increased [cardiovascular] events is of great concern . . . [and] I just can't wait to be the one to present those results to senior management!").

95. Huff, *supra* note 92.

96. See Mathews & Martinez, *supra* note 92 (reporting conversations between prominent Stanford researchers and a Merck chief executive, in which the executive bluntly "suggested that if this continued, [the researcher] would 'flame out' and there would be consequences for [the doctor] and for Stanford.").

97. Steinbrook, *supra* note 88, at 2.

98. Press Release, Sen. Chuck Grassley, Sens. Grassley, Dodd Seek (Jan. 30, 2007), available at <http://1.usa.gov/VnqMx4> [hereinafter Bold Reforms for Drug Safety].

99. *Id.*

information about clinical trials by expanding data that is already made available at [clinicaltrials.gov](http://clinicaltrials.gov).<sup>100</sup> The main objective of the FACT Act was to operate a data bank of information on clinical trials, to include

(1) a clinical trials registry of health-related interventions conducted to test the safety or effectiveness of any drug, biological product, or device intended to treat serious or life-threatening diseases and condition; and (2) a clinical trial results database of health-related interventions to test the safety or effectiveness of any drug, biological product, or device.<sup>101</sup>

Whereas the FACT Act's focus was primarily on public access to the clinical trial process, FDASA sought to enhance the drug-safety monitoring system. Its goal was to bring a new level of priority and independence to the post-market surveillance of drugs by establishing an independent center within the FDA responsible for monitoring the safety of drugs once they are on the market.<sup>102</sup> This center would have the authority to take corrective action if a drug is a risk to patients.<sup>103</sup> In essence, the FACT Act would have armed the FDA with a greater ability to regulate pharma and would have provided reliable assurance that the drugs on the market are in fact safe for consumers.

Although these acts provided a means of superior regulation in both pre- and post-market drug surveillance, neither act was passed into law. Nonetheless, there are several constructive takeaways from the ideas of Senators Dodd and Grassley. American consumers need structural accountability from pharma-sponsored testing that consistently underreports negative results, paints unsupportive results in a brighter light, and publishes almost every positive test.<sup>104</sup> Although there are notable benefits to companies not going through the lengthy and cost-prohibitive constraints of the regulatory process, it is imperative for consumer safety and fiscal responsibility (*i.e.*, by prohibiting fraud against the government) that research results are founded upon reliable data.

The FACT Act and FDASA were dedicated to affording greater transparency of clinical trials, providing greater accountability of

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100. *Id.*

101. *Summary of the Fair Access to Clinical Trials Act of 2007*, GOVTRAC.US, <http://bit.ly/TSqJbA> (last visited Oct. 23, 2012).

102. Bold Reforms for Drug Safety, *supra* note 98.

103. *Id.*

104. Marc-Andre Gagnon and Sergio Sismondo, *Is Drug Research Turning Into a Scam?*, THE MARK (May 11, 2011), <http://bit.ly/XREsn5> (reporting that pharma systematically failed to publish negative studies on several antidepressants; of 74 trials, 38 positive and 36 negative, 94% of the positive tests were published, compared to only 23% of the negative tests).

pharma, and offering objective, post-market surveillance of pharmaceuticals. In the Obama administration's recent FDA budget request for 2013, it sought a significant increase in industry-paid user fees. To reduce the effect of gag clauses on clinical-trial reporting, user fees could sponsor an independent center to perform equivalent clinical testing. This independent center, with no financial incentive to promulgate unsubstantiated results or conceal negative tests, could be relied on to bring forth the actual results of clinical trials. The independent center would be responsible for publishing the trial results in a database such as [clinicaltrials.gov](http://clinicaltrials.gov), thus inserting this information into the public domain. If the pharma-sponsored clinical trials were in line with the independent testing, then pharma could publish the results. This alternative would ensure that the drug industry was not merely publishing favorable results and skewing public knowledge.

Another alternative, which could supplement the suggestion above, would be to create a user-fee-sponsored independent testing center that conducts post-market testing on drugs deriving a significant portion of their profit from off-label uses. As the struggle against ghostwriting persists, off-label uses continue to gain prevalence, and pharma continuously avoids accountability. Independent post-market testing of drugs prominently prescribed for non-FDA approved off-label uses would bring certainty and clarity to the efficacy of such off-label uses. Doctors' access to actual results would be greater, providing for surety and safety in prescribing practices. The FDA approval process is time-consuming and costly, and there is acknowledged benefits to bypassing this process at times. However, such benefits should never outweigh concerns for public safety. Although additional changes to the entire process should be considered, the authors hope that these two ideas provide at least a well-conceived starting point for greater discussion.

### III. WHAT WE GAIN AND LOSE FROM OFF-LABEL REGULATIONS

The fight between proponents and opponents of off-label marketing is endless, and combines a mixture of both theoretical and practical costs and benefits. The primary benefit of off-label promotion is to keep the health care community informed about scientific advances that will benefit patients.<sup>105</sup> This information will in turn improve the quality of health care without waiting for the lengthy FDA approval process.<sup>106</sup> On the other hand, there is a strong temptation for manufacturers to promote off-label use of their drugs purely for profit, without concern for public

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105. Greene, *supra* note 54, at 47.

106. *Id.*

health.<sup>107</sup> Profit-driven off-label promotion can expose the public to severe health risks and the drug manufacturer to legal liability.<sup>108</sup>

A. *Proponents' Arguments in Support of Off-Label Promotion*

As mentioned, the arguments for and against off-label marketing range from the practical to the theoretical. Proponents argue that off-label medicine is necessary to ensure that patients receive the most effective treatment.<sup>109</sup> Underlying this argument, proponents theorize that drug companies are in the best position to provide doctors with current medical research and treatments, given the vast amount of medical literature and the lack of time doctors have to read it.<sup>110</sup> Building on this idea is the fact that the FDA approval and review process lags behind the availability of the most innovative approaches and therapies, validating that pharmaceutical companies and their sales reps are in the best position to make doctors aware of cutting-edge technologies and practices.<sup>111</sup> Provided that doctors are experts in this field, proponents further argue that they are “best able to evaluate the information and [i]nsure that patients receive appropriate treatment[s]”—an argument supported by the American “learned intermediary” tort doctrine.<sup>112</sup>

The strongest and most readily identified supporting argument for off-label marketing is its cost-containment potential. Avoiding the lengthy and extensive FDA approval process can decrease costs “both in terms of controlling price increases and in saving tax dollars channeled to FDA efforts.”<sup>113</sup> By allowing off-label uses, drug companies should experience increased sales volume allowing them to decrease sales price.<sup>114</sup> Allowing manufacturers to sell their products off-label will also save them the time, money, and resources that they otherwise would expend to become FDA approved.<sup>115</sup>

However, this cost-cutting theory holds little weight when the actual numbers are analyzed. Between 1990 and 1999—the prime decade of expansion for off-label marketing efforts—Medicaid spending on

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107. *Id.* at 43.

108. *Id.*

109. Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L.J. 967, 980 (2007).

110. *Id.* at 980-81.

111. Ascroft, *supra* note 30, at 99.

112. Johns, *supra* note 109, at 981.

113. Greene, *supra* note 54, at 48.

114. Johns, *supra* note 109, at 981.

115. *Id.*

prescription drugs more than tripled from \$4.8 billion to \$17 billion.<sup>116</sup> In fact, between 1990 and 2002, the total amount spent in the U.S. on prescription drugs increased from \$40.6 billion to \$162 billion.<sup>117</sup> During that same time, prescription drug prices increased 7.4 percent, compared to inflation rising merely 2.5 percent.<sup>118</sup> On that same note, prices for the 200 top-selling drugs are currently rising three times faster than the country's inflation rate.<sup>119</sup> As Margaret Johns highlights, "[T]he price of Claritin, the top-selling allergy pill, was raised thirteen times over five years, an increase of more than 50%—more than four times the rate of inflation."<sup>120</sup> Given this data, projections estimate that national spending on prescription drugs will increase an average of 10.7 percent until 2013.<sup>121</sup> Thus, although the argument that off-label promotion will drive cost-cutting is theoretically tenable, the statistics indicate otherwise.

Authors Mackey and Liang present a novel approach to the regulation of off-label medicine based on relaxed regulatory standards for drugs intended for vulnerable patient and orphan disease patient populations.<sup>122</sup> As discussed in Part IV *infra*, there are merits to this proposal when considering the costs of regulatory approval—even under the Orphan Drug Act of 1983—and the expected financial incentives. These authors argue that, since the vulnerable patient and orphan disease patient populations have relatively few, if any, options for recovery by FDA approved drugs and are already at risk of death, the FDA's regulatory protections based on ensuring safety and efficacy are not as relevant.<sup>123</sup> However, the D.C. Circuit ruled that vulnerable patient populations, like healthy populations, have no fundamental right of access to experimental drugs that have not gone through the FDA approval process.<sup>124</sup> Citing the U.S. Supreme Court in *United States v. Rutherford*, 442 U.S. 544, 555-56 (1979), the court in *Abigail Alliance* noted "that '[f]or the terminally ill, as for anyone else, a drug is unsafe if its potential for inflicting death or physical injury is not offset by the possibility of therapeutic benefit.'"<sup>125</sup> In the court's view, because a drug cannot be proven either safe or effective for a certain use without going

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116. Greene, *supra* note 54, at 43.

117. Johns, *supra* note 109, at 972.

118. *Id.*

119. *Id.* at 973.

120. *Id.* at 982.

121. Johns, *supra* note 109, at 972.

122. See generally Mackey & Liang, *supra* note 65.

123. See *id.*

124. See *Abigail Alliance for Better Access to Devl. Drugs v. von Eschenbach*, 495 F.3d 695, 714 (D.C. Cir. 2007).

125. *Id.* at 713.

through all phases of FDA approval, its potential for inflicting death or injury is not offset by the possibility of therapeutic benefit. Therefore, unapproved drugs are categorically deemed unsafe.

The authors' proposal, however, can be distinguished from the plaintiffs in *Abigail Alliance* because it focuses on off-label uses of drugs that have already been approved, not drugs that have yet to receive any FDA approval. Yet, one can read from the main holding in *Abigail Alliance* an argument against relaxing prohibitions on off-label marketing in the absence of proven therapeutic benefits for off-label uses.<sup>126</sup>

*B. Opponents' Arguments against Off-Label Promotion*

The aforementioned benefits and overarching (albeit unsubstantiated) financial cost argument must also be "balanced with the FDA's underlying mission to ensure the safety and efficacy of products."<sup>127</sup> The major concern stems from the possibility that manufacturers who are purely concerned with their bottom-line—whether trying to maximize profits before patents expire or searching to expand the market for an approved drug—will "seek to market a product for a new use by bypassing the formal FDA approval process and its costs."<sup>128</sup> If off-label promotion is allowed, opponents argue that drug companies will have no incentive to conduct the rigorous testing the FDA requires and will completely avoid responsibility for establishing that a drug is safe and effective for the off-label use they are promoting.<sup>129</sup> Opponents corroborate this argument with several examples of off-label drug uses gone horribly wrong (notably, Vioxx, Fen-phen, and Neurontin), to demonstrate that drug company research conducted outside of the FDA oversight process is suspect given the inherent conflicts of interest.<sup>130</sup> Opponents further posit that, because of the onslaught of ghostwritten academic articles in distribution, "the doctor's role as a learned intermediary has been severely compromised."<sup>131</sup>

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126. As will be discussed in Part IV.C.2 *infra*, "Track Two" of our proposal addresses a common issue raised by Mackey and Liang's proposal. However, a major difference is that the lever for regulatory change in our proposal is the existence of compelling and trustworthy efficacy data produced by PCORI, not the presence of a vulnerable patient population.

127. Greene, *supra* note 54, at 48.

128. *Id.*

129. Johns, *supra* note 109, at 981.

130. *Id.*

131. *Id.* at 981-82.

C. *Why Pharmaceutical Companies Continue to Promote Off-Label*

It is understandable why pharma plays the double-game of denying that they illegally promote particular off-label usages while asserting in general that off-label usage is good for the public. Off-label marketing affords drug manufacturers increased market growth and obvious cost-cutting and profit-increasing possibilities from circumventing the FDA approval process. In contrast, “Rigorous clinical trials of new uses of previously approved products are not only costly, but can also be extremely risky for a firm that has a lucrative product on the market.”<sup>132</sup>

Obtaining FDA approval for a drug is a monetarily exhausting and time-consuming process. The “approval process takes six to fifteen years and costs between \$100 million and \$880 million per drug.”<sup>133</sup> The approval process demands the successful navigation of three increasingly larger sets of human clinical trials, known as Phases I through III.<sup>134</sup> Following the conclusion of Phase III, the manufacturer must submit a NDA to the FDA, which is supposed to report on all phases of testing.<sup>135</sup>

After all three phases of research is complete and the FDA approves the NDA, the manufacturer may, on its own volition, conduct additional Phase IV research.<sup>136</sup> Phase IV research may or may not be subject to the same restrictions and informed consent requirements that manufacturers face during Phase I-III research, depending on the purpose underlying the Phase IV research.<sup>137</sup> Most drug companies that choose to conduct Phase IV research opt to study side effects that possibly went undetected in the initial trials, which is the route that does not face stringent FDA restrictions.<sup>138</sup>

A study on the effects of hormone replacement therapy (HRT) on the risk of heart disease in post-menopausal women is a prime example of the risk that rigorous clinical trials pose to a drug manufacturer that is

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132. Eisenberg, *supra* note 18, at 718-19, 732 (using the drug Vioxx to explain that, “[f]rom the perspective of a firm that has a lucrative pharmaceutical product on the market, rigorous clinical trials of new indications present a risk of generating results that could destroy the value of the product rather than enhance it”).

133. Johns, *supra* note 109, at 973-74.

134. *Id.* at 988.

135. *Id.* at 974.

136. *Id.* at 988.

137. Johns, *supra* note 109, at 988.

138. *Id.* at 989 (describing further how research under this heading is not unusually swindled into becoming a marketing effort of the drug to doctors, where manufacturers pay doctors to enroll patients into drug trials that are not randomized nor weighed against a comparison group, making it nearly impossible to draw any reliable conclusions).

already enjoying substantial off-label sales.<sup>139</sup> HRT, previously approved for relief of menopausal symptoms, was at the time also being prescribed regularly to lower the risk of heart disease for these women.<sup>140</sup> Although HRT manufacturers were formally banned from promoting HRT for this off-label purpose, they were reaping the benefits of significantly increased sales from prescriptions in reliance on the results of prior observational studies (which ultimately ended up being discredited).<sup>141</sup> Thus, HRT manufacturers had little economic reason to subject the use of HRTs to more rigorous testing.

HRT manufacturers' windfall profits abruptly ended when the National Institutes of Health (NIH) conducted a long-term, controlled study with over 16,000 patients.<sup>142</sup> The NIH results "indicated an increased risk of heart disease (as well as increased risks of other diseases) in women receiving HRT."<sup>143</sup> Not surprisingly, this study decimated sales of the hormone treatment.<sup>144</sup> Industry's prior position that this study was unnecessary is indefensible as, "[i]n this case, government funding provided valuable and credible information that the product's manufacturer had little incentive to uncover on its own[,] and the information resulting from it is of undeniable value to patients, physicians, health insurers, and policy makers."<sup>145</sup>

#### IV. MITIGATING THE HARMS AND REAPING THE BENEFITS: ALLOWING A SAFE HARBOR TO PROMOTE OFF-LABEL RESEARCH CONDUCTED UNDER THE PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

As discussed above, current off-label marketing restrictions are subject to several powerful criticisms: (1) they restrict flow of information that could help both doctors and patients; (2) the rules are inefficient and lead to companies willfully breaching the law; and (3) such rules may violate the First Amendment rights of pharmaceutical companies.

All of the above critiques have persuasive force only if we have confidence that industry communications regarding specific off-label usages are indeed accurate. However, as previously mentioned, there is ample evidence that pharma has corrupted the practice of off-label

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139. *Id.* at 989; see also J.E. Rossouw et al., *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial*, 288 JAMA 321 (2002).

140. Eisenberg, *supra* note 18, at 732.

141. *Id.*

142. *Id.*

143. *Id.*

144. *Id.*

145. Eisenberg, *supra* note 18, at 732.

prescribing. Its contemporary form is far removed from its origins as a way of preserving physician autonomy in practicing the “art of medicine” and allowing for innovation. Instead, it has become a backdoor for pharma to generate substantial profits on patented drugs by creating new markets without proving to the public that such uses are safe and effective. Further, there is ample evidence that many of the off-label studies sponsored by pharma are not trustworthy and are the fruit of questionable practices such as gag clauses, cherry-picked data, and ghostwriting. Consequently, patients and third party payors likely incur harms because medically unproven therapies raise issues of both patient safety and unnecessary healthcare expenses.

This begs the question of what would happen if the off-label research being disseminated by drug companies was actually reliable and produced by independent researchers using sound methodology? Should evidence of these research characteristics significantly change FDA rules on restricting off-label marketing? In this section, we argue in the affirmative: that is, in the presence of research criteria that can be validated as trustworthy, the FDA should allow for wider and less restricted dissemination of off-label study findings.

This section proposes (1) to amend the Patient Protection and Affordable Care Act (PPACA) and the role of the Patient Centered Outcomes Research Institute (PCORI) to increase the amount of trustworthy comparative effectiveness research (CER) on off-label drug uses, and (2) to amend FDA regulations to create a “safe harbor” for off-label marketing of CER studies generated through this process. The rationale behind this proposal is that promoting off-label uses to physicians is not intrinsically harmful and, in fact, could be beneficial if there is some way to ensure the validity of the disseminated speech. Recognizing that the incentives for conducting CER on off-label uses can vary greatly depending on particular circumstances, the proposal sets forth two different research tracks: one track to be initiated and funded by PCORI; and a second track to be initiated and funded by pharmaceutical companies, but that is overseen by PCORI.

*A. What is Comparative Effectiveness Research?*

Using evidence based medicine (EBM) and comparative effectiveness research (CER) to guide treatment decisions is not a novel concept. In the 1970s, for example, the founder of the Dartmouth Atlas Project, Dr. Jack Wennberg, analyzed Medicare utilization data and uncovered dramatic geographic variation in the utilization of healthcare resources. Wennberg identified an epidemic of hysterectomies in some areas of Maine, where the data predicted that 70 percent of the women in

one town would receive this procedure sometime during their lifetime.<sup>146</sup> Medical need was not driving this epidemic, but rather local medical practice and fee-for-service economic incentives.

In the 1980s, the predecessor of the Centers for Medicare and Medicaid Services (CMS), the Health Care Financing Administration (HCFA), “launched an aggressive program of research on outcomes of care that would serve as the basis of medical practice guidelines and even coverage policy for federal health insurance programs.”<sup>147</sup> However, HCFA and CMS have always faced political pushback from manufacturers of costly medical devices and other health care stakeholders who were rightly concerned that robust CER data could undermine profits stemming from expensive care with little or no demonstrable benefits.

In 1999, the Health Care Research and Quality Act established the Agency for Healthcare Research and Quality (AHRQ) to generate a “broad base of scientific research” to assess the effectiveness and appropriateness of health care services and improve outcomes.<sup>148</sup> As before, political considerations moved Congress to specify that the AHRQ could not “mandate national standards of clinical practice”,<sup>149</sup> in other words, its recommendations could not directly guide coverage decisions.

More recently, in an influential article published in *The New Yorker*, medical author Atul Gawande used Dartmouth Atlas data to highlight “why two border towns in Texas of similar size, location, and circumstances—McAllen and El Paso—should cost Medicare such enormously different amounts of money.”<sup>150</sup> Costs in McAllen were twice as much as in El Paso due to physicians ordering “vastly more diagnostic tests, hospital admissions, operations, specialist visits, and home nursing care.”<sup>151</sup> Further, Gawande concluded that the quality of care in McAllen “is not appreciably better, and by some measures, it is worse.”<sup>152</sup> In other words, without credible evidence of safety and efficacy, more healthcare—whether in the form of off-label prescriptions or diagnostic tests—can be costly and dangerous.

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146. Alix Spiegel, *The Telltale Wombs of Lewiston, Maine*, NPR (Oct. 9, 2008), <http://n.pr/6FPAm>.

147. Eleanor D. Kinney, *Comparative Effectiveness Research Under the Patient Protection and Affordable Care Act: Can New Bottles Accommodate Old Wine?*, 37 AM. J. L. & MED. 522, 527 (2011).

148. *Id.* at 531.

149. *Id.*

150. Atul Gawande, *The Cost Conundrum Redux*, THE NEW YORKER (June 23, 2009), <http://nyr.kr/LPFBH>.

151. *Id.*

152. *Id.*

In 2009, the American Recovery and Reinvestment Act (ARRA) directed the Institute of Medicine (IOM) to develop a report that defined CER and its importance in setting research priorities:<sup>153</sup>

CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.<sup>154</sup>

Notably, ARRA set aside \$1.1 billion to fund CER through several federal agencies: the AHRQ, the NIH, and the Office of the Secretary of the Department of Health and Human Services (DHHS).<sup>155</sup> All of these efforts informed the creation of PCORI, which has the potential to incorporate more broadly CER and evidence based medicine (EBM) into the structure of healthcare in the U.S. and bring it more in line with the healthcare systems of other developed nations.

*B. What is the Patient Centered Outcomes Research Institute?*

As stated on its website: “PCORI was established by Congress through the 2010 Patient Protection and Affordable Care Act but is by law an independent, non-profit organization.”<sup>156</sup> A 21-member board governs PCORI, and it actively seeks “input from a broad range of stakeholders to guide its work.” In January 2012, PCORI released its “Draft National Priorities for Research and Research Agenda” and opened it up to comments from the public.<sup>157</sup> PPACA defines the role of PCORI as the following:

The purpose of the Institute is to assist patients, clinicians, purchasers, and policy-makers in making informed health decisions by advancing the quality and relevance of evidence concerning the manner in which diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated,

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153. American Recovery and Reinvestment Act of 2009, Pub. L. No. 111-5, § 804, 123 Stat. 115, 187-88 (codified at 42 U.S.C. § 299b-8 (2006 & Supp. 2010)).

154. COMM. ON COMPARATIVE EFFECTIVENESS RESEARCH PRIORITIZATION, INST. OF MED. OF THE NAT’L ACADS., INITIAL NATIONAL PRIORITIES FOR COMPARATIVE EFFECTIVENESS RESEARCH 13 (2009).

155. *Comparative Effectiveness Research Funding*, U.S. DEP’T OF HEALTH & HUMAN SERVS., <http://1.usa.gov/y1UCU> (last visited Oct. 23, 2012).

156. *About Us*, PCORI, <http://bit.ly/piYn0m> (last visited Oct. 23, 2012).

157. PATIENT-CENTERED OUTCOMES RESEARCH INST., DRAFT NATIONAL PRIORITIES FOR RESEARCH AND RESEARCH AGENDA VERSION 1 (2012), *available at* <http://bit.ly/ygf16e> [hereinafter DRAFT NAT’L PRIORITIES].

monitored, and managed through research and evidence synthesis that considers variations in patient subpopulations, and the dissemination of research findings with respect to the relative health outcomes, clinical effectiveness, and appropriateness of the medical treatments, services. . . .<sup>158</sup>

To address concerns from pharma and medical device manufacturers (and affiliated politicians) that CER might be used to “ration” healthcare or, more hyperbolically, to establish “death panels,” PPACA expressly limits PCORI findings from being used “to mandate coverage, reimbursement, or other policies for any public or private payer.”<sup>159</sup> Nevertheless, nothing in PPACA prevents Medicare or private payors from being influenced by PCORI findings in determining what is “medically necessary” and hence subject to coverage.

PPACA created the Patient-Centered Outcomes Research Trust Fund (PCORTF) to generate funding and provide oversight of PCORI spending.<sup>160</sup> PCORTF is funded by a transfer of funds from Medicare Part A and B and fees levied on private insurers and self-insured employer health plans.<sup>161</sup> Given that funding studies on certain drugs could be seen as picking winners and losers, PCORI did not identify specific research projects but instead five general areas of research it considers as top priorities: preventative care, healthcare systems, communication and dissemination, healthcare disparities, and research methodologies.<sup>162</sup> Going forward, these broad categories will likely be fleshed out with more detailed descriptions of specific research projects, “taking into account factors of disease incidence, prevalence, and burden in the U.S. (with emphasis on chronic conditions)” and “gaps in evidence in terms of clinical outcomes.”<sup>163</sup>

Is there reason to trust the legitimacy of PCORI findings more than studies currently being conducted under the direction of industry? PCORI states that research commissioned by it “will produce information patients and their health care providers can trust.”<sup>164</sup> PCORI

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158. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119 (2010).

159. *Id.* § 6301, 124 Stat. 119; see also Angie D. Holan, *Palin “Death Panel” Claim Sets Truth-O-Meter Ablaze*, POLITIFACT (Aug. 10, 2009, 6:58 PM), <http://bit.ly/y5Sm0> (“As more Americans delve into the disturbing details of the nationalized health care plan that the current administration is rushing through Congress, our collective jaw is dropping, and we’re saying not just no, but hell no!” wrote Palin in a note posted Aug. 7, 2009.”).

160. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 1320e(b)(3).

161. *Id.*

162. DRAFT NAT’L PRIORITIES, *supra* note 157.

163. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 1320e(d)(1).

164. DRAFT NAT’L PRIORITIES, *supra* note 157.

can credibly make this claim because the statutory language that created it has robust requirements for ensuring (1) transparency of research results, (2) conflict of interest disclosures, and (3) best practices in research methodologies. For instance, all PCORI research data will be publicly available, negating legitimacy issues tied to industry practices of gag clauses, manipulating or suppressing data. Conflict of interest rules can prevent issues associated with “ghostwriting” or researchers being financially dependent on funding from pharmaceutical companies, which might influence their findings if they want follow-up research contracts. Methodological oversight is important as “[m]any medical professionals maintain that findings from current clinical trials used to test the safety and efficacy of pharmaceutical products and medical devices do not reflect the conditions of medical practice and thus their findings are less relevant to medical practitioners.”<sup>165</sup>

*C. Where Does Off-Label Research Fit Within PCORI’s Mission?*

Given the prevalence of off-label usage for many chronic conditions and the gaps in knowledge regarding the safety and effectiveness of these uses, it seems that a broad class of off-label research fits within PCORI’s mission. As described above, in general the pharmaceutical and medical device industries are extremely wary of CER because it can conclusively demonstrate that many expensive and profitable products are no more effective than less costly alternatives. In this situation, there is a strong public interest in PCORI conducting CER on these off-label uses, especially since pharmaceutical companies have a strong financial incentive in avoiding such comparisons if they cannot control the data or are uncertain that the research will be in their favor. However, there might be some instances where a drug company might want research validation of a promising off-label use, but the potential market is too small (*i.e.*, an “orphan disease”) to justify a full-blown sNDA. Additionally, since insurers often reject coverage of such off-label use on grounds that it is “experimental,” validation by PCORI testing could open the door for third-party reimbursement. Would PCORI research on this off-label use fit its mission? It does not seem to fit the priorities set by PPACA in creating this institute. Further, there is an argument that prioritizing such research would not be the most efficient or equitable use of PCORTF funds. Considering the above analysis, our proposal sets forth two different off-label research tracks for PCORI. Track One is to be initiated by PCORI for “public interest” considerations, and Track

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165. Eleanor Kinney, *Prospects For Comparative Effectiveness Research Under Federal Health Reform*, 21 ANN. HEALTH L. 79, 86 (2012).

Two is to be initiated by pharmaceutical companies seeking validation of off-label uses for their drugs.

### 1. Track One

If a drug reaches a certain threshold of off-label usage (by either monetary value or percentage of total prescriptions of drug), PCORI should initiate drug testing in this case because drug companies have little incentive to do further testing in this instance and eliminate “gaps in evidence.” For instance, drugs such as Neurontin and Zyprexa would fit this category.<sup>166</sup> For a company that already has a lucrative off-label market presence for its drug, further testing carries significant risk because additional testing could reveal that the drug is not safe or effective in this additional off-label use.

The funding for these studies can come from the PCORTF, the traditional funding source for PCORI. There is an equitable rationale for funding this type of research from this pool: these payors can benefit financially from eliminating unnecessary costs for unproven treatments that have a high level of prevalence in the marketplace. Further, such an effort dovetails with PPACA’s promotion of Accountable Care Organizations, entities structured to benefit from improved patient outcomes and not necessarily from the increased utilization of healthcare.<sup>167</sup>

### 2. Track Two

An “orphan disease” is a relatively rare medical condition that the pharmaceutical industry has little financial incentive to pursue because the cost of full regulatory approval and marketing is not economically justified by the size of the market. For example, in the case of rare cancers, existing drugs might be effectively used in an off-label manner, but pharmaceutical companies might be wary of promoting these uses because the financial payoff might not outweigh the regulatory risk.

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166. See Evans, *supra* note 23.

167. The Centers for Medicare and Medicaid Services (CMS) defines Accountable Care Organizations as

groups of doctors, hospitals, and other health care providers, who come together voluntarily to give coordinated high quality care to their Medicare patients. The goal of coordinated care is to ensure that patients, especially the chronically ill, get the right care at the right time, while avoiding unnecessary duplication of services and preventing medical errors. When an ACO succeeds both in both delivering high-quality care and spending health care dollars more wisely, it will share in the savings it achieves for the Medicare program.

*Accountable Care Organizations*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Apr. 5, 2012, 10:20 AM), <http://go.cms.gov/J6vURy>.

Additionally, insurance companies might reject coverage of such uses as “experimental.”

The incentives in this track are reversed from the case described above in “Track One,” as a pharmaceutical company would likely want additional studies performed on these off-label uses if they could more assertively communicate (*i.e.*, market) such information to doctors. Therefore, this article proposes a second track of research, “Track Two,” which would allow pharmaceutical companies to directly petition PCORI to conduct studies on the safety and effectiveness of off-label usages for orphan diseases. In contrast with “Track One,” funding for these studies would not come from PCORTF, but user fees paid by the pharmaceutical companies. This method would parallel the model already set up by the FDA for clinical drug trials under the Prescription Drug User Fee Act (PDUFA).<sup>168</sup> However, opening up access to PCORI’s research agenda by itself is likely not enough incentive for pharmaceutical companies to incur such research expenses. However, as described below, if the FDA rules on marketing off-label findings to physicians were relaxed for studies generated through PCORI, this could nudge pharmaceutical companies to fund such testing. In this scenario, the drug companies face little risk from such testing because they do not currently have a large market for such off-label usages, but their reward in the form of relaxed marketing rules to doctors could provide enough incentive. Once again, the benefit of conducting such research under the auspices of PCORI is readily apparent because it would have to follow rules regarding transparency, conflict of interest, and proper methodology.

#### *D. Research Capacity*

The question remains whether this proposal is feasible given the relatively small footprint of PCORI. If this proposal were implemented, it would certainly increase the administrative burden of PCORI. However, PPACA anticipates and allows for outsourcing of PCORI research outside of the government (*e.g.*, NIH, NSF, and DHHS) to academic and private research institutions.<sup>169</sup> Thus, this proposal is feasible to the extent that it would not rely solely on extending the federal government’s research capacity. The additional oversight burden of regulating the outsourced research for “Track Two” studies would require more administrative resources, but, as described above, user fees levied on pharmaceutical sponsors could shoulder this burden.

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168. Prescription Drug User Fee Act, 21 U.S.C. § 301 (2006).

169. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 1320e(d)(2)(B).

E. *Amending FDA Rules on Off-Label Marketing and Dissemination of Research Findings*

If the research process dictated by PCORI cures the legitimacy problems currently facing off-label studies, then it seems from a practical and First Amendment perspective that the FDA should create a “safe harbor” for drug companies more liberally promoting such CER studies to doctors. However, such safe harbor rules should not allow direct-to-consumer (DTC) marketing because that would undermine any incentive drug companies would have to undergo more rigorous sNDA testing. Indeed, if a drug company receives positive study results from either Track One or Track Two, these results could provide it with more incentive to apply for a sNDA in order to open up the possibility of DTC marketing.

F. *First Amendment and Commercial Speech*

In either continuing or amending its regulatory ban on off-label marketing, the FDA has to consider that it is regulating commercial speech that is protected by the First Amendment. Further, as discussed below, the Supreme Court has recently expanded the scope of First Amendment protection afforded to corporations. This substantial change makes existing FDA restrictions on off-label marketing vulnerable to legal attack by pharma.

For the last three decades, the four-part test in *Central Hudson Gas & Electric Corporation v. Public Service Commission of New York* has guided courts on how to determine whether a restriction on commercial speech was viable.<sup>170</sup> The general principle from the test is that truthful commercial speech is entitled to First Amendment protection. If the government attempts to restrict such speech, it needs a substantial governmental interest and must directly advance this interest in a narrowly tailored fashion. The government body must prove that “the harms it recites are real and that its restriction will in fact alleviate them to a material degree.”<sup>171</sup> Lastly, the government need not use the least restrictive means; however, there must be a “reasonable fit between the legislature’s ends and the means chosen to accomplish those ends . . . a means narrowly tailored to achieve the desired objective.”<sup>172</sup> Essentially, *Central Hudson* held that commercial speech regulations should be reviewed with an intermediate level of scrutiny, reflecting the inherent

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170. *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n of N.Y.*, 447 U.S. 557, 566 (1980).

171. *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 555 (2001).

172. *Id.* at 556.

differences between commercial and political speech within the First Amendment and the government's broader power to regulate commerce. While *Central Hudson* has not been overruled, with two recent cases, *Citizens United v. Federal Election Commission*<sup>173</sup> and *Sorrell v. IMS Health Inc.*,<sup>174</sup> it appears that the Court is fundamentally rethinking the lower level of protection afforded to commercial speech under *Central Hudson*.

In the much discussed 2010 ruling in *Citizens United*, the Court expressed disapproval for what it characterized as speaker-based discrimination in the Bipartisan Campaign Reform Act of 2002 (BCRA).<sup>175</sup> The Court ruled that BCRA's two-tiered approach of restricting corporate and union speech, while allowing individual speech, unconstitutionally discriminated on the basis of "corporate identity."<sup>176</sup> In applying strict scrutiny to strike down central components of the law, the Court explained that the government violated the First Amendment because "certain disfavored associations of citizens—those that have taken on the corporate form—are penalized for engaging in the same political speech" as other entities (individuals and unincorporated associations).<sup>177</sup>

In *Sorrell*, which was decided in 2011, the Vermont legislature passed a regulation that prohibited pharmacies and other regulated entities from selling or disseminating prescriber-identifying information for marketing.<sup>178</sup> Vermont argued that it was merely a commercial restriction with an incidental burden on protected expression, necessary to protect medical privacy, including physician confidentiality, avoidance of harassment, and the integrity of the doctor-patient relationship.<sup>179</sup> The Court held the regulation to be more than an incidental burden; and, in so determining, the Court decided that the statute was not sufficiently narrow or proportional to the asserted interest protected.<sup>180</sup>

*Sorrell* did not overrule *Central Hudson*, but the majority opinion by Justice Kennedy, who also authored *Citizens United*, strongly suggested that corporate commercial speech might be deserving of the same protection as corporate political speech: "A consumer's concern for free flow of commercial speech may often be keener than this concern

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173. *Citizens United v. FEC*, 130 S. Ct. 876 (2010).

174. *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011).

175. *Citizens United*, 130 S. Ct. at 900.

176. *Id.* at 900.

177. *Id.* at 908.

178. *Sorrell*, 131 S. Ct. at 2659-60.

179. *Id.* at 2659, 2661.

180. *Id.* at 2668-69.

for urgent political dialogue.”<sup>181</sup> Justice Kennedy further analogized Vermont’s statute to one that restricted political discourse, “but the State may not burden protected expression in order to tilt public debate in a preferred direction.”<sup>182</sup>

Thus, the Supreme Court held that speech in aid of pharmaceutical marketing is a form of expression protected by the free speech clause of the First Amendment.<sup>183</sup> Furthermore, the Court opened the door for drug manufacturers to make the credible legal argument that they have a First Amendment right to market off-label uses and that the State has a high burden to justify its content-based law as consistent with the First Amendment.<sup>184</sup> *Sorrell* requires the State’s interests to be proportional to the resulting burdens placed on speech and inhibits the law from seeking to suppress a disfavored message.<sup>185</sup>

The proposal set forth in this article seems to pass the heightened level of scrutiny in *Sorrell*. Here, the government can argue that it has a substantial interest in regulating such speech because the FDA can empirically demonstrate that drug companies have abused the off-label usage research process and have disseminated information that has been misleading and harmful to both patients and third-party payors (*e.g.*, Medicare, Medicaid, and private insurers). The proposal will openly regulate speech (as opposed to commercial activity) and will need to survive the heightened scrutiny standard discussed in *Sorrell*. Further, it is important that imposed restrictions advance this interest in a narrowly tailored fashion. To the extent that the proposal would lessen concerns about the legitimacy of off-label research because of PCORI oversight, this should consequently lessen the weight of the government’s interest in restricting such speech.

Therefore, the creation of the “safe harbors” (allowing pharma to disseminate more freely the results of PCORI testing to doctors on the

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181. *Sorrell*, 131 S. Ct. at 2664 (quoting *Bates v. State Bar of Ariz.*, 433 U.S. 350, 364 (1977)).

182. *Id.* at 2671.

183. *Id.* at 2659.

184. *Id.* at 2667. Note that this is a different standard than *Abigail Alliance*. See *Abigail Alliance for Better Access to Devl. Drugs v. von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007). In *Abigail Alliance*, the D.C. Circuit held that no person has a fundamental right of access to experimental drugs. *Id.* at 705-07. The First Amendment, alternatively, declares that manufacturers have a fundamental right of protected expression guaranteed by the free speech clause. Thus, in *Abigail Alliance*, the court applied the rational basis test, and it was the petitioner’s burden to prove that the government’s restriction did not bear a rational relationship to a legitimate state interest; whereas, under the strict or heightened scrutiny test here, it is the State’s burden to justify its law as consistent with the First Amendment. *Id.*

185. *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2668 (2011).

benefits of off-label usage) is not only justified based on public policy initiatives, one could also argue that they might be essential from a First Amendment perspective to ensure that factually true speech is not being suppressed.

Indeed, the potential impact of using *Sorrell* and *Citizens United* to attack FDA restrictions on off-label marketing has not escaped the attention of drug makers. Consequently, going forward, all restrictions on pharmaceutical marketing (a protected expression under the First Amendment's free speech clause) must directly advance a substantial government interest in a narrowly tailored fashion.

## V. CONCLUSION

The world of prescription drugs is plagued with a crisis of legitimacy. Although many functional problems exist with the current U.S. system of regulating off-label medicine, it all starts with the pharmaceutical companies themselves. Until these companies understand that it is their responsibility to act with the utmost candor and integrity in their relationships with physicians and patients, they will continue to circumvent the FDA approval process and take advantage of the system.

In the United Kingdom (U.K.), a system is in place that is substantially regulated by non-government entities and the drug manufacturers themselves.<sup>186</sup> Statutory authority that is very comparable to what exists in the U.S. is supplemented with a detailed code of practice that helps to remove ambiguity in the law.<sup>187</sup> Pharmaceutical companies have a high level of engagement with the entire process because they developed and adopted the code that exists in the U.K.<sup>188</sup> These companies regularly examine their business practices, limit the extent of their hospitality to MECCs and medical practitioners, and exercise influence over other drug manufacturers.<sup>189</sup> Moreover, competitors, former employees, physicians, and patients can bring complaints against drug manufacturers for violating the rules and regulations against off-label promotion.<sup>190</sup> As a result, the U.K. has in place a transparent system that resolves conflicts expeditiously.<sup>191</sup>

Such a system is likely not feasible in the U.S. given that one central government body serves as the gatekeeper and that the FDA and

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186. See Osborn, *supra* note 21, at 340-52.

187. *Id.* at 340.

188. *Id.* at 341.

189. *Id.* at 347.

190. *Id.* at 345.

191. See Osborn, *supra* note 21, at 342.

pharmaceutical companies have never worked in unison to eliminate unethical interactions between manufacturers and physicians. Nevertheless, there are still valuable takeaways from the U.K. system. The U.S. system is in dire need of clarity. Clarity would make it easier for enforcing bodies to prosecute misbehaving drug companies, and the defined limitations would allow courts to make straightforward, transparent determinations. By fair application of unambiguous rules, and by promoting drug manufacturer awareness of the problems resulting from off-label marketing, not only would the amount of federal tax dollars spent on off-label drugs be decreased, the incidence rate of health concerns stemming from improper off-label prescriptions will assuredly be reduced.