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

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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.”\(^1\) Once the FDA approves a drug for the market, doctors can legally prescribe the drug in any manner they choose. This is because 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.”\(^2\) Physicians are permitted to do this 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.”\(^3\) In fact, doctors often prescribe drugs for medical indications other than the FDA

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\(^2\) Id. at 105.

\(^3\) Id.
tested and approved uses in a practice known as “off-label” drug use.  

To maximize profits, major pharmaceutical companies ("pharma") primarily rely on two disparate business practices: innovation and marketing. 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 pharmaceutical companies to actively market these “off-label” uses without securing FDA approval for these additional indications. Pharmaceutical companies, 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. How this off-label usage


5 Craft, Jr., supra note 1 (“Pharma” refers to multi-national pharmaceutical companies that principally rely on patented drugs, as opposed to generic drugs, for their profits).

6 Id.
information reaches doctors is a contentious legal point.\(^7\) 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].”\(^8\)

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.\(^9\) In 2002, before the Department of Justice (DOJ) began actively investigating the prevalence of off-label marketing,\(^10\) the ten largest pharmaceutical companies spent thirty-one percent of their revenues on marketing.\(^11\) Comparatively, these same ten companies spent only fourteen percent on R&D.\(^12\) Given these numbers, it comes as no surprise that a 2001 study revealed that

\(^7\) Id.
\(^8\) Id.
\(^9\) Id. 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 additional smaller companies settled suits for hundreds of millions of dollars.
\(^11\) Craft, Jr., supra note 1, at 104.
\(^12\) Id.
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doctors prescribed drugs in an off-label manner twenty-one percent of the time.\textsuperscript{13} However, the truly alarming fact associated with this finding is that seventy-three percent of these off-label drug usages had little or no scientific support.\textsuperscript{14} 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”;\textsuperscript{15} (2) if “the results of such tests show that such drug is unsafe for use under such conditions or

\begin{footnotesize}
\begin{enumerate}
\item Id.
\item 21 U.S.C. § 355(d)(1).
\end{enumerate}
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do not show that such drug is safe for use under such conditions”; or (3) if “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.” Basically, the FDA will not accept a NDA unless there is substantial evidence that regulators could fairly and responsibly conclude that the drug will have the effect it purports to have under the conditions of use prescribed or recommended in its proposed labeling.

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,” pharmaceutical companies have 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 huge financial risk for drug manufacturers in seeking official approval as the clinical trials might disprove the prevailing medical notions regarding the safety and efficacy of the off-label uses. Consequently,

there is a substantial gap in the quality of data supporting the safety and efficacy of drugs used in an off-label manner.\textsuperscript{19}

As a result of this very real problem of 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 drug manufacturers.\textsuperscript{20} These three bodies have prosecuted manufacturers guilty of illegal off-label promotion as being violations of the Food, Drug, and Cosmetic Act of 1938 (FDCA) and the federal False Claims Act (FCA).\textsuperscript{21} 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.\textsuperscript{22} Moreover, since May 2004, Pfizer, Eli Lilly &

\textsuperscript{19} Id. at 731.

\textsuperscript{20} Craft, Jr., supra note 1, at 105.

\textsuperscript{21} See id. at 107-108, 112-115; 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 (2010).

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Off-Label Promotion of Medicine Co., Bristol-Myers Squibb CO., and four other drug companies have paid a total of $7 billion in fines and penalties.\(^{23}\) However, at the same time, Pfizer made $16.8 billion in revenue from selling the medicines it was fined for from 2001 to 2008, and Eli Lilly made $36 billion in revenue from off-label prescribing of a single drug between 2000 to 2008.\(^{24}\) 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% of overall sales for the drug) came from off-label use.\(^{25}\) While these fines may seem staggering in isolation, their deterrent effect pales in comparison with the huge financial profits stemming from off-label marketing. In other words, pharma might cynically conclude that such fines are a “cost of doing business” and not substantially change their illegal business practices.\(^{26}\)


\(^{24}\) Id.

\(^{25}\) Id.

\(^{26}\) Id.
In the forthcoming sections, 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. Section II will discuss the regulations in place governing off-label promotion and detail the practice of ghostwriting and its associated concerns. Section III will analyze the costs and benefits of off-label marketing and practice of medicine, and utilize a case study to demonstrate the predicament of drug manufacturers. Section IV sets out our proposal to use the newly created Patient-Centered Outcomes Research Institute to generate unbiased research on off-label uses and in turn create a safe harbor for drug companies to widely disseminate studies generated through this process to the medical community. Finally, Section V presents concluding thoughts and discusses 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.27

The FDA draws its statutory authority to regulate the sale and marketing of drugs in the U.S. via the FDCA.28 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.29 Labeling is broader than just the label on the bottle; it is defined under the FDCA

27 Eisenberg, supra note 18, at 733.
28 Osborn, supra note 21, at 308.
29 Id.
to include all tangible material that accompanies a drug. More specifically, labeling includes the product’s package insert and promotional materials including the detailing brochures used by the manufacturer to promote sales of the product; 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. “One theory is ‘...promoted for off-label use is “misbranded” if it has inadequate directions for the unapproved use or because the manufacturer has provided “false or misleading” information regarding the product.’” The second theory allowing a manufacturer to be prosecuted for the off-label promotion of FDA approved drugs is a separate misbranding violation – holding that it constitutes the introduction of an unapproved new drug into interstate commerce.

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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).

31 Ascroft, supra note 30, at 100.

32 Craft, Jr., supra note 1, at 107.

33 Id. at 108.
A. Legal Implications of FDA’s Broad Definition of “Labeling”

As for the first theory dealing with 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 regulation’s coverage is broad, stemming from the fact that the FDA defines “labeling” to include virtually anything that a company or its employees might produce or present, even materials that do not accompany the drug such as promotions and advertisements.\(^{34}\) 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, or otherwise concerns any use that has not been approved expressly by the FDA, regardless of whether it is truthful or accurately reflects good medical practice.”\(^{35}\)

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

\(^{34}\) Osborn, supra note 21, at 308.

\(^{35}\) Id. at 308-09.
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interest.\textsuperscript{36} Their argument 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 on off-label usage ignores the risks of relaxing current limitations on off-label marketing and credulously accepts the “truthful” nature of studies funded by pharmaceutical companies. As discussed below, pharmaceutical companies have become quite adept at manipulating and gaming the information marketplace. One tactic is to use contractual gag clauses to prevent clinical investigators from publishing unfavorable results that would negatively impact the financial interests of the pharmaceutical company.\textsuperscript{37} 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.

\textsuperscript{36} The commonly identified benefits of off-label medicine will be detailed in Section III of this Note.

associated with long-term use of this product.\(^{38}\) 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.\(^{39}\) Without curbing these abuses, there will remain a valid suspicion that dissemination of “truthful” off-label findings can still 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.\(^{40}\) As mentioned, it is sometimes irrelevant that the drug has already received approval for marketing and distribution by the FDA, as a drug is considered “new” when it is promoted for uses that have not been FDA approved.\(^{41}\)

\(^{38}\) Id.

\(^{39}\) Id.

\(^{40}\) Craft, Jr., supra note 1, at 108.

\(^{41}\) Id.
The term “new” takes on an extended meaning - in turn, 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.”\textsuperscript{42} Thus, although FDAMA allows drug manufacturers to distribute information of off-label uses within strict limitations, the FDCA effectively counters this permission by requiring that each so-called intended use be FDA approved, and if not, 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 make a false statement that leads to a false or fraudulent claim paid or

\textsuperscript{42} Osborn, supra note 21, at 309.
approved by the government. The application of the FCA to off-label promotion is convoluted, and includes several links to ultimately find the drug manufacturers liable. The circuitous chain of liability is as follows: (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) who in turn sell to pharmacies and other providers; (4) who in turn file claims with the government (e.g., Medicare and Medicaid). The essence of this claim is that off-label promotion causes false claims to be submitted to the government for improper off-label uses. The theory of

43 Osborn, supra note 21, at 310.

44 Id. at 310-11.

45 Craft, Jr., supra note 1, at 113 (explaining how “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
liability is convoluted because it is not the drug manufacturer’s direct actions that cause it liability. Rather, they are only contributory, and it is the pharmacies and providers that file claims with the government and ultimately make the manufacturer’s off-label promotion illegal under the FCA.

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

Another cornerstone of the FCA is its availability of a qui tam suit, or whistleblower provisions, which allow individuals who are aware of fraud against the government to file suit on the government’s behalf and receive a portion of the recovered funds.46 “Whistleblowers can file suit under the FCA for fraud resulting from off-label promotion due to negative effects it has on state and federally funded programs such as Medicaid, “medically necessary” prescriptions and not “experimental” medications, are now contesting the off-label prescriptions they were forced to cover alleging they lost billions of dollars as a result of being forced to cover such off-label prescriptions).

46 Craft, Jr., supra note 1, at 113.
which may prohibit reimbursement for off-label prescriptions.”

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 thirty percent of any settlement the company makes with the government.

The pertinent time in determining liability under the FCA on the basis of labeling is the time the off-label speech occurs. As with liability under the FDCA, the truth or medical accuracy of the information asserted and promoted is basically irrelevant. 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 at any time marketed off-label.

47 Id.; see also Evans, supra note 23 (shedding light on how a former Pfizer employee was instrumental on 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 (D. Mass. 2001) (ruling generally that a
Thus, from a fairness 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 time-exhaustive (arguably, inefficient) FDA approval process.

A separate fairness argument drug manufacturers can aptly make 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% of fines incurred by the pharmaceutical companies, it is more than plausible that some people in a position to blow the whistle might attempt to game the system. For example, a former employee of Parke-Davis (later purchased by Pfizer), acted as a whistle-blower when he sued on behalf of taxpayers to recover money the government paid for drugs illegally promoted off-label.\(^{51}\) The questionable part of this story is that Franklin holds a Ph.D. in microbiology 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, \textit{supra} note 23.
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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. Franklin is also married to a lawyer. Given his background in science and medicine, and his wife’s legal acumen, one can question why he agreed to perform tasks that he likely knew a priori were illegal. While speculative, a plausible reason might be the ability of all whistleblowers to receive a substantial amount of the fine handed down on the drug manufacturers, even if they blow 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.” No private right of action

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52 Id.
53 Id.
54 Craft, Jr., supra note 1, at 113; see also Stephanie Greene, False Claims Act Liability for Off-Label Promotion of
exists under the AKS, which is why the FCA has served as the necessary vehicle for whistleblowers to bring fraud claims for AKS violations.\textsuperscript{55} Allowing whistleblower actions via the FCA for violations of the AKS is an integral part of federal regulation as it helps reduce two violations at once: it helps cut down on the propensity of inducements and rewards being paid to doctors for referrals involving federal health care business, while 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.\textsuperscript{56} The WLF challenged the FDA’s restrictions on distribution of off-label information by manufacturers on First Amendment freedom of speech grounds.\textsuperscript{57} The WLF decisions allow manufacturers to disseminate scientific


\textsuperscript{55} Greene, \textit{supra} note 54, at 56-57.

\textsuperscript{56} Osborn, \textit{supra} note 21, at 311.

\textsuperscript{57} Ascroft, \textit{supra} note 30, at 103.
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publications concerning the off-label use of their products to 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.\(^5^8\) Moreover, manufacturers can have open involvement with continuing medical education (CME) seminars that discuss off-label uses by providing financial support and suggesting the content or the speakers for the event.\(^5^9\)

In response to the WLF cases, Congress passed FDAMA in 1997. Before the 1997 passage of the Food and Drug Administration Modernization Act (FDAMA), the FDA strongly opposed the dissemination of off-label information of any kind by a drug manufacturer.\(^6^0\) Section 401 of FDAMA included the first provision to allow pharmaceutical companies to disseminate off-label information under certain circumstances.\(^6^1\)

FDAMA allowed drug companies to disseminate off-label information only to health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, and

\(^{58}\) 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.
governmental agencies. Manufacturers were only allowed to circulate authorized information contained in either unabridged peer-review journals or certain qualified reference publications. 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. Most importantly, 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 that such approval would be cost-prohibitive or unethical. Thus, while FDAMA opened the door


63 Ascroft, supra note 30, at 102.

64 Id.

slightly to drug manufacturers, it placed 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 muddied, however, by the WLF cases and this ambiguity was exacerbated by FDAMA’s expiration on September 30, 2006.66 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. Drug companies subsequently took advantage of this opening by practicing the scientifically 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 actions would not be taken if they conformed with certain requirements.”).

66 Tim Mackey and Bryan A. Liang, supra note 65, at 8.
and ethically questionable practice of “ghostwriting.”

Ghostwriting is the process by which a pharmaceutical company contracts with or hires a medical education and communications company to draft articles about new uses for FDA-approved drugs or medical devices. The company itself or the medical education and communications company (MECC) it contracts with will then work with prominent physicians and scientists, and pay the academic to sign off his or her name as the author to increase the likelihood that the article will be published in important medical journals. Thus, when the article appears in the press, the doctor appears as the author, while the

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


69 See generally id.; see also Sen. Charles E. Grassley, Ghostwriting in Medical Literature, Minority Staff Report (2010).
contribute the ghostwriter and the pharmaceutical company remain hidden.\textsuperscript{70}

Medical literature on off-label medicine can have benefits as it makes physicians, especially in rural areas, aware of contemporary medical techniques and newfound uses for previously approved drugs. But these benefits only occur if the information is accurate. The concern about ghostwriting, however, “is that doctors might change their prescribing habits after reading certain articles, unaware they were commissioned by a drug company.”\textsuperscript{71} Ghostwritten articles always contain undisclosed conflicts of interests, making it impossible for a doctor to know whether an article is legitimate or not.\textsuperscript{72} “[A] ghostwriter of original research will package the message of the research paper so that it fits into the marketing plan for the drug.”\textsuperscript{73} Moreover, when prominent physicians and scientists lend


\textsuperscript{71} Singer, \textit{supra} note 68.

\textsuperscript{72} Moffatt and Elliott, \textit{supra} note 70, at 24.

\textsuperscript{73} \textit{Id.} at 22.
their names to an article, it raises the credibility of the findings and conclusions presented.\textsuperscript{74}

An example of the potential harm caused by ghostwriting is exemplified by 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.\textsuperscript{75} Ghostwritten articles emphasizing the benefits of the two hormones were published in medical journals from 1998-2005.\textsuperscript{76} However, in 2002, a federal study on hormone therapy evidenced that menopausal women that took certain hormones had an increased risk of invasive breast cancer, heart disease, and stroke.\textsuperscript{77}

Although 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,”\textsuperscript{78} this example shows blatantly how medical research can take swift and dangerous turns, and further why participating in the required

\textsuperscript{74} Sen. Grassley, supra note 69, at 2.
\textsuperscript{75} Singer, supra note 68.
\textsuperscript{76} Id.
\textsuperscript{77} Id.
\textsuperscript{78} Id.
FDA testing is so important to ensure the safety of America’s citizens.

The lack of transparency in ghostwriting creates several causes for concern. As described, there is an inherent conflict of interest with all ghostwritten articles. The MECCs that draft the articles are getting paid directly by the pharmaceutical companies to include research — whether substantiated or not — that supports the drug’s use for off-label purposes. Secondly, the academic that signs off on the draft as being scientifically accurate is receiving kickbacks from the education and communications company. Thus, not only is the article assuredly biased in favor of the drug manufacturers, but it also runs the risk of lacking credibility.

When questioned about the credibility of the data, pharmaceutical companies will often deny their affiliated academics the opportunity to review.\(^79\) This occurred with Proctor & Gamble (P&G) and Aubrey Blumsohn, a senior lecturer in the Bone Metabolism Unit at Sheffield University.\(^80\) In 2002 Blumsohn contracted with P&G to perform research and speak on the company’s behalf about new uses for drugs.\(^81\) However, when

\(^{79}\) See Moffatt and Elliott, supra note 70, at 21.

\(^{80}\) Id.

\(^{81}\) Id. at 21-22.
he finally became convinced that P&G was skewing 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. This instance reveals that the research-driven data that pharmaceutical companies give to MECCs and academics might not only lack credibility, but could also be totally falsified.

The prevalence of ghostwriting works to exacerbate the problem. The Journal of the American Medical Association (JAMA) found evidence of ghostwriting in 11% of papers in six leading journals. More specifically, a study solely focusing on medical literature devoted to the Pfizer’s drug, Zoloft, found that in three years approximately 57% (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 Zoloft.

As a result of this lack of transparency, inherent conflict of interest, problems with credibility and falsification, and its prevalence, the whole system of ghostwriting is a fraud on journals, their readers, and patients. Pharmaceutical companies have mastered the secrecy of the process and repeatedly sneak

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82 Id. at 21.
83 Id. at 22.
84 Id. at 22-23.
their ghostwritten articles by respected medical journal’s safeguards. Readers, often doctors, are also not aware what has or has not been ghostwritten and are deceived into believing as truth often falsified statistics and literature. In turn, patients are affected as doctors put these unsubstantiated treatments into practice - which is either unbeneificial or possibly dangerous to the patient. Thus, although there are certain theoretical benefits to the practice, in practicality, ghostwriting is a farce with costs far outweighing its benefits.

H. Unethical and Aggressive Courting of Physicians

In addition to ghostwritten articles, many pharmaceutical companies will go even further to implement its off-label promotional scheme. Besides ghostwriting, the following tactics are often used: (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 individuals hired to provide scientific knowledge rather than sell a manufacturer’s drug; (3) pay doctors to allow its sales representatives to participate in discussions with patients regarding treatment options; (4) pay doctors to travel to lavish locations to attend consultant or
Dr. Fazal Khan & Justin Holloway  Off-Label Promotion of Medicine advisory meetings that exclusively discuss off-label uses of the company’s drugs; (5) host teleconferences where the company pays doctors to instruct other doctors about newly discovered off-label uses; and (6) host CME seminars that are intended to give the appearance of providing independent medical education regarding off-label uses. 85

These tactics represent potentially multiple AKS violations; and although hosting CME seminars were decided in the WLF decisions to be within a manufacturer’s rights, the practices are obviously deceptive and aimed to increase the market for their drugs in a dishonest manner. Due to drug manufacturers proactively trying to expand the market for their drugs without properly applying for additional FDA-approval, it is obvious why the FDA and DOJ are so adamant about investigating these companies for the illegal circumventing of the system. As former Associate Attorney General Robert McCallum stated, “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.” 86

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85 Craft, Jr., supra note 1, at 115-16.
86 Craft, Jr., supra note 1, at 127.
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. Gag clauses frequently appear in clinical-trial agreements and serve to prevent investigators from examining the data independently or publishing the results without first obtaining the consent of the sponsor.\textsuperscript{87} As such, negative results are routinely underreported, or go unreported altogether.

Pharma’s control over the clinical-trial process causes a lack of transparency and a resulting unsafe environment for American consumers. Pharma retains this control due to the monetary support they provide academic institutions, unaffiliated medical centers, and contract research organizations (CROs). As a result, all three research bodies are forced to compete with each other over pharma-sponsored clinical-trial agreements. Therefore, their ability to contract out of pharma-inspired gag clauses is essentially diminished.

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.”\textsuperscript{88} 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.\textsuperscript{89} And 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 the ongoing competition for research sponsorship.

The argument against gag clauses continues to gain traction since the unfortunate Vioxx disaster and the uncovered internal emails of pharmaceutical giant, Merck. It is well documented that Merck knew years before pulling Vioxx off the shelves that the drug had increased risks of heart disease and stroke as

\textsuperscript{88} Id.

\textsuperscript{89} Id.
compared to industry competitors, aspirin and naproxen.\textsuperscript{90} Although Vioxx was not taken off the market until September 2004, reports indicate that Merck knew of the life-threatening side effects as early as 1996.\textsuperscript{91} Merck conducted tests intentionally withholding people with increased risk of heart disease from participating as they did not want to risk the chance of profuse negative results.\textsuperscript{92}


\textsuperscript{91} Veracity, supra note 90, at 1, 3.

\textsuperscript{92} Id. at 3 (uncovering one email from a Vice President stating, “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!”).
The profound negative side effects of Vioxx were also explained to Merck’s directors by the company’s research directors. In March 2000, Merck’s research chief, Edward Scolnick, wrote in an email his belief that test results expressed unmistakable affirmation that heart problems associated with Vioxx were “clearly there” and that it was a “shame.”\(^93\) 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.\(^94\) This demonstrates that not only is pharma willing to cease sponsoring academic institutions who insist on publishing the truth (albeit negative), but companies have no fear risking the health of the nation as they discretely scheme behind the backs of American consumers.

As concern mounts about public safety, distrust of the pharmaceutical industry, and advocacy within the medical community for greater openness in conducting and reporting

\(^93\) E. Huff, supra note 4, at 90.

\(^94\) See Mathews and Martinez, supra note 90 (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.”
clinical trials, progress against gag clauses may be forthcoming.\textsuperscript{95} Senators Chris Dodd and Chuck Grassley confronted this challenge head on and attempted to pass legislation such as Fair Access to Clinical Trials (FACT) Act of 2007 and the Food and Drug Administration Safety Act of 2007 (FDASA).\textsuperscript{96}

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.\textsuperscript{97} It sought to ensure that the scientific community and the general public have access to basic information about clinical trials by expanding on the data already available at clinicaltrials.gov.\textsuperscript{98} 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

\textsuperscript{95} Robert Steinbrook, supra note 87, at 2.


\textsuperscript{97} Id. at 4.

\textsuperscript{98} Id.
clinical trial results database of health-related interventions to test the safety or effectiveness of any drug, biological product, or device.” 99

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 postmarket surveillance of drugs by establishing an independent center within the FDA responsible for monitoring the safety of drugs once they are on the market. 100 This center would have the authority to take corrective action if a drug is a risk to patients. 101 In essence, this act would have armed the FDA with a greater ability to regulate pharma and provide 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 postmarket drug surveillance, unfortunately neither was passed into law. However, there are several constructive takeaways from the ideas of Senators Dodd and


100 Bold Reforms for Drug Safety, supra note 96, at 1.

101 Id.
Grassley. American consumers need a safe harbor from pharma-sponsored testing that consistently underreports negative results, paints unsupportive results in a brighter light, and publishes almost every positive test.\textsuperscript{102} Although there are notable benefits to companies not going through the time-extensive and cost-prohibitive constraints of the regulatory process, it is imperative for consumer safety and to prohibit fraud against the government that research results have the transparency needed to ensure certainty that said results are not predicated on gamed information.

The FACT Act and FDASA were dedicated to affording greater transparency of clinical trials, accountability of pharma, and an objective center focused on postmarket 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 affect gag clauses have

\textsuperscript{102} Pharma Has Developed New Forms of ‘Research’ to Serve its Own Interests, http://www.themarknews.com/articles/5110-is-drug-research-turning-into-a-scum (reporting that pharma systematically failed to publish negative studies on several antidepressants; of 74 trials (38 positive, 36 negative), 94% of the positive tests were published, compared to only 23% of the negative tests).
Dr. Fazal Khan & Justin Holloway  Off-Label Promotion of Medicine 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, 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 would act to ensure that the drug industry was not merely publishing favorable results and skewing public knowledge.

Another idea that could be supplemental to the suggestion above or in addition thereto, would be a user-fee-sponsored independent testing center that conducts postmarket testing on drugs deriving a significant portion of their profit from off-label uses. As the struggle against ghostwriting persists, off-label uses gain prevalence and pharma continuously avoids accountability. Independent postmarket testing of drugs prominently prescribed for off-label uses not FDA approved would bring a certainty and clarity to the efficacy of such off-label uses. Doctor’s 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 are
acknowledged benefits to bypassing this at times. However, such benefits never outweigh the public safety concerns at risk. Certain changes to the entire process need to be considered and these two ideas provide a well-conceived starting point.

III. What We Gain and Lose From Off-Label Regulations

The fight between proponents and opponents of off-label 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.\textsuperscript{103} This will in turn improve the quality of health care without waiting for the lengthy FDA approval process.\textsuperscript{104} 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 health.\textsuperscript{105} Profit-driven off-label promotion can expose the public to severe health risks and the drug manufacturer to legal liability.\textsuperscript{106}

\textsuperscript{103} Greene, supra note 54, at 47.

\textsuperscript{104} Id.

\textsuperscript{105} Id. at 43.

\textsuperscript{106} Id.
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. Underlying this argument, proponents theorize that drug companies are in the best position to provide doctors with up-to-date medical research and treatments, given the vast amount of medical literature and the lack of time doctors have to read it. 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. Provided that doctors are experts in this field, proponents further argue that they are best able to evaluate the

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108 Id. at 980-81.
109 Ascroft, supra note 30, at 99.
information and insure that patients receive appropriate treatments – an argument supported by the American “learned intermediary” tort doctrine.\textsuperscript{110}

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 in terms of both controlling price increases and in saving tax dollars channeled to FDA efforts.\textsuperscript{111} By allowing off-label uses, drug companies should experience increased sales volume allowing them to decrease sales price.\textsuperscript{112} Allowing manufacturers to sell their products off-label will also save them the time, money, and resources that they otherwise would have to expend to become FDA approved.\textsuperscript{113}

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 prescription drugs more than tripled from $4.8 billion to $17 billion.\textsuperscript{114} In fact, between 1990 and 2002,

\begin{flushleft}
\textsuperscript{110} Johns, supra note 107, at 981. \\
\textsuperscript{111} Greene, supra note 54, at 48. \\
\textsuperscript{112} Johns, supra note 107, at 981. \\
\textsuperscript{113} Id. \\
\textsuperscript{114} Greene, supra note 54, at 43.
\end{flushleft}
the total amount spent in the U.S. on prescription drugs increased from $40.6 billion to $162 billion.\(^{115}\) During that same time span, prescription drugs prices increased 7.4%, compared to inflation rising merely 2.5%.\(^{116}\) On that same note, currently prices for the 200 top-selling drugs are rising three times the country's inflation rate.\(^{117}\) In fact, the price of Claritin, the top-selling allergy pill, was raised thirteen times over five years, an increase of more than 50%.\(^{118}\) Given this data, projections estimate that national spending on prescription drugs will rise an average of 10.7% until 2013.\(^{119}\) Thus, although the argument that off-label promotion will drive cost-cutting is theoretically tenable, the statistics clearly 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.\(^{120}\) As discussed in below Section

\(^{115}\) Johns, supra note 107, at 972.

\(^{116}\) Id.

\(^{117}\) Id. at 973.

\(^{118}\) Id. at 982.

\(^{119}\) Id. at 972.

\(^{120}\) See generally Tim Mackey and Bryan A. Liang, supra note 65.
IV, 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.\footnote{Id.} However, the D.C. Circuit reaffirmed in the \textit{Abigail Alliance} case 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.\footnote{Abigail Alliance for Better Access to Developmental Drugs \textit{v.} Andrew von Eschenbach, 495 F.3d 695, 698 (2007) [hereinafter Abigail Alliance].} Citing the U.S. Supreme Court in \textit{United States v. Rutherford}, 442 U.S. 544 (1979), the court in \textit{Abigail Alliance} noted “that ‘for 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.’”\footnote{Id. at 713.} In the court’s view, since a drug cannot be proven to be either safe or effective for a certain use without going
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.\(^{124}\)

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

\(^{124}\) As discussed below, “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.
efficacy of products. 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. 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. Opponents corroborate this argument with several examples of off-label drug uses gone horribly wrong (e.g., Vioxx, Fen-phen, and Neurontin (or gabapentin)), to demonstrate that drug company research conducted outside of the FDA oversight process is suspect given the inherent conflicts of interest. Opponents further posit that as a result of the onslaught of ghostwritten academic articles in distribution, the

125 Greene, supra note 54, at 38.
126 Id.
127 Johns, supra note 107, at 981.
128 Id.
doctor’s role as a learned intermediary has been severely compromised.\(^{129}\)

C. Why Pharmaceutical Companies Continue to Promote Off-Label

Given the plethora of persuasive and potentially life-threatening arguments that opponents threaten could result from allowing off-label marketing, it is still understandable to see why a pharmaceutical company would fight vigorously to allow it. 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, “[r]igorous 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.”\(^{130}\)

\(^{129}\) Id. at 981-82.

\(^{130}\) Eisenberg, supra note 18, at 718-19, 732 (using the drugs Vioxx and Prempro to explain how “[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.”).
To obtain FDA approval for a drug is an incredibly monetarily-exhausting and time-consuming process. The approval process takes six to fifteen years and costs between $100 million and $880 million per drug. The manufacturer is required to conduct three phases of clinical trials, obtain the patients’ informed consent, and report the results to the FDA. This pre-approval stage is referred to as Phase I through III research. 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.

After Phase I-III research is complete and the NDA is approved by the FDA, the manufacturer may on its own volition conduct additional Phase IV research. 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. Most drug companies that choose to conduct Phase IV research...

131 Johns, supra note 107, at 973-74.
132 Id. at 988.
133 Id. at 988.
134 Id. at 974.
135 Id. at 988.
136 Id.
research opt to study side effects that possibly went undetected in the initial trials - the route that does not face stringent FDA restrictions.\textsuperscript{137}

A depictive example of the risk that rigorous clinical trials pose to a drug manufacturer that is already enjoying substantial off-label sales is soundly demonstrated by a study on the effects of hormone replacement therapy (HRT) on the risk of heart disease in post-menopausal women.\textsuperscript{138} 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.\textsuperscript{139} Although HRT manufacturers were formally

\begin{flushleft}\textsuperscript{137} 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 manufactures 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).\end{flushleft}

\begin{flushleft}\textsuperscript{138} Id.; see also Writing Group for the Women’s Health Initiative Investigators, 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).\end{flushleft}

\begin{flushleft}\textsuperscript{139} Eisenberg, supra note 15, at 732.\end{flushleft}
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 marred in falsity). Thus, HRT manufacturers had little economic reason to subject the use of HRTs to more rigorous testing.

The bottom-line profit windfall the manufacturer was incurring, however, was abruptly put to an end when the National Institute of Health (NIH) conducted a long-term, controlled study with over 16,000 patients. To much surprise, the results were astonishing. The NIH results “indicated an increased risk of heart disease (as well as increased risks of other diseases) in women receiving HRT.” This study reduced sales of the hormone drastically; however, it is indefensible to argue that the study was unnecessary. “In 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

\[\text{140 Id.}\]
\[\text{141 Id.}\]
\[\text{142 Id.}\]
\[\text{143 Id.}\]
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undeniable value to patients, physicians, health insurers, and
policy makers.  

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: one, they restrict
flow of information that could help both doctors and patients;
two, the rules are inefficient and lead to companies willfully
breaching the law as having to apply for a sNDA is too cost
prohibitive in terms of time and money in most cases; and three,
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 the messaging concerning off-label usage is
indeed accurate. However, as discussed above, there is ample
evidence that pharma has corrupted the practice of off-label
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

144 Id.
has become a backdoor for pharma to generate huge profits on patented drugs by creating new markets without proving to the public that such uses are actually 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 as medically unproven therapies raise issues both of patient safety and unnecessary healthcare expenses.

This begs the question - what 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 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 to i) 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 ii) 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 very beneficial if there is some way of ensuring the validity of the speech being disseminated. Recognizing that the incentives for conducting CER on off-label uses can vary greatly depending upon 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. For example, in the 1970’s Dr. Jack Wennberg, the founder of the Dartmouth Atlas Project, analyzed Medicare utilization data and uncovered dramatic geographic variation in the utilization of healthcare resources. For example, Wennberg identified an epidemic of hysterectomies in some areas of Maine, where the data predicted that 70% of the women in one town would
receive this procedure sometime during their lifetime. 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.” 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.\textsuperscript{147} As before, political considerations moved Congress to specify that the AHRQ could not “mandate national standards of clinical practice”;\textsuperscript{148} in other words, its recommendations could not directly guide coverage decisions.

More recently, in an influential article 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.”\textsuperscript{149} 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.”\textsuperscript{150} Further, Gawande concluded that the quality of care in McAllen

\begin{footnotesize}
\begin{itemize}
\item \textsuperscript{147} Id. at 531.
\item \textsuperscript{148} Id.
\item \textsuperscript{150} Id.
\end{itemize}
\end{footnotesize}
“is not appreciably better, and by some measures, it is worse.”

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 both costly and dangerous.

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

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.

More importantly, ARRA set aside $1.1 billion to fund CER through several federal agencies: the AHRQ, the National Institutes of Health (NIH), and the Office of the Secretary of

151 Id.


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the Department of Health and Human Services (DHHS). All of these efforts informed the creation of PCORI, which has the potential to more broadly incorporate CER and evidence based medicine (EBM) into the structure of healthcare in the United States 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.” A twenty-one 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.


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, 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 . . . .

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.”

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prevents Medicare or private payers 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.\textsuperscript{159} 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.\textsuperscript{160} 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.\textsuperscript{161} Going forward, these broad categories will

\textsuperscript{159} PPACA, § 1320e(b)(3).
\textsuperscript{160} Id.
\textsuperscript{161} Draft National Priorities.
likely be fleshed out with more detailed descriptions of specific research projects, “taking into account factors of disease incidence, prevalence, and burden in the United States (with emphasis on chronic conditions)” and “gaps in evidence in terms of clinical outcomes.”  

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

PCORI can credibly make this claim as the statutory language that created it has robust requirements for ensuring i) transparency of research results, ii) conflict of interest disclosures, and iii) 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

162 PPACA, § 1320e(d)(1).

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.”

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 in how safe and effective these uses are, 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. But, there might be some instances where a drug company might want research validation of

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a promising off-label use, but the potential market is too small (i.e., “orphan disease”) to justify a full-blown sNDA and insurers are rejecting coverage of this use on grounds that it is “experimental.” 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 nor equitable use of PCORTF funds. Considering the above analysis, our proposal sets out two different off-label research tracks for PCORI. Track one is to be initiated by PCORI for “public interest” considerations and track two is to be initiated by pharmaceutical companies seeking validation of off-label uses for their drugs.

i. Track One

If a drug reaches a certain threshold of off-label usage (either by monetary value or percentage of total prescriptions of drug), PCORI should initiate drug testing in this case as 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.\footnote{See Evans, supra note 23.} For a drug company that already has a lucrative off-label market presence for its drug, further testing carries significant

\footnote{See Evans, supra note 23.}
downside risk as 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 as 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 the increased utilization of healthcare.166

ii. Track Two

166 The Centers for Medicare and Medicaid Services 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.”, https://www.cms.gov/ACO/, (last visited March 20, 2012).
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. 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. However, in contrast to “track one,” funding for these studies would not come from PCORTF, but user fees paid for by the pharmaceutical companies. This would parallel the model already set up by the FDA for clinical drug
However, opening up access to PCORI’s research agenda by itself is likely not enough incentive for pharmaceutical companies to incur such research expense. However, as described below, if 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 since 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. Also, once again, the benefit of conducting such research under the auspices of PCORI is clear as it would have to follow rules regarding transparency, conflict of interest, and proper methodology.

D. Research Capacity

Is this proposal feasible given the relatively small footprint of PCORI? If implemented this proposal would certainly increase the administrative burden of PCORI. However, PPACA anticipates and allows for outsourcing of PCORI research

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outside of the government (e.g., NIH, NSF, DHHS) to academic and private research institutions.\textsuperscript{168} 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, this can be funded by user fees levied on pharmaceutical sponsors.

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 (see Sorrell discussion below) 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 still not allow direct-to-consumer (DTC) marketing as 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 two, this could

\textsuperscript{168} PPACA, § 1320e(d)(2)(B).
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 impact of its rules. The U.S. Supreme Court held in *Sorrell v. IMS Health Inc.*, 131 S.Ct. 2653 (2001), that speech in aid of pharmaceutical marketing is a form of expression protected by the free speech clause of the First Amendment. Since manufacturers do have a First Amendment right to market off-label, unlike how persons do not have a fundamental right of access to experimental drugs, it is the State’s burden to justify its content-based law as consistent with the First Amendment.

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170 *Id.* at 2667 (Note, however, that this is a different standard than *Abigail Alliance*. In *Abigail Alliance*, it was held that no person has a fundamental right of access to experimental drugs. The First Amendment, alternatively, declares that manufacturers have a fundamental right of protected expression guaranteed by
As set forth by the Court in Central Hudson Gas & Electric Corp. v. Public Service Commission of New York, 447 U.S. 557 (1980), a four-part analysis is proper to determine the viability of the restriction. First, the particular expression (off-label marketing) must be protected by the First Amendment. In order for commercial speech to come within that provision, it must concern lawful activity and not be misleading. Next, we ask whether the asserted governmental interest is substantial. If both answers are positive, we then determine whether the regulation directly advances the government interest asserted. Finally, and often most critical, we determine whether the regulation is not more extensive than is necessary to serve that interest.\textsuperscript{171}

The general principle from the test is that truthful commercial speech is entitled to first amendment protection and if the government is going 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.”\(^{172}\) Last, 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.”\(^{173}\) These standards ensure that the State’s interests are proportional to the resulting burdens placed on speech and inhibit the law from seeking to suppress a disfavored message.\(^{174}\)

Regarding restrictions on the marketing of off-label usages, there does seem to be a substantial First Amendment issue — to the extent such information is truthful, can the government restrict the manner in which companies disseminate such information? In Sorrell, the Vermont legislature passed a


\(^{173}\) Id. at 556.

\(^{174}\) Sorrell, supra note 169, at 2668.
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regulation that prohibited pharmacies and other regulated entities from selling or disseminating prescriber-identifying information for marketing. 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. The Court held the regulation to be more than an incidental burden; and in so determining, decided that the statute was not sufficiently narrow or proportional to the asserted interest protected.

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, private insurers). The proposal will openly regulate speech (as opposed to commercial activity) and will have to survive the heightened scrutiny standard discussed in Sorrell. Thus, it is important that restrictions imposed advance this interest in a narrowly tailored fashion. To the extent the proposal would lessen concerns about the legitimacy of off-label research because of PCORI oversight, this consequently should 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 such PCORI testing to doctors on the benefits of off-label usage) not only can be justified on the basis of public policy initiatives, but one could argue that they might be essential from a First Amendment perspective.

Indeed, the potential impact of using _Sorrell_ to attack FDA restrictions on off-label marketing has not escaped the attention of pharma. Therefore, 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. Policies Surrounding the Issue and Concluding Thoughts**

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.\textsuperscript{175} 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 current status of the law.\textsuperscript{176} Pharmaceutical companies have a high level of engagement with the entire process, as they developed and adopted the code that exists in the U.K.\textsuperscript{177} 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.\textsuperscript{178} Moreover, competitors, former employees, physicians, and patients can bring complaints against drug manufacturers for violating the rules and regulations against off-label promotion.\textsuperscript{179} As a result, the U.K. has in place a transparent system that resolves conflicts expeditiously.\textsuperscript{180}

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\textsuperscript{175} See Osborn, \textit{supra} note 21, at 340-52.
\textsuperscript{176} Id. at 340.
\textsuperscript{177} Id. at 341.
\textsuperscript{178} Id. at 347.
\textsuperscript{179} Id. at 345.
\textsuperscript{180} Id. at 342.
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Although such a system is likely not feasible in the U.S., given we have one central government body serving as gatekeeper, the FDA, and pharmaceutical companies have never worked in unison to eliminate this problem, there are still valuable takeaways that can be incorporated. 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 promoting drug manufacturer awareness of the problems resulting from off-label marketing, the amount of federal tax dollars spent on off-label drugs will likely be reduced and the incidence rate of health concerns stemming from improper off-label prescriptions will assuredly be reduced.