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Off-Label Promotion Reform: A Legislative Proposal Addressing Vulnerable Patient Drug Access and Limiting Inappropriate Pharmaceutical Marketing

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OFF-LABEL PROMOTION REFORM: A LEGISLATIVE PROPOSAL ADDRESSING VULNERABLE PATIENT DRUG ACCESS AND LIMITING INAPPROPRIATE PHARMACEUTICAL MARKETING

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Off-label promotion occurs when pharmaceutical manufacturers engage in promotion of unapproved or "off-label" uses of their drugs. These off-label uses may lack adequate clinical data to substantiate marketing claims, have led to corporate investigations and penalties, and can endanger public health. However, there is adequate evidence to suggest that off-label uses are entirely appropriate for some vulnerable patient populations, and that physicians have accepted such uses as standard. Historically, U.S. law has prohibited direct off-label promotion to physicians and patients. However, failed government guidance, industry-based litigation, and the diminished capacity of regulators to police illegal practices have had dire consequences for patient safety and the prevention of healthcare fraud and abuse. Worse still, because of these policies, vulnerable disease patients and their physicians are often unaware of appropriate off-label treatments, and the lack of information places these patients at risk. To address these concerns, we propose the creation of a targeted and regulated off-label promotion system that enables vulnerable patient populations to access life-saving treatments and simultaneously creates clear incentives to avoid inappropriate off-label promotion. This federal legislation would create FDA-targeted exemptions of off-label prohibitions for vulnerable patient populations, if certain requirements of enrollment, risk management, and pharmacovigilance are met. Any proposed off-label promotion would also be pre-reviewed by the FDA to ensure that the program was safe and properly monitored. To create incentives for appropriate off-label marketing and avoid the problem of repeat corporate offenders, additional penalties would be available without preempting other causes of action. This system of carrots and sticks would increase drug access for vulnerable patient populations while discouraging illegal marketing that could threaten patient safety and public health.

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INTRODUCTION

The practice of promoting "off-label" use by pharmaceutical manufacturers is defined as the promotion and marketing of pharmaceutical indications that have not been approved by the U.S. Food and Drug Administration (FDA). These "off-label promotions" are often not supported by adequate clinical data.[1] Though the FDA provides for a comprehensive review of new pharmaceuticals before they obtain marketing approval, once they are approved, physicians are free to prescribe them for any indication they see fit.[2] This clinical practice, commonly referred to as "off-label use" or "off-label prescribing," allows physicians to maintain autonomy in the practice of medicine, creating opportunities in which pharmaceuticals can be prescribed for alternative uses that may ultimately improve treatment.

Off-label use is common in medical practice. Studies report that it accounts for roughly one of every five (21 percent) drug uses, with a majority (73 percent) lacking evidence of clinical efficacy.[3] Indeed, the prevalence of off-label prescribing has been estimated to be as high as 83 percent for certain kinds of drugs.[4] In addition, pharmaceutical marketing, estimated at some $29.9 billion in expenditures in 2005, continues to drive these forms of product promotion to increase use and market share.[5]

Off-label use and promotion are complex issues involving both potential benefits and adverse consequences for clinical interventions. Inappropriate, or bad off-label promotion can create difficulties in patient care and outcomes. This includes inducing demand for inappropriate and dangerous drugs. However, appropriate, or good off-label promotion can potentially provide patient advantages through clinical practice innovation, increased access

1. *See* Bruce Psaty & Wayne Ray, *FDA Guidance on Off-Label Promotion and the State of the Literature From Sponsors*, 299 J. AM. MED. ASS'N 1949, 1949–50 (2008).

2. *See* Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 396 (2006) (noting the government's intention not to interfere with health care providers' prescription of legally marketed products for legitimate medical reasons).

3. *See* David Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1023 (2006).

4. *See id.* at 1021, 1023 (finding high off-label prescription rates for drugs including gabapentin (83%), amitriptyline hydrochlorine (81%), and desamethasone (79%)).

5. *See* Julie Donohue et al., *A Decade of Direct-to-Consumer Advertising of Prescription Drugs*, 357 NEW ENG. J. MED. 673, 675 (2007). Note that pharmaceutical marketing expenditure estimates vary based on data source and methodology and may suffer from underreporting. *See id.* at 680. This has made it difficult to obtain accurate assessments of pharmaceutical marketing expenditures given the lack of accurate and publicly accessible data. *See id.*

for vulnerable patient populations, and dissemination of valid treatment options for underserved patients if used properly.[6]

However, current policy does not provide the appropriate incentive and disincentive mechanisms. Though existing laws penalize inappropriate off-label marketing, repeat offenses by drug companies continue to occur. At the same time, vulnerable patients with rare diseases and the physicians who treat them continue to lack access to crucial information regarding treatment options. Existing laws preclude the dissemination of this information even though off-label use may be the only option for these patient populations.

To address these issues, this Article describes the current regulatory landscape of off-label promotion, its benefits and disadvantages, enforcement actions, and potential policy solutions. Part I examines the current regulatory structure of off-label promotion and marketing activities. Upon assessment, it is clear that the current regulatory framework has been diminished by a history of litigation limiting the scope and authority of potential surveillance and enforcement. In addition, regulation is insufficient to properly identify and regulate off-label promotion and does not provide adequate guidance to clinicians and the pharmaceutical industry.

Part II of this Article explores the current debate over off-label promotion in more detail. This examination reveals that off-label use and promotion may improve both clinical care and access to pharmaceuticals. However, it also reveals that off-label uses and promotion may have negative consequences for patient safety—potentially endangering vulnerable populations, escalating health-system costs, and heightening the risk of fraud and abuse.

Part III presents an empirical survey of efforts to stem inappropriate off-label marketing. We review case studies and find that enforcement of off-label promotion prohibitions produced record-breaking settlements. We also found that whistleblowers, rather than regulators, often initiated these actions. However, these efforts have failed to sufficiently identify, address, and proactively deter negative forms of off-label promotion that continue to endanger public health and patient safety.

In Part IV, we summarize the limitations of the current regulatory framework and propose significant policy reform. We recommend federal legislation to enable the FDA to approve off-label use of drugs for specific, vulnerable patient populations, if certain requirements of enrollment, risk-management, and

6. *See* Randall Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008).

pharmacovigilance are met.[7] An FDA advisory committee with expertise in vulnerable patient populations would provide review and recommendations for the FDA Commissioner. Further, we propose the creation of a general off-label system to pre-approve proposed off-label marketing, again using an advisory-committee structure. This simple process would also allow courts to determine whether drug companies are engaging appropriately in off-label marketing. The proposed statute also clarifies approved off-label promotion for manufacturers and provides a reduced-cost means of serving vulnerable patient populations. Furthermore, to discourage repeat inappropriate off-label marketing, penalties under the new system for unauthorized off-label marketing would be severe. In addition to fraud and abuse penalties, the offending drug company would be banned from participating in the off-label program, and repeat violations would be subject to mandatory exclusion from serving any public health program.

Part V reviews how the new policy could benefit patients, government agencies, and manufacturers themselves. Here, we conclude that our proposals offer significant benefits for all stakeholders, including increased access and information; clearer regulatory rules and powers; specified definitions for appropriate off-label use; and reduced costs of investigating other, smaller markets for manufacturers.

Finally, the Conclusion offers some closing remarks. We advocate for a comprehensive solution that promotes beneficial uses of drugs off-label and penalizes adverse off-label promotion. Such a solution would protect patient safety and ensure the availability of scientifically sound clinical interventions for those most vulnerable.

I. REGULATION OF OFF-LABEL PROMOTION

A. FDA Off-label Regulation

It is important to examine the current regulatory landscape that has evolved around off-label promotion and use it to understand the complex underpinnings of the debate on these issues. Though off-label promotion was originally prohibited, current regulation of

7. Pharmacovigilance is the practice of premarketing-and-postmarketing risk assessment, risk management, and risk minimization. *See* FOOD & DRUG ADMIN., U.S. DEP'T. OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT 2 (2005), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf.

off-label promotion is more unclear, leading to industry and regulator confusion and limited enforcement due to legal ambiguity.[8]

Prior to 1997, the FDA primarily relied on two interpretations of the Food, Drug, and Cosmetic Act (FDCA) to prohibit off-label marketing by manufacturers. The first of these allowed the FDA to prohibit a manufacturer from introducing a drug into interstate commerce with the intent of off-label use.[9] The second interpretation categorized a product promoted for off-label use as illegally "misbranded."[10] This interpretation allowed the FDA to strictly prohibit direct advertising or explicit promotion of off-label uses by manufacturers and enabled the agency to pursue substantial enforcement actions such as injunctions, seizures, and criminal penalties.[11]

Importantly, this prohibition of off-label marketing did *not* apply to the practice of medicine. Hence, physicians could prescribe any FDA-approved pharmaceutical off-label for whatever indication they deemed appropriate.[12] The lack of regulation of medical practice is historically well-grounded. Physicians occupy a class of professionals that has enjoyed autonomy and discretion in patient treatment and drug prescribing.[13] This "indirect" promotion created a regulatory gap, caused confusion, and created an environment in which physicians could legally act as marketing proxies for the pharmaceutical industry through creative promotional strategies. For example, scientific literature or Continuing Medical Education (CME) courses promoting off-label uses could encourage practicing physicians to engage in off-label use themselves.[14]

The FDA attempted to regulate these forms of indirect promotion by issuing guidance documents outlining what constituted permissible dissemination of scientific literature and manufacturer

8. *See* Steven Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 183, 189 (1999).

9. *See* Michelle Mello et al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 NEW ENGL. J. MED. 1557, 1558 (2009).

10. *See id.*

11. *See* Wash. Legal Found. v. Henney, 202 F.3d 331, 333 (D.C. Cir. 2000) ("While a manufacturer's direct advertising or explicit promotion of a product's off-label uses is likely to provoke an FDA misbranding or 'intended use' enforcement action, manufacturers have sought to employ more indirect methods of informing physicians about their products' off-label uses."). For a discussion of injunctions for FDCA violations of misbranding, see George Craft, *Promoting Off-Label in Pursuit of Profit: An Examination of a Fraudulent Business Model*, 8 HOUS. J. HEALTH L. & POL'Y 103, 108 (2007). *See also* Mello et al., *supra* note 9, at 1558.

12. *See* Wash. Legal Found. v. Friedman (*WLF I*), 13 F. Supp. 2d 51, 55 (D.D.C. 1998).

13. *See* Salbu, *supra* note 8, at 190.

14. *See WLF I*, 13 F. Supp. 2d at 57–59.

sponsorship of CME programs in 1996 and 1997, respectively.[15] Collectively these guidance documents placed significant restraints on manufacturers' ability to legally promote off-label uses to physicians, but they were short-lived. These efforts by the FDA were halted by litigation contending that regulation of off-label promotion was unconstitutional. This protracted legal action has brought with it confusion for both regulators and drug manufacturers in determining what is legally permissible in off-label promotion activities.

B. Washington Legal Foundation Litigation

Following the issuance of the FDA guidance policies, the Washington Legal Foundation (WLF) challenged the provisions in court. WLF is a non-profit, conservative legal organization that primarily promotes "pro-business" policies. It acts as a public interest law firm and think tank to shape public policy away from what it determines is intrusive regulation by state or federal government agencies.[16]

WLF brought two lawsuits against the FDA challenging its authority to regulate off-label promotion by pharmaceutical companies because such restrictions violated principles of commercial free speech. This litigation, which questioned the FDA's authority and its ability to fulfill its mandate to promote public health and safety, shaped the subsequent regulatory landscape for off-label promotion. Unfortunately, these legal challenges failed to provide the regulatory clarity needed to encourage beneficial forms of off-label promotion, which can better educate patients and improve their access to potentially life-saving treatment options.

In the first decision, (WLF I), a district court struck down the policies set forth in the 1996 and 1997 guidance documents and enjoined their enforcement, finding that they violated the protections of free speech afforded by the First Amendment.[17] The court ruled both that manufacturers' dissemination of and support of CME programs promoting off-label uses constituted commercial

15. For 1996 FDA guidance, see Guidance for Industry Funded Dissemination of Reference Texts, 61 Fed. Reg. 52,800, 52,801 (Oct. 1, 1996). For 1997 FDA guidance, see Guidance for Industry: Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,093, 64,094, 64,096–99 (Dec. 3, 1997).

16. *See* Jacob Rogers, Essay, *Freedom of Speech and the FDA's Regulation of Off-Label Drug Uses*, 76 GEO. WASH. L. REV. 1429, 1435 (2008) (describing the Washington Legal Foundation's philosophy).

17. *WLF I*, 13 F. Supp. 2d at 74.

speech and that the FDA guidance documents impermissibly restricted that speech.[18]

Shortly after WLF I, Congress passed the Food and Drug Modernization Act of 1997 (FDAMA). For the first time, a federal statute specifically permitted certain regulated forms of off-label marketing and promotion.[19] FDAMA effectively overrode and replaced the FDA guidance documents struck down by WLF I.[20]

Though FDAMA opened the door to certain forms of information dissemination to promote off-label uses to physicians, it also imposed restrictive requirements: manufacturers could only disseminate "authorized information;" proposed off-label use required FDA approval and the filing of a supplemental new drug application (sNDA); and off-label promotion required concurrent disclosure of certain information.[21] Furthermore, FDAMA also included provisions that enabled corrective actions by the FDA.[22] Many considered these restrictions highly prohibitive because they significantly limited the type of information that could be presented to physicians. For example, only peer-reviewed, academic journal articles required disclosures that such information was not "approved or cleared by the [FDA]," and required manufacturers to conduct research and apply for drug approval for new indications through a sNDA application.[23] Hence, although FDAMA was the first law to specifically authorize off-label promotion, it did so with the assumption that such off-label promotion would be followed by the necessary formal drug approval, and that physicians

18. *Id.* After determining that FDA guidance document regulated commercial free speech, the court in *WLF I* applied the four-part test set forth in *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n*, 447 U.S. 557, 566 (1980). This test is used to determine if policy restrictions on commercial free speech exceed constitutional limits. *Id.* Policy restrictions meeting all four criteria of the test are held to not violate the First Amendment. *Id.* In applying the *Central Hudson* test, the *WLF I* court found that the guidance document satisfied only three of the required four criteria. *WLF I*, 13 F. Supp. 2d at 65–74. The guidance satisfied parts one, two, and three of the test as it involved legal activity and was not misleading, it involved substantial governmental interest in incentivizing manufacturers to seek FDA approval for off-label uses, and it directly advanced this interest; but it failed the fourth part of the test requiring that such restrictions be narrowly tailored to achieve this objective. *See id.*

19. *See* Salbu, *supra* note 8, at 211.

20. *See Wash. Legal Found.*, 202 F. 3d at 334.

21. *See* 21 U.S.C. §§ 360aaa(b), 360aaa-1(a) (2006); Salbu, *supra* note 8, at 212–16. The FDAMA permitted manufacturers to engage in off-label promotion to certain healthcare groups and professionals provided they have filed an appropriate application for the promoted product. *See* Salbu, *supra* note 8, at 211–12. "Authorized information" that could be disseminated only included unabridged peer-reviewed articles or qualified reference publications that were indexed in the National Library of Medicine of the National Institutes of Health, significantly limiting the type of information for off-label promotion. *See id.* at 213–14.

22. *See id.* at 216.

23. *See id.* at 213–16 (citing 21 U.S.C. § 360aaa(b) (1997)).

and patients in the interim would be informed that off-label uses had not been adequately tested or reviewed by FDA.

After passage of FDAMA, the FDA and Department of Health and Human Services (DHHS) sought to limit the scope of the injunction imposed by the WLF I court on the 1996 and 1997 guidance documents.[24] However, this attempt by the FDA and DHHS to reassert its right to regulate off-label promotion was unsuccessful. In a later action brought by WLF in 1999 (WLF II), the court also struck down FDAMA's sNDA application requirement.[25] Upon appeal of WLF II by the FDA and DHHS, the appellate court dismissed and vacated the decision on the ground that both the 1996 and 1997 guidance documents, as well as the provisions contained in FDAMA concerning off-label promotion, were forms of safe harbors.[26] As safe harbors, they did not in fact prohibit speech or certain conduct, but merely ensured manufacturers that enforcement action would not be taken if they conformed to certain requirements.[27]

WLF II had far-reaching impact. Which forms of off-label promotion would result in enforcement action and which would not became increasingly unclear, and it conceptually shifted the FDA's permitted role from active regulation to a more passive and minimalistic role. Another factor muddying the regulatory waters was that FDAMA expired on September 30, 2006, and was not renewed; this formally ended its off-label promotion requirements.[28]

Overall, these constitutional challenges to the regulation of off-label promotion and similar forms of commercial speech have made it difficult for regulators and industry alike to determine which off-label promotion is permitted and which is prohibited. As long as this confusion persists, regulators lack the tools to effectively enforce rules against illegal promotion and manufacturers lack the guidance to determine if their actions will be subject to enforcement.

24. *See* Craft, *supra* note 11, at 111.

25. *See id.* (citing *Wash. Legal Found.*, F. Supp. 2d at 87).

26. *See Wash. Legal Found.*, 202 F.3d at 335–36; Mello et al., *supra* note 9, at 1559.

27. *See* Craft, *supra* note 11, at 111–12.

28. *Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm (last updated Aug. 6, 2009).

C. Safety and Access Concerns

1. FDA Drug Approval Regulation

Any patient benefit that might be derived from off-label use is tempered by the FDA's full or sNDA drug approval process. The process hinders more proactive and innovative forms of clinical practice even after evidence-based data emerges supporting a new treatment pathway because of the long, costly process of testing for safety and efficacy of new drugs prior to market approval.[29] There are also no systems that permit abbreviated marketing approval to reach vulnerable patient populations and their physicians.

Drug approval delay is exceedingly pertinent to vulnerable and rare-disease populations. A slow FDA approval process can be injurious to patients who lack information about and access to effective treatments and it is especially harmful to those who have *no* approved treatment options available. To add insult to injury, FDA review and approval of new drugs and devices are not guarantees of safety or efficacy, as reflected by a number of high-profile recalls of drugs such as that of Merck's blockbuster anti-inflammatory and pain management drug, Vioxx.[30]

Further, the current regulatory scheme allows manufacturers to game the system by seeking indications that are easier or more likely to be approved.[31] This strategy speeds up the market approval process and allows manufacturers to develop marketing campaigns to promote off-label uses at the same time.[32] This enables manufacturers to avoid the more rigorous testing and scrutiny for safety and efficacy applied to an approved indication, even though an off-label use may be marketed more extensively than the approved indication itself.[33] Such use of off-label promotion to explicitly

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29. *See id.*

30. *See COX-2 Selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)*, FOOD & DRUG ADMIN., http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm103420.htm (last updated Mar. 3, 2010).

31. This practice is known as applying for "decoy" indications, while in parallel developing extensive off-label marketing campaigns for other more common indications. *See* Adriane Fugh-Berman & Douglas Melnick, *Off-Label Promotion, On-Target Sales*, 5 PLOS MED. 1432, 1433 (2008). Manufacturers may also target rare diseases such as orphan indications and use them as decoy indications to expedite the review process. *See id.*

32. *See id.*

33. *See* Mark Ratner & Trisha Gura, *Off-Label or Off-Limits?*, 26 NATURE BIOTECHNOLOGY 867, 870–71, 873 (2008) (quoting Jerry Avorn of Harvard Medical School and Brigham and Women's Hospital regarding lack of incentives for evidence-based research when off-label promotion is an option).

avoid comprehensive safety and efficacy testing can have dire consequences for patient safety.

2. Recent FDA Off-Label Guidance

Off-label regulation is an important safety concern. Pharmaceutical manufacturers have an inherent conflict of interest when marketing their products because they are attempting to maximize profit.[34] This conflict encourages the illegal promotion of off-label uses in the medical literature that may misrepresent safety and efficacy data.[35] Such efforts aim to create larger pools of patient populations, especially for drugs that have narrow indications.[36]

Yet recent guidance documents finalized in January 2009 reemphasized the limited role the FDA plays in regulating off-label promotion by manufacturers. These guidelines significantly diminish the FDA's oversight of off-label promotion by no longer requiring sNDA applications for new indications and by removing the requirement that the FDA review journal articles used for such promotion prior to dissemination.[37] While the FDA still requires peer review for journal articles, practices such as selective publication; manipulation of data; omission of critical data necessary for evaluation of off-label use; and undermining of the NDA review process, as well as the overall risk posed by conflict of interest situations that may bias data in studies; have called into question the propriety of the FDA's hands-off approach.[38]

In addition, the guidance lacks meaningful penalties for manufacturer violations. This lack of oversight caused Rep. Henry Waxman (D-CA) to describe the new guidelines as a "long-coveted parting gift" to the pharmaceutical industry by the former Bush administration; Waxman and others have indicated that future legislative action may be necessary.[39] Most observers in the

34. *Cf.* Bryan Liang & Tim Mackey, *Confronting Conflict: Addressing Institutional Conflicts of Interest in Academic Medical Centers*, 36 AM. J.L. & MED. 136, 137, 143–44 (2010) (discussing the institutional conflicts of interest inherent among academic medical centers doing business with profit-driven pharmaceutical companies).

35. *See id.* at 142, 147 n.42, 154 n.82.

36. *See, e.g.*, Fugh-Berman & Melnick, *supra* note 31, at 1432 (discussing pharmaceutical corporations seeking a narrow indication for a rare disease like rabies, and promoting for a wider indication such as cancer).

37. *See id.* at 1433.

38. *See* Psaty & Ray, *supra* note 1, at 1949–50.

39. *See* Chris Adams, *Late Move on Drugs by Bush FDA Could Be Dangerous*, MCCLATCHY (Feb. 1, 2009), http://www.mcclatchydc.com/2009/02/01/61113/late-move-on-drugs-by-bush-fda.html. Note that Rep. Waxman was considering introducing additional legislation to address recent FDA guidance to better assess whether dissemination of journal articles by

pharmaceutical industry have viewed the release of these recent guidelines favorably because they provide more certainty that these off-label promotions will not be actively prosecuted.[40]

D. Policy Inadequacy

Given the ambiguity of recent guidance and the realities of limited scrutiny of off-label practices, many public interest groups feel the current policy is inadequate.[41] In addition, provider groups such as the Academy of Managed Care Pharmacy and the American Society of Health-System Pharmacists have commented that the new policy does not provide adequate guidance regarding distribution of biased reprints that may mislead physicians about off-label uses.[42]

These recent FDA trends, deregulation of off-label promotion and reliance on industry self-policing, are fraught with conflicts of interest that could endanger public health. As recently as 2008, the Government Accountability Office (GAO) released a report detailing its findings that the FDA lacked adequate systems and procedures for review and oversight of off-label promotional

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pharmaceutical corporations is appropriate. *See* Mike Mitka, *Critics Say FDA's Off-Label Guidance Allows Marketing Disguised as Science*, 299 J. AM. MED. ASS'N 1759, 1760 (2008).

40. *See* Anna Wilde Mathews & Avery Johnson, *Boost for Off-Label Drug Use: FDA Would Let Firms Keep Doctors Informed on Unapproved Methods*, WALL ST. J., Feb 16, 2008, at A3.

41. *See* Stephen Barlas, *New FDA Guidance on Off-Label Promotion Falls Short for Everyone*, 34 PHARMACY & THERAPEUTICS 122, 122 (2009). In 2008, the Patient and Consumer Coalition, an organization comprised of public interest groups such as the Center for Science in the Public Interest, Consumer Union, the Prescription Project, National Physician's Alliance, and others, issued comments strongly criticizing the proposed FDA guidance. *See* Comments of the Patient & Consumer Coal. to the U.S. Food & Drug Admin., Good Reprint Practices for the Distribution of Med. Journal Articles & Med. or Scientific Reference Publ'ns on Unapproved New Uses of Approved Drugs & Approved or Cleared Med. Devices, Draft Guidance, Docket No. FDA-2008-D-0053 (Apr. 18, 2008), *available at* http://www.cspinet.org/new/pdf/20080421_group_comments_on_fda_off-label_draft_guidelines.doc [hereinafter Comments]. These comments argued that the guidance was too lenient, lacked enforcement tools, undermined the FDA's authority to prohibit illegal off-label promotion, and lowered incentives for manufacturers to seek FDA approval of drugs. *Id.*

42. *See* Barlas, *supra* note 41, at 122–23 (noting how provider groups view existing guidance as lacking, and advocate for off-label use education in CME). Drug manufacturers and physician associations have also challenged the constitutionality of limited off-label promotion regulation by the FDA, arguing they violate the First Amendment. *See* Mary Anne Pazanowski, *Surgeons' Group Supports Motion to Enjoin FDA's Restrictions on Off-Label Promotions*, 4 MED. DEVICES L. & INDUSTRY REP. (BNA) 294, 294 (2010). In addition, hopes that the Obama administration would address off-label marketing failed to be realized in the recent healthcare reform bill. *See* Barlas, *supra* note 41, at 122; Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119 (2010).

materials and activities.[43] The FDA's most recent guidance, which raises doubt about future proactive regulation in this arena, has only exacerbated this lack of oversight.

More recently, regulators and prosecutors have considered increasing enforcement efforts by targeting industry executives directly. Such actions would hold them criminally responsible for the risk to public health that results from illegal marketing.[44] These prosecutions could occur even if company officials were unaware of the illegal activity.[45] In response, WLF issued a statement criticizing this brand of enforcement as unproductive.[46]

Past practices of off-label promotion, litigation brought by WLF, the sunset of the FDAMA provisions, and inconsistent FDA guidance have resulted in a policy landscape that is confusing and ineffectual. Litigation has dictated the course of off-label regulation, yet it has neither provided a clear path for manufacturers to engage in responsible off-label promotion nor given regulators or courts the tools to effectively detect and police illegal off-label promotion. Importantly, this ambiguity provides no benefit to patients that are denied access to important treatments or prescribed inappropriate drugs.

II. PROS AND CONS OF OFF-LABEL PROMOTION

Both the potential benefits and potential disadvantages of off-label promotion in clinical practice have been hotly debated. However, regulators and policy makers have not addressed how to appropriately utilize off-label promotion given these pros and cons, even though the consequences are very real for patients and the public health.

43. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-08-835, PRESCRIPTION DRUGS: FDA'S OVERSIGHT OF THE PROMOTION OF DRUGS FOR OFF-LABEL USES 5–6 (2008), *available at* http://www.gao.gov/new.items/d08835.pdf.

44. *See* Mandy Jackson, *Drug, Device Executives Targeted*, L.A. DAILY J., Oct 25, 2010, at 1.

45. *See id.*

46. *See* Brian Broderick, *Legal Group Pushes Back at FDA on Plans to Prosecute More Executives*, 4 MED. DEVICES L. & INDUSTRY REP. (BNA) 755, 755 (2010), *available at* www.wlf.org/Upload/misc/pressclips/102810BNA.pdf.

A. Potential Benefits

1. Clinical Use and Application

With more than one in five of all drug prescriptions for an off-label use,[47] it is clear that the promotion of off-label use is widespread and in some cases may represent a valid and necessary form of clinical practice. Off-label use is not only highly prevalent, but also a necessary component of medical practice that increases access for underserved populations to treatment options, increases the diffusion of scientific knowledge, hastens the development of innovative clinical treatment methods, and represents a viable form of cost-containment when compared to the costly regulatory process of FDA drug approval.[48]

Indeed, off-label prescribing allows for creativity and innovation in the practice of medicine by physicians who may alter treatment standards based on emerging evidence supporting new therapies.[49] Such action can be construed as proactive, with physicians on the "front lines" of clinical practice, dealing with patients directly and interacting on a personal level. The direct monitoring of and interaction with patients allow physicians to react to changing conditions and patient feedback in order to deliver better care through off-label uses.[50] The potential benefits of off-label use are reflected in evidence-based literature, including clinical-trial data. Some clinical practice guidelines also adopt off-label prescribing as part of their recommendations.[51] Such inclusion of off-label uses can have a profound impact on adoption, reimbursement, professional liability, and quality measurements in clinical care.[52]

For example, off-label use of drugs in the treatment of cancer has become widespread, with an estimated 50–75% prevalence.[53] This increased use is due to a number of factors, including: (a) the

47. *See* Radley, *supra* note 3, at 1021.

48. *See* Salbu, *supra* note 8, at 193–198.

49. *See* Stafford, *supra* note 6, at 1427.

50. *See* Salbu, *supra* note 8, at 196–97.

51. *See* Harold C. Sox, *Evaluating Off-Label Uses of Anticancer Drugs: Time for a Change*, 150 ANNALS INTERNAL MED. 353, 353–54 (2009). Clinical practice guidelines are professional consensus regarding the most appropriate drugs for specific clinical situations. *See id.* at 353. These can vary greatly based on the available evidence and the organization issuing the guidelines. *See id.*

52. *See id.* Note that inclusion of off-label uses in clinical practice guidelines and medical compendium, which lists drugs and their recommended uses, is the subject of debate given that it is built on available evidence and may vary based on the issuing organization. *See id.*

53. Tracy Hampton, *Experts Weigh in on Promotion, Prescription of Off-Label Drugs*, 297 J. AM. MED. ASS'N 683, 683 (2007).

large number of cancer types; (b) evidence-based support for off-label use in multiple cancer indications; (c) the impracticality of seeking approved drug indication status for all cancer types; and (d) lack of financial incentives to seek additional indications for manufacturers, especially after patent exclusivity has expired.[54] These benefits have established off-label use of cancer drugs as a mainstay in oncology practice, and it is now viewed as a highly effective, accepted, and innovative route of treatment.[55]

Accordingly, off-label use has been credited as beneficial in many other areas of clinical practice, and commentators have observed that off-label use may maximize the utility of a drug and enable access to the greatest number of potential patients.[56] Other beneficial examples include the off-label use of anti-retroviral combination therapy in the treatment of AIDS as well as the widespread use of prescription aspirin to reduce the risk of heart attack.[57]

2. Vulnerable Patient Populations: Information and Access

In addition to permitting advances in medical care treatment, off-label promotion is especially important for those who suffer from life-threatening diseases and do not have access to FDA-approved therapy. Large clinical trials used to assess the safety and efficacies of such drugs are extremely difficult in these relatively small populations, because they often lack sufficient study subjects. This inability to conduct trials necessitates some alternative method of access.[58] Appropriate off-label promotion to vulnerable patient populations and their physicians may provide such a method while disseminating information about promising treatments. This is particularly needed because physicians have been shown to possess limited knowledge of treatment alternatives for orphan disease and other underserved patients.[59]

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54. *See* P.G. Casali, *The Off-Label Use of Drugs in Oncology: A Position Paper by the European Society for Medical Oncology (ESMO)*, 18 ANNALS ONCOL. 1923, 1923 (2007).

55. *See* Salbu, *supra* note 8, at 193–94.

56. *See id.* at 194.

57. *See id.* at 194–95. Note that aspirin does not fall under the traditional definition of off-label use or promotion as it is an over-the-counter, rather than prescription, drug. However, though its primary packaging indicates that it should be used for pain relief and fever reduction, aspirin is also heavily promoted as reducing the risk of heart attacks and ischemic strokes. *See id.* The FDA only approved these additional indications in the 1980s and late 1990s. *See* Charles H. Hennekens et al., *Aspirin as a Therapeutic Agent in Cardiovascular Disease*, 96 CIRCULATION 2751 (1997).

58. *See* Casali, *supra* note 54, at 1923–24.

59. *See* Bryan A. Liang & Tim Mackey, *Reforming Off-Label Promotion to Enhance Orphan Disease Treatment*, 327 SCIENCE 273, 273–74 (2010).

a. Orphan Disease Patients

Appropriate forms of off-label use, prescribing, and promotion can improve access to beneficial clinical treatment for underserved populations. This includes patients diagnosed with "orphan" conditions that lack an approved treatment pathway.[60] In fact, approximately 90 percent of the thirty million patients suffering from such rare diseases are prescribed at least one drug for off-label use.[61] This statistic underscores the need for patient access to off-label clinical treatments.

Patient groups such as the National Organization for Rare Disorders (NORD), which advocates on behalf of underserved patient populations affected by rare diseases, have acknowledged the potential benefit of off-label use with appropriate medical justification in administration of their Medication Assistance Programs.[62] NORD has also emphasized the importance of establishing appropriate mechanisms for reimbursement of off-label uses by payers in future healthcare legislation.[63] This is a response to the growing insurance practice of denying coverage by classifying off-label drug use as experimental, further limiting access and clinical options for patients who may have few other alternatives.[64]

Recently, the FDA launched an orphan disease drug development database to encourage manufacturers to develop drugs for rare diseases by identifying products that have already received FDA approval and that have potential to treat rare diseases through added indications.[65] This development emphasizes the need for further research to promote orphan drug discovery and treatments, but fails to address the need to provide appropriate incentive mechanisms for manufacturers to incur the cost of

60. *See id.* An orphan condition is one that afflicts less than 200,000 patients in the US. *See generally* Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

61. *See Treating Rare and Neglected Pediatric Diseases: Promoting the Development of New Treatments and Cures: Hearing Before the S. Comm. on Health, Education, Labor, and Pensions*, 111th Cong. 4 (2010) [hereinafter *Hearing*] (statement of Diane Dorman, Vice President for Public Policy, National Organization for Rare Disorders (NORD)), *available at* http://www.help.senate.gov/imo/media/doc/Dorman1.pdf.

62. Medication Assistance Programs administered by NORD provide life-saving drugs to uninsured and underinsured patients who cannot otherwise gain access to treatment and are done in partnerships with pharmaceutical companies which determine eligibility criteria. *See* Marlene Krammer, *The National Organization for Rare Disorders and the Experience of the Rare Disorder Community*, THE NATIONAL ORGANIZATION OF RARE DISORDERS 11, 1–34 (2003).

63. *See Hearing*, supra note 61, at 4–5.

64. *See id.* at 4.

65. Amy Dockser Marcus, *FDA Database Aims to Spark Orphan-Disease Drug Development*, WALL ST. J. HEALTH BLOG (June 18, 2010, 7:30 AM), http://blogs.wsj.com/health/2010/06/18/fda-database-aims-to-spark-orphan-disease-drug-development/.

expanded approved labeling, which has been described as unprofitable and unattractive from a business perspective.[66]

The potential benefits of off-label promotion and subsequent use by vulnerable patient populations are significant and should be taken into account by regulators and lawmakers. As current policy stands, drug manufacturers have little incentive to seek costly FDA approval for an indication that has little chance of return on investment. For potentially fatal and debilitating diseases, off-label use may be one of the only ways to provide effective treatment to these patients in the absence of other clinical pathways.[67]

b. Pediatric and Pregnant Patients

Two additional sets of patients that depend on off-label use and promotion are the pediatric population and pregnant women. Off-label use is already widely accepted in pediatric care. An estimated 75 percent of marketed prescription drugs have no labeling indications for pediatric populations, making all use of these drugs in children off-label.[68] Like orphan disease patients, pediatric populations are a relatively small percentage of the total patient population, and clinical research involving children can be prohibitively expensive and ethically challenging.[69] Because pharmaceutical manufacturers have little incentive to engage in development of drugs or drug guidelines for these populations,[70] off-label may be the *de facto* norm in pediatric prescribing.[71]

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66. Ben Moscovitch, *FDA Hopes to Bring Rare Disease Uses On-Label With New Database*, HEALTHPOLICYNEWSSTAND, (June 24, 2010, 8:47 PM), http://healthpolicynewsstand.com/FDA-Week/FDA-Week-06/25/2010/fda-hopes-to-bring-rare-disease-uses-on-label-with-new-database/menu-id-315.html (describing pharmaceutical industry view that expanding drug label indications is not profitable for firms).

67. Examples include the use of drugs such as Zenapax for the treatment of multiple sclerosis, John Rose, *Monoclonal Antibody Treatment in MS*, U.S. DEPARTMENT VETERANS AFF., http://www.va.gov/MS/articles/Monoclonal_Antibody_Treatment_for_MS.asp (last updated Dec. 2009), and the majority of cancer treatments, which are provided off label. *Cf. Off-label Drug Use: What is Off-Label Drug Use?*, AM. CANCER SOC'Y, http://www.cancer.org/Treatment/TreatmentsandSideEffects/TreatmentTypes/Chemotherapy/off-label-drug-use (last revised Mar. 14, 2011).

68. *See* Fugh-Berman & Melnick, *supra* note 31, at 1432.

69. *Cf.* Geert Jong et al., Correspondence, *Unapproved and Off-Label Use of Drugs in a Children's Hospital*, 343 NEW ENGL. J. MED. 1125, 1125 (2000).

70. *See* Jeffrey L. Blumer, *Off-Label Uses of Drugs in Children*, 104 PEDIATRICS 598, 598–602 (1999) (noting the pharmaceutical industry's low incentive to develop drugs for children and infants).

71. Studies have shown that close to 80 percent of hospitalized children may be receiving drugs off-label. *See, e.g.*, Samir Shah et al., *Off-Label Drug Use in Hospitalized Children*, 161 ARCHIVES PEDIATRIC ADOLESCENT MED. 282, 282–83 (2007) (finding in a study of hospital-

Lack of approved indications for these populations has led to a paucity of drugs that are properly formulated or approved for use by children. The resulting widespread off-label prescribing includes treatment regimens modified by hospital pharmacies for dosage, frequency, dosage form, or route of administration.[72] Medical literature also reflects this lack of attention; important physician reference material, such as the Physicians' Desk Reference, do not include or address dosage, safety, or efficacy information for administration of drugs in children or infants.[73] With few formally approved options to treat pediatric populations, off-label use in this population has been seen as both necessary and appropriate.[74]

Pregnant women also rarely participate in clinical trials; therefore, they also need access to off-label information. Widespread exclusion of pregnant women from clinical trials presents significant challenges in administering approved treatments. This is especially true given that the various and complex physiological changes that occur during pregnancy make determining appropriate dosages difficult, hence necessitating off-label use by clinicians.[75] Examples include the off-label use of methotrexate, which is widely regarded as an effective treatment of ectopic pregnancy.[76] Since ectopic pregnancy occurs only in approximately 0.64 percent of pregnancies in the U.S., and since pregnant women have been historically underrepresented in clinical studies, treatment for this condition must be off-label.[77] This is an example of both the widely accepted

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ized patients eighteen years or younger that at least one drug was prescribed off label in 78.7 percent of cases).

72. *See* Jong et al., *supra* note 69, at 1125.

73. The Physicians' Desk Reference is a compilation of prescribing information for prescription drugs provided to physicians in order to aid them in writing prescriptions. *See 2011 Physicians' Desk Reference*, PDR BOOKSTORE.COM, https://www.pdrbookstore.com/ProdDetails.asp?ID=9781563637803&PG=1&Type=BL&PCS=PDR (last visited Sept. 3, 2011); Blumer, *supra* note 70, at 598.

74. *See* Blumer, *supra* note 70, at 602.

75. *See* Françoise Baylis, *Pregnant Women Deserve Better*, 465 NATURE 689, 689–90 (2010).

76. Methotrexate is approved by the FDA for treatment of choriocarcinoma. *Trexall*, RXLIST, http://www.rxlist.com/trexall-drug.htm (last reviewed Nov. 20, 2007). Studies have shown that off-label use of methotrexate for ectopic pregnancies has had an overall success rate over 90 percent. *See, e.g.*, Gary Lipscomb et al., *Analysis of Three Hundred Fifteen Ectopic Pregnancies Treated With Single-Dose Methotrexate*, 178 AM. J. OBSTETRICS & GYNECOLOGY. 1354, 1354–55 (1998).

77. *See* Karen Hoover et al., *Trends in the Diagnosis and Treatment of Ectopic Pregnancy in the United States*, 115 OBSTETRICS & GYNECOLOGY 495, 499 (2010) (discussing low rate of ectopic pregnancy in the United States). For a discussion on how pregnant women are routinely excluded for clinical trials and their need for off-label use of medication, see Fugh-Berman & Melnick, *supra* note 31, at 1432.

beneficial use of a drug off-label, as well its administration to a population in need.

B. Negative Effects

1. Safety and Regulatory Concerns

While the potential benefits of off-label use—such as preserving the autonomy of physicians to innovate in their clinical practice, better treatment options for underserved patients, and the possibility of faster delivery of clinically viable uses of drugs—are legitimate, potential negative consequences also require close examination.[78] There are significant concerns regarding safety and efficacy of unapproved and under-evaluated uses. They include discouragement of more viable evidenced-based practices and clinical testing, wasted financial resources, conflicts of interest, and opportunities for pharmaceutical manufacturers to bypass regulatory approval and the expense of more thorough clinical study.[79]

Perhaps the most important criticism of off-label promotion and use of drugs without full FDA approval is that such a policy creates disincentives for robust testing.[80] This can be especially problematic for off-label use of prescription drugs with a high-risk profile and whose widespread unsafe use can lead to public health emergencies.[81] Studies have also questioned the safety and effectiveness of off-label uses of medications in pediatrics, arguing that minimizing potential safety risks requires more effective testing and monitoring.[82]

As well, beyond limited scientific testing, these drugs do not have appropriate labeling for the off-label indication, may not have proper dosage information, and do not report important risk information, all of which can represent a risk to public health and patient safety.[83] Indeed, lack of a standardized label may contribute to confusion as to which uses are approved and which are not.

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78. *See* Stafford, *supra* note 6, at 1427–28.

79. *See id.*

80. *See* Salbu, *supra* note 8, at 201, 205–06.

81. *See id.* at 202–03 (regarding general lack of regulatory control for off-label applications, such as the wide-spread use of fenfluramine (fen-phen), resulting in unnecessary harm to patients).

82. *See* Julie M. Zito et al., *Off-Label Psychopharmacologic Prescribing for Children: History Supports Close Clinical Monitoring*, 2 CHILD & ADOLESCENT PSYCHIATRY & MENTAL HEALTH 24 (Sep. 15, 2008), http://www.capmh.com/content/2/1/24.

83. *See* Salbu, *supra* note 8, at 202.

Off-label promotion also is problematic from a regulatory incentive perspective. Although pharmaceutical companies can obtain FDA approval for new indications through a sNDA, this process requires rigorous safety and efficacy testing for the new indication. The costs of new clinical trials and potential for adverse data, which could reduce or eliminate future off-label use or negatively affect existing sales of products already prescribed off-label, discourages the use of this system. This regulatory system hinders business; hence, the balance of incentives favors off-label promotion.[84]

2. Bioethical Arguments

There are also bioethical arguments regarding off-label use and whether it constitutes experimentation on human subjects that requires a patient's informed consent. Since off-label use and promotion are not well-known or well-understood concepts, patients may suffer from lack of adequate disclosure of information regarding the benefits and risks of off-label uses. This informational asymmetry gives rise to concerns about informed consent and complicates the challenge of addressing this issue.

It is clear that most patients have little if any knowledge of the subtleties of off-label versus FDA-approved indications for drugs. For example, recent surveys suggest that patients believe drugs are always prescribed as approved by the FDA.[85] In fact, patients may have limited knowledge about the widespread practice of off-label prescribing, since there is no FDA requirement of informed consent for these activities. This contrasts with clinical trials and other clinical interventions, which both require full disclosure.[86]

The result is that physicians administer drugs to patients off-label without disclosing that the treatment deviates from FDA-approved indications and that, in fact, there may be limited evidence-based data supporting the off-label use.[87] This practice is encouraged by illegal off-label promotion activities by pharmaceutical companies and, in combination with undisclosed potential financial conflicts of

84. *See* Ratner & Gura, *supra* note 33, at 870.

85. *See* Margaret Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L.J. 967, 968 (2007).

86. *See id.* at 974.

87. *See* Michael Wilkes & Margaret Johns, *Informed Consent and Shared Decision-Making: A Requirement to Disclose to Patients Off-Label Prescriptions*, 5 PLOS MED. 1553, 1553–55 (2008). Informed consent involves the disclosure to a patient of the nature of the intervention, the potential negative and positive risks and benefits of intervention, alternatives to the intervention, and the risks and benefits of potential alternatives. *See id.* at 1554.

interest and/or inaccurate medical literature, may result in increased inappropriate prescribing with patients shouldering the risk.[88] Hence, physicians have an ethical obligation to disclose and patients have the fundamental right to know when a drug is being prescribed off-label, and both should be encouraged to make a shared decision on whether to accept such a treatment option.[89]

Consequently, bioethical arguments surrounding off-label use and prescribing as well as the shift to greater patient autonomy in the clinical setting have led to calls to mandate the disclosure of off-label use by physicians under the legal doctrine of informed consent.[90] Proponents of this position argue that off-label use and prescribing is inherently experimental, and the potential risks, benefits, and alternatives need to be disclosed so that patients can make informed decisions about their own care.[91] However, others have warned that such a disclosure mandate could stifle clinical innovation and would be unduly burdensome for physicians to implement given the difficulty in determining the risks and benefits of off-label use.[92]

3. Tainted Literature

The publication of clinical studies is crucial to both the approval and marketing of pharmaceuticals, including off-label use and promotion. Scientific articles and journals are used to validate the efficacy and safety of drugs, advertise a drug's benefits, and inform physicians in their clinical practices.

One of the primary concerns regarding off-label promotion is the validity and accuracy of off-label clinical publications that are distributed by industry representatives.[93] However, this distribution of published articles to promote off-label uses may mislead physicians. These concerns surround three basic areas: selective publishing, systematic manipulation of literature, and the absence of analysis regarding the safety and efficacy of off-label uses.[94]

88. *See id.*

89. Note that in medical practice informed consent is required prior to starting a treatment or performing a test. *See id.* at 1553.

90. *See id.* at 1554.

91. *See id.* at 1555.

92. *See id.*

93. *See* Liang & Mackey, *supra* note 34, at 153, 154 n.82.

94. *See* Psaty & Ray, *supra* note 1, at 1950.

a. Selective Publishing

Selective publishing raises issues regarding whether manufacturers are adequately representing the current state of knowledge and fully disclosing all study data regarding risks and benefits of their products.[95] Research has shown that manufacturers do not publish unfavorable clinical results regarding their products due to potential negative economic consequences and an absence of any affirmative obligation.[96] Selective publication is symptomatic of the conflict of interest that exists in sponsor-initiated clinical trials. Sponsors have little or no incentive to publish or distribute findings that may negatively affect sales. This gives rise to a systemic bias in published work and subsequent pharmaceutical sales pitches—known as "detailing"—based on these "studies."[97]

This situation also raises serious questions about the validity and reliability of information physicians receive and use in their clinical practice, further undermining the integrity of appropriate off-label drug use. Without any third-party oversight of distribution and review of medical literature that may promote off-label uses, it is impossible to ensure that the information provided is a complete and fair representation of the actual clinical data favoring or opposing off-label use.

b. Literature Manipulation: Ghostwriting

Sponsors of clinical studies have also systematically manipulated data by controlling the design, research, and analysis of such studies.[98] Even the authorship of a study can be altered for marketing purposes through a practice known as ghostwriting.[99] Scientific ghostwriting is the practice of pharmaceutical companies either authoring papers in house or hiring medical education and communication companies (MECC) to write clinical papers favorable to their products, while not providing full disclosure regarding authorship.[100]

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95. *See id.*
96. *See id.*
97. *See id.*
98. *See id.*
99. *See id.*
100. These pharmaceutical companies may not only write the papers, but may also hire experts and well-known academics to "author" the papers by co-writing or collaborating with a ghostwriter to review, revise or, in some cases, simply sign their name to a manuscript. *See* Barton Moffatt & Carl Elliot, *Ghost Marketing: Pharmaceutical Companies and Ghostwritten Journal Articles*, 50 PERSP. BIOLOGY & MED. 18, 19 (2007). These hired experts lend credibility

Ghostwriting exacerbates previous concerns regarding validity and reliability of potentially biased clinical research that appears in the medical literature. When articles list well-known experts as authors, physicians even further rely upon these "studies" in developing their clinical practice, even though they may actually be the product of marketing campaigns coordinated by pharmaceutical companies.

Unfortunately, ghostwritten papers often include the promotion of off-label uses. For example, support for the off-label use of the drug Gabapentin was generated by a marketing plan and payments made to MECCs to develop materials, rather than by evidence-based research.[101] Ghostwritten articles may unduly influence and mislead physicians about the benefits and risks involved with certain forms of off-label promotion that can endanger public health.[102] The prevalence of ghostwriting is alarming, and unlike the process by which new drugs are approved by the FDA, selective publishing and ghostwriting limit the ability of regulators and physicians to adequately identify and scrutinize clinical data.[103]

c. Lack of Safety Assessments

Off-label drug use is often untested for clinical efficacy and safety in the targeted population, and, as suggested above, may not be adequately supported by unbiased and reliable evidence-based medical literature.[104] The combination of untrustworthy scientific data and illegal off-label promotion by manufacturers can lead to adverse effects. Drugs may be prescribed in inappropriate dosage levels, used in patient populations whose physiological or psychological conditions may make such use unsafe, or even prescribed in direct contravention of FDA warnings.[105] For example, the appetite

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and neutrality to such papers. Stephanie Ngai et al., *Haunted Manuscripts: Ghost Authorship in the Medical Literature*, 12 ACCOUNTABILITY RES. 103, 104 (2005). However, this practice raises questions regarding the credibility of findings, negative consequences of potential conflicts of interests, and issues regarding accountability and responsibility over content. See Moffat & Elliot, *supra* note 100, at 23–24.

101. *See* Psaty & Ray, *supra* note 1, at 1950.

102. *See* Moffatt & Elliot, *supra* note 100, at 23–24.

103. *See* Paul Basken, *Medical 'Ghostwriting' Is Still a Common Practice, Study Shows*, CHRON. HIGHER EDUC. (Sept. 10, 2009), http://chronicle.com/article/Medical-Ghostwriting-Is-a/48347/. For a discussion of the difficulty of regulators and the public in identifying and scrutinizing the presence of ghost authors in published studies, see Psaty & Ray, *supra* note 1, at 1951.

104. *See* Fugh-Berman & Melnick, *supra* note 31, at 1432–33.

105. *See* Johns, *supra* note 85, at 968–69.

suppressant fenfuramine[106] had eighteen million prescriptions written off-label for weight loss prior to the discovery of adverse events due to long-term use, resulting in some 285,000 patients suffering heart damage.[107] Similarly, off-label use of Botox in the treatment of limb spasticity associated with cerebral palsy in children has been linked to serious medical problems including hospitalization and death.[108] Off-label use has also been associated with increased frequency and severity of adverse events in children, where off-label prescribing is dominant.[109]

Indeed, even the presence of express warnings do not preclude physician prescribing for off-label uses. For example, Eli Lilly's marketing of Zyprexa was subject to legal penalties for illegal off-label promotion that pushed the drug's use for dementia in the elderly, which represented clear patient safety risks.[110] In fact, there was a black box warning on Zyprexa's package insert that specifically indicated that studies had revealed a risk of increased mortality in elderly patients with dementia associated with the drug.[111] Yet physicians continued to prescribe the drug inappropriately based on off-label promotion.[112]

III. EMPIRICAL INFORMATION FROM ENFORCEMENT ACTIONS

Despite languishing regulatory oversight, federal and state prosecutors have targeted inappropriate off-label promotion. Indeed, prosecutions involving fraudulent or misleading off-label promotion have led to record-breaking settlements. The statutory bases for these prosecutions include the False Claims Act and the Anti–Kickback Statute, among others.[113] Importantly, this litigation also serves to provide information on how some industry actors

106. *See* Fugh-Berman & Melnick, *supra* note 31, at 1432 (describing fenfluramine (Pondimin), an appetite suppressant approved for short-term use which was promoted off-label as "fen-phen" for longer durations).

107. *See* Johns, *supra* note 85, at 977.

108. *See* Rita Rubin, *Off-Label Botox Use Linked to Serious Side Effects*, U.S.A. TODAY, Feb. 11, 2008, at 12D.

109. Fugh-Berman & Melnick, *supra* note 31, at 1432.

110. *See* Alex Berenson, *Drug Files Show Maker Promoted Unapproved Use*, N.Y. TIMES, Dec. 18, 2006, at A1.

111. *See Zyprexa Drug Description*, RXLIST, http://www.rxlist.com/zyprexa-drug.htm (last reviewed Jan. 18, 2011).

112. *See* Berenson, *supra* note 110; *see also* John Carey, *Do Cholesterol Drugs Do Any Good?*, BUSINESSWEEK, Jan. 28, 2008, at 52 (quoting Dr. Howard Brody and Dr. Bryan Liang on inappropriate but effective off-label marketing of drugs like Lipitor by Pfizer).

113. *See* False Claims Act, 31 U.S.C. §§ 3729–3733 (2006); Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b) (2006).

inappropriately promote off-label drug use.[114] Yet even with these prosecution, fraudulent and misleading off-label promotion continues to be a problem.

A. False Claims Act and Anti–Kickback Provisions

1. False Claims Act

Using the False Claims Act (FCA), corporate whistleblowers can file suit on behalf of the government for false claims submitted to federal or state funded programs resulting from illegal off-label promotional activities.[115] In these cases, manufacturers are deemed to have submitted false claims by promotion of off-label uses that are not authorized for reimbursement by the government through Medicare and Medicaid programs.[116] The FCA has been widely used to enforce pharmaceutical marketing regulations by the federal government through reimbursement in government healthcare programs.[117]

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114. *See* Stafford, *supra* note 6, at 1428 (noting how litigation arising out of off-label promotion of gabapentin and olanzapine (Zyprexa) raises important questions about this practice).

115. *See* 31 U.S.C. §§ 3729–3733. The False Claims Act ("FCA") is a federal law that allows for prosecutions of individuals and entities that fraudulently bill the U.S. government, including federal and state healthcare payers such as Medicare and Medicaid. *See id.* The Act specifically prohibits (a) submitting a false claim; (b) making or using a false record or statement for a false claim; and (c) conspiring to commit a violation of the FCA; among other provisions. *See id.* It also imposes triple damages on a party found guilty under the FCA. *See id.* "*Qui tam*" provisions under the False Claims Act allow private individuals acting as *qui tam* "relators" to bring a suit on the federal government's behalf involving past or present fraudulent acts. *See id.* § 3730(b). Relators can bring suit against defendants who have knowingly submitted or caused the submission of a false or fraudulent claim to the U.S. government. *See id.* Such suits have been used extensively in healthcare fraud and abuse claims. Relators are given an incentive to report fraud and abuse because they share in a certain percentage of the recoverable damages, ranging from 15–30 percent in addition to legal fees and other related costs. *Id.* § 3730(d). Hence, off-label promotion may be prosecuted as a false claim submitted to the government for improper off-label uses. For discussion of FCA provisions as they apply to off-label use and promotion, see Craft, *supra* note 11, at 112–14.

116. *See* Craft, *supra* note 11, at 112–13.

117. *See* Sally Wang, *False Claims Act: The Right Treatment for Off-Label Marketing?*, 38 J.L. MED. & ETHICS 708, 708–09 (2010); Robert Blume et al., *2010 Year-End False Claims Act Update: Part 1*, THOMSON REUTERS NEWS & INSIGHT (Mar. 24, 2011), http://newsandinsight.thomsonreuters.com/Legal/insight/2011/03_-_march/2010_year-end_false_claims_act_update___part_1/. Note that the federal government does not regulate the practice of medicine, which is governed by state law of medical licensure and malpractice tort law. *Physician Licensure: An Update of Trends*, AM. MED. ASS'N, http://www.ama-assn.org/ama/pub/about-ama/our-people/member-groups-sections/young-physicians-section/advocacy-resources/physician-licensure-an-update-trends.page (last visited September 3, 2011). It should also be noted that, in the case of *Hopper v. Solvay Pharmaceuticals, Inc.*, 588 F.3d 1318, 1330 (11th Cir.

Originally enacted during the Civil War in 1863 to prevent fraud perpetuated by private contractors, the FCA has been used to prosecute illegal off-label marketing primarily involving kickbacks.[118] In 2010, the Department of Justice negotiated a $422.5 million civil and criminal settlement with Novartis AG for illegally promoting its anti-epileptic drug, Trileptal, for off-label use to treat psychiatric conditions while also providing kickbacks to healthcare professionals to encourage them to prescribe their drugs.[119] This settlement represents a prime example of successful FCA prosecutions in this area.

2. Anti-Kickback Statute Violations

At the same time, if a marketing campaign includes any payments or remuneration, directly or indirectly, to drive referrals of federal healthcare dollars, there may also be a cognizable claim under the Anti-Kickback Statute.[120] These kickbacks can come in

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2009), the 11th Circuit ruled that a plaintiff must demonstrate intent to market off-label. The court held that the relators under a *qui tam* action must plead specific allegations of false claims with particularity to survive dismissal under the Federal Rules of Civil Procedure, Rule 9(b). *Id.* at 1330–31. Even if a relator provides a complaint with factual allegations that may indicate false claims were submitted to the government, a relator must show and plead specific and actual instances of false claims to avoid dismissal under 31 U.S.C. § 3729(a)(1). *Id.* at 1324. In this case the relator's complaint failed to provide specific instances of fraud and a motion to dismiss the claims by defendant was granted by the trial court and upheld by the 11th Circuit. *Id.* at 1325. This ruling potentially creates significant challenges for future whistleblower-initiated FCA prosecutions of off-label promotion. However, the implications of this ruling were somewhat curtailed by passage of the Fraud Enforcement and Recovery Act in 2009, which extended anti-retaliation protection to whistleblowers. *See* Fraud Enforcement and Recovery Act of 2009, Pub. L. No. 111-21, § 4(d), 123 Stat. 1617 (amending 31 U.S.C. § 3730(h)).

118. *See* Wang, *supra* note 117, at 708–12.

119. *See* Press Release, U.S. Dep't of Justice, Novartis Pharmaceuticals Corporation to Pay $422.5 Million for Off-Label Drug Marketing (Sept. 30, 2010), *available at* http://www.justice.gov/usao/pae/News/Pr/2010/Sept/novartis_release.pdf.

120. The Anti-Kickback Statute is a federal statute that prohibits the offering, payment, solicitation, or receipt of any remuneration in order to induce referrals to another person or entity for the purpose of furnishing or arranging to furnish any items or service that may be paid for in whole or in part by a federally funded healthcare program. *See* Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b) (2006). Criminal and civil penalties may apply to violations of the statute, including treble damages, imprisonment, and exclusion from federally funded healthcare programs. *Id.*; 42 C.F.R. § 1001.952 (2006). A court must find that the accused individual or entity knowingly and willfully intended to engage in the prohibited action to impose liability. *See* 42 U.S.C. § 1320a-7b(b). In addition, a number of safe harbors or exemptions to the Anti-Kickback Statute exist which allow certain transactions or arrangements within the healthcare setting. *See* 42 C.F.R. § 1001.952. Such exempted arrangements must precisely meet the terms of safe harbors and are assessed on a case-by-case basis. *See id.* Parties may request an advisory opinion from the Office of the Inspector General to help them determine if their proposed arrangement is in violation of the statute. The

the form of conduct that causes or influences physicians to prescribe off-label such as payment of consulting fees, reimbursements for travel and entertainment, and various other kinds of payments made to physicians.

Litigation involving illegal off-label promotion by manufacturers usually includes both of the above elements, and allows the government to assert both criminal and civil claims. The Novartis prosecution and the case studies detailed below reflect a sample of some of these enforcement actions and provide a great deal of information regarding the methods and motivations to promote off-label use.

B. Case Studies

1. Eli Lilly

The off-label promotion of Zyprexa, a powerful drug used to treat schizophrenia and bipolar disorder, is a compelling case study of both illegal pharmaceutical marketing and government enforcement initiated by FCA *qui tam* relators. The prosecution of Eli Lilly involved a violation of the FCA through the implementation of a misleading marketing campaign that promoted off-label uses.

The controversy surrounded a multiyear advertising campaign by Eli Lily to promote its new drug, Zyprexa.[121] The campaign, called "Viva Zyprexa," encouraged sales representatives to suggest that physicians prescribe the drug for patients, including elderly patients, suffering from symptoms of dementia—a clearly unapproved indication.[122] This marketing included instructions that "dementia should be the first message" targeted towards primary care physicians, and acknowledged that this promotion might lead to off-label prescribing.[123] The drug also had a black-box warning from the FDA stating that it increases the risk of death in older patients with dementia-related psychosis.[124] In addition, Eli Lilly apparently was aware that Zyprexa could cause significant weight gain and obesity, side effects that could increase the risk of hyper-

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Anti-Kickback Statute represents another tool for both federal and state prosecutors in seeking enforcement against fraudulent off-label promotion. *See* 42 U.S.C. § 1320a-7b(b). For further discussion on application of the Anti-Kickback Statute involving off-label promotion and use, see Craft, *supra* note 11, at 1132–114.

121. *See* Craft, *supra* note 11, at 123.

122. *See* Berenson, *supra* note 110.

123. *See id.*

124. *See Zyprexa Drug Description*, *supra* note 111.

glycemia and diabetes.[125] Despite its knowledge of these adverse risks, Eli Lilly continued to market the drug as "an everyday agent in primary care."[126]

During this period of off-label promotion, Zyprexa was Eli Lilly's bestselling drug, prescribed to approximately twenty million patients worldwide, with some $4.2 billion dollars in sales in 2005 alone.[127] The success of the marketing campaign is quantified by data showing that overall sales of the drug *doubled* from $1.5 billion to $3 billion between 1999 and 2002, the period during which the marketing campaign was active.[128]

Eli Lilly's off-label promotion of Zyprexa eventually led to state and federal investigations in 2005.[129] At the conclusion of these investigations, the Department of Justice (DOJ) levied a $1.415 billion fine, including a $515 million dollar criminal fine, which at that time was the largest fine ever imposed in a healthcare case and largest criminal fine ever imposed on an individual corporation.[130] This enforcement action involved a civil settlement in which the company admitted that it caused false claims for payment to be submitted to federal and state insurance programs for off-label uses that were not approved for coverage, a violation of the FCA.[131] In addition to the fine, Eli Lilly entered a plea agreement admitting guilt to a criminal charge of misbranding, entered into civil settlement stating that it submitted false claims to federal insurance programs, and entered into a Corporate Integrity Agreement (CIA) for a period of five years.[132]

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125. *See* Alex Berenson, *Eli Lilly Said to Play Down Risks of Top Pill*, N.Y. TIMES, Dec. 17, 2006, at A1.

126. Zosia Kmietowicz, *Eli Lily Pays Record Fines of $1.4bn for Promoting Off-Label Use of Olanzapine for Common Disorders*, 338 BMJ 191, 191 (2009), *available at* http://www.bmj.com/content/338/bmj.b217.full.

127. Berenson, *supra* note 110.

128. *See id.*

129. *See id.*

130. *See* Press Release, Dep't of Justice, Eli Lilly and Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-Label Promotion of Zyprexa (Jan. 15, 2009), *available at* http://www.usdoj.gov/opa/pr/2009/January/09-civ-038.html [hereinafter Eli Lilly Press Release] ("The civil settlement resolves four *qui tam* actions filed in the Eastern District of Pennsylvania: *United States ex rel. Rudolph, v. Eli Lilly and Company*, Civil Action No. 03-943 (E.D. Pa.); *United States ex rel. Faltaous v. Eli Lilly and Company*, Civil Action No. 06-2909 (E.D. Pa.); *United States ex rel. Woodward v. Dr. George B. Jerusalem*, Civil Action No. 06-5526 (E.D. Pa.); and *United States ex rel. Vicente v. Eli Lilly and Company*, Civil Action No. 07-1791 (E.D. Pa.). All of those cases were filed by former Eli Lilly sales representatives.").

131. *See id.*

132. *See id.* Corporate Integrity Agreements (CIAs) are negotiated agreements imposing compliance obligations on certain healthcare providers as part of settlements of federal civil false claim violations and investigations. *See Corporate Integrity Agreements*, OFFICE OF INSPECTOR GEN., http://oig.hhs.gov/fraud/cias.asp (last visited Jan. 18, 2011). These agreements are negotiated between the U.S. Department of Health & Human Services

These investigations unearthed several aspects Eli Lilly's off-label promotion effort. Eli Lilly was accused of promoting Zyprexa off-label for a number of unapproved uses.[133] In addition, Eli Lilly actively engaged in wrongful off-label promotion by developing marketing materials promoting off-label uses, training its sales force to disregard the law and promote to both the long-term care market and primary care physicians, and promoting through funding of CME and grants.[134]

2. Pfizer

In September 2009, the record settlement against Eli Lilly was eclipsed by a $2.3 billion fine against the pharmaceutical giant Pfizer, Inc. for its illegal off-label promotion of multiple products.[135] Included in this result was the largest ever healthcare fraud settlement, a guilty plea to a felony violation of the FDCA, and a $1.195 billion criminal fine—the largest ever for any matter.[136] The settlement included $1 billion to settle false claim allegations to government payer programs and civil settlements involving kickbacks paid to healthcare providers to promote and prescribe drugs.[137]

Again, this settlement was brought about by whistleblowers acting as *qui tam* relators under the FCA. These whistleblowers produced evidence of illegal off-label promotion and shared in a payment of $102 million.[138] Pfizer was also required to enter into a

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Office of Inspector General (OIG) and the healthcare provider to avoid exclusion from participation in federal healthcare programs. *Id.* CIAs are generally five years in length and include requirements such as appointing a compliance officer/committee; development of compliance standards and policies; implementation of compliance training programs for employees; independent review of claims submitted for federal healthcare programs; restriction of employment of ineligible persons; active reporting of certain events/overpayments; establishment of confidential disclosure programs; and providing annual updates and compliance implementation reports to OIG. *See id.*

133. For example, these included the treatment of dementia, including Alzheimer's dementia prevalent in the elderly; agitation; aggression; hostility; depression; and generalized sleep disorder. Eli Lilly Press Release, *supra* note 130.

134. *See id.*

135. *See* Press Release, U.S. Dep't of Health & Human Servs., Justice Dep't Announces Largest Health Care Fraud Settlement in its History (Sept. 2, 2009), *available at* http://www.hhs.gov/news/press/2009pres/09/20090902a.html.

136. *See id.*

137. *See id.*

138. *See id.*

CIA requiring annual compliance to certain certifications and requiring greater transparency of marketing.[139]

The landmark settlement detailed Pfizer's systematic off-label promotion of the sale of Bextra, a painkiller that was withdrawn from the market in 2005 because of safety concerns.[140] The investigation unearthed a corporate culture that permeated Pfizer's leadership and sales force, and that actively encouraged illegal off-label promotion to generate sales,[141] in direct contravention of the law and with apparent disregard for patient safety. Sales representatives were told to distribute samples to physicians for unapproved uses at different dosages and carried out marketing plans to influence physicians to prescribe. Employees who questioned off-label marketing were fired.[142] However, put into context, the record-breaking fine has been estimated to amount to less than three weeks of sales at Pfizer.[143]

This was not Pfizer's first illegal off-label promotion case. In 2004, Pfizer subsidiary Warner-Lambert pleaded guilty to the criminal charge of misbranding and agreed to pay more than $430 million to resolve both criminal charges and civil liabilities associated with its anti-seizure drug Neurotin (gabapentin).[144] This FCA *qui tam* litigation revealed that Warner-Lambert widely promoted Neurotin off-label for the treatment of epilepsy, various pain syndromes, psychiatric conditions, migraines, and other unapproved uses through a comprehensive campaign.[145] This campaign included marketing and financial support of certain physicians, the participation in and support of educational programs, and the selective publication and manipulation of medical literature.[146] Pfizer was also required to enter into a CIA to address these compliance

139. *See id.* Note that this also includes posting payments made to physicians on its website, a condition now required by law under the Patient Protection and Affordable Care Act. *See* Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 6002, 124 Stat. 119 (2010).

140. *See* Gardiner Harris, *Pfizer Pays $2.3 Billion to Settle Marketing Case*, N.Y. TIMES, Sept. 3, 2009, at B4. Drugs also subject to the enforcement action included Geodon (an antipsychotic), Zyvox (an antibiotic), and Lyrica (used for treatment of neuropathic pain). *Id.*

141. *See id.*

142. *See, e.g.*, Rita Rubin, *Pfizer Fined $2.3 Billion for Illegal Marketing in Off-Label Drug Case*, USA TODAY (Sept. 3, 2009), http://www.usatoday.com/money/industries/health/2009-09-02-pfizer-fine_N.htm (detailing the story of one Pfizer employee who was fired after questioning the company's marketing strategy and suing).

143. *See* Harris, *supra* note 140.

144. *See* Press Release, 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://www.justice.gov/opa/pr/2004/May/04_civ_322.htm.

145. *See id.*

146. *See* Michael Steinman et al., *Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents*, 145 ANNALS INTERNAL MED. 284, 285–90 (2006).

issues,[147] which was subsequently still in place during its settlement in 2009.[148]

More recently, new allegations against Pfizer have emerged. In October 2010, a federal court approved a DOJ motion to intervene in a FCA *qui tam* lawsuit involving Wyeth Pharmaceuticals, a subsidiary of Pfizer, which alleges illegal off-label promotion of the kidney transplant drug Rapamune.[149] The suit alleges that Wyeth promoted Rapamune for off-label uses, including liver and lung transplants and for immunosuppressant therapy, using systematic marketing campaigns promoting unapproved dosages, uses, and combinations in violation of the FCA.[150] The promotion allegedly included aggressive marketing of unapproved uses and payment of kickbacks and grants to physicians to encourage off-label prescribing.[151] These actions occurred despite "black box" warnings from the FDA cautioning against using the drug for other transplants and therapies, including those specifically targeted by Pfizer's marketing.[152]

In addition to the allegations of off-label promotion for unapproved uses, DOJ prosecutors and the House Oversight and Reform Committee have begun an investigation into whether Wyeth's promotion also specifically targeted certain vulnerable patient populations, including high-risk African American patients and patients seeking a second transplant.[153] This includes the off-label promotion of transplant drug Rapamune, that had an increase in sales from $169.8 million to $364.8 million from 2003–2007.[154] Timing of the litigation is also crucial in relation to when Wyeth was acquired by Pfizer, as it potentially jeopardizes Pfizer's status under its current CIA from the 2009 settlement.

3. Other Enforcement Actions

The practice of illegal off-label promotion and marketing is not limited to a few pharmaceutical manufacturers. Other high-profile

147. *See* Harris, *supra* note 140.

148. *See* Office of Inspector General, Corporate Integrity Agreement (Aug. 31, 2009), *available at* http://www.oig.hhs.gov/fraud/cia/agreements/pfizer_inc.pdf.

149. *Seee Court Approves DOJ Motion to Intervene In Suit Over Pfizer's Marketing of Rapamune*, 14 HEALTH CARE FRAUD REP. (BNA) 837 (Oct. 20, 2010) (discussing United States *ex rel.* Sandler v. Wyeth, Civil Action No. 05-6609 (E.D. Pa.)).

150. *See id.*

151. *See* Marcia Semmes, *New Case Filing Alleges Wyeth Caused Submission of False Claims for Rapamune*, 14 HEALTH CARE FRAUD REP. (BNA) 450 (June 1, 2010).

152. *See supra* note 149.

153. *See id.*

154. *See* Semmes, *supra* note 151.

cases of FCA *qui tam* litigation and enforcement actions have further confirmed that such illegal promotional activities occur throughout the industry. In 2005, the Swiss corporation Serono agreed to pay $704 million in criminal and civil penalties associated with its illegal off-label promotion of the AIDS-wasting drug Serostim, then the third-largest healthcare-fraud recovery in U.S. history.[155] In 2007, Purdue Pharma, as well as three of its current and former executives, also pleaded guilty to criminal charges of misbranding its prescription painkiller OxyContin, and together agreed to pay $634.5 million in penalties.[156] More recently, in April 2010, AstraZeneca agreed to a civil settlement of $520 million regarding allegations of off-label promotion of its anti-psychotic drug Seroquel, which involved false claims and illegal kickbacks to physicians who treat vulnerable populations such as pediatric, adolescent, elderly, and prison patients.[157] There have been several other recent settlements against drug manufacturers as well.[158] Together, these settlements highlight both the effectiveness of whistleblower incentives to report off-label promotion, but also

155. *See* Press Release, Dep't of Justice, Serono to Pay $704 Million for the Illegal Marketing of AIDS Drug (Oct. 17, 2005), *available at* http://www.justice.gov/opa/pr/2005/October/05_civ_545.html.

156. *See* Barry Meier, *Narcotic Maker Guilty of Deceit Over Marketing*, N.Y. TIMES, May 11, 2007, at A1.

157. *See* Press Release, Dep't of Justice, Pharm. Giant AstraZeneca to Pay $520 Million for Off-Label Drug Mktg. (Apr. 27, 2010), *available at* http://www.justice.gov/opa/pr/2010/April/10-civ-487.html. Note that this settlement also included a corporate integrity agreement requiring certain certifications and disclosing payments made to physicians on its website.

158. *See, e.g.*, Press Release, Dep't of Justice, Allergan Agrees to Plead Guilty and Pay $600 Million to Resolve Allegations of Off-Label Promotion of Botox, (Sept. 1, 2010), *available at* http://www.justice.gov/opa/pr/2010/September/10-civ-988.html (discussing the September 2010 agreement of Allergen Inc. to pay criminal and civil penalties for off-label Botox promotion); Press Release, Dep't of Justice, Novartis Pharm. Corp. to Pay $422.5 Million for Off-Label Drug Mktg., (Sept. 30, 2010), *available at* http://www.justice.gov/usao/pae/News/Pr/2010/Sept/novartis_release.pdf (detailing the October 2010 agreement of Novartis Pharmaceutical Corp. to pay $422.5 million in criminal and civil fines related to the promotion of its epilepsy drug Trileptal and five other drugs; this action was also initiated by whistleblowers); Mary Anne Pazanowski, *Stryker Settles Mass. Off-Label Allegations; Criminal Charges Still Alive in Federal Court*, 4 MED. DEVICES L. & INDUS. REP. (BNA) 652 (Sept. 22, 2010) (discussing how in September 2010, Stryker Biotech LLC settled with the state of Massachusetts for $1.35 million allegations of off-label promotion and misleading healthcare providers about its products; a federal case under the same facts is still pending). *Qui tam* law suits against medical device manufacturers such as Medtronic, Inc. and Abbott Laboratories, as well as DOJ investigations targeting Johnson & Johnson and Boston Scientific Corp. for illegal off-label promotion of their products, indicate more robust enforcement of the medical device industry. *See* Mary Anne Pazanowski, *Lawsuit Accuses Medtronic of Violating FCA By Off-Label Promotions of Biliary Stents*, 4 MED. DEVICES L. & INDUS. REP. (BNA) 178 (Mar. 10, 2010).

emphasize the pervasiveness of the problem and the failure of current regulations to identify and prevent these activities.

More recently, private insurers have also initiated enforcement actions against pharmaceutical manufacturers involved in illegal off-label promotion by engaging in civil litigation designed to recover money lost from use of drugs that were unapproved and fraudulently marketed.[159] In November 2010, Kaiser Permanente successfully sued Pfizer in California for illegal off-label promotion associated with the Neurontin settlement in 2004.[160] Kaiser's victory against the pharmaceutical industry opens the door to future civil litigation by insurers and other parties for illegal off-label promotion and capitalizes on enforcement actions taken by state and federal actors.[161]

At the end of 2010, the DOJ announced that it recovered $2.5 billion in fiscal year 2010 for healthcare fraud civil claims, which included prosecutions for illegal off-label promotion.[162] These enforcement actions illustrate recent enforcement efforts taken by regulators to combat healthcare fraud and abuse as well as the scope and pervasiveness of the problem. These efforts also include the creation of a new interagency task force to increase enforcement called the Health Care Fraud Prevention and Enforcement Action Team (HEAT); a two-year record recovery of $4.6 billion under the False Claims Act; $3 billion in recoveries under the Food, Drug, and Cosmetic Act; and twenty-five criminal convictions against healthcare providers and industry.[163]

However, such recent enforcement results are not sufficient. In essence, they represent continued reliance upon industry self-policing and financial incentives to avoid illegal off-label promotions through fraud and abuse settlements initiated by *qui tam* realtors.[164] Such a system fails to proactively address illegal off-label promotion before the fact, which continues to place public health and the economic viability of the healthcare system at risk.

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159. *See* Evan George, *Kaiser Says Pfizer Defrauded HMO*, L.A. DAILY J., Feb. 22, 2010.

160. *See* Emma Gallegos, *Health Plans Lead Attack on Drug Makers*, L.A. DAILY J., Nov. 9, 2010.

161. *See id.*

162. *See* Press Release, Dep't of Justice, Dep't of Justice Recovers $3 Billion in False Claims in Fiscal Year 2010 (Nov. 22, 2010), *available at* http://www.justice.gov/opa/pr/2010/November/10-civ-1335.html (discussing settlements against Pfizer, Inc., AstraZeneca, and Novartis Pharmaceutical group).

163. *See id.*

164. Whistleblowers may find it more difficult to bring suit against manufacturers after recent court rulings as well, further undermining any effective regulation in this area. *See* Wang, *supra* note 117, at 708 (discussing the decision in *Hopper v. Solvay Pharmaceuticals, Inc.*, 588 F.3d 1318 (11th Cir. 2009), requiring demonstration of intent to market off-label in FCA *qui tam* lawsuits).

V. POLICY PROPOSALS

A. Reform Considerations

1. Patients

There is a need for appropriate off-label use and promotion, particularly for vulnerable and orphan-disease patients and their physicians who have limited access and knowledge of potentially beneficial treatments. These populations rely heavily upon off-label uses because of the lack of treatment pathways, the lack of awareness from physicians and patients about optimal clinical options and appropriate dosing information, and inadequate financial incentives for drug manufacturers to seek additional indications for these small and underrepresented patient populations. The current system discriminates against these stakeholders, who are swept up in off-label marketing prohibitions, and creates barriers to effective medical management for these patients while also risking patient safety by failing to create systemic monitoring of off-label use.

2. Industry

The limitations of the current regulatory framework fail to address off-label promotion activities by drug companies. The preceding enforcement case studies suggest that a more proactive regulatory framework is essential to effectively police inappropriate marketing. Given that pharmaceutical manufacturers continue to engage in illegal off-label promotion with attendant risks to patient safety, a new system of incentives is required to ensure approved drugs are not promoted by manufacturers for dangerous and unapproved indications that are unsupported by clinical or evidence-based data. This is especially important for at-risk and minority populations, which have been subject to unscrupulous, illegal off-label marketing in the past.[165]

Simultaneously, the state of off-label regulation requires clarification. With current vague and limited guidance on off-label promotion, drug companies that desire to responsibly market off label to vulnerable disease populations are not given systemic FDA or other guidance. Others take risks and accept multiple prosecutions as a small cost of doing business. Hence, the current system

165. *See* Semmes, *supra* note 151.

fails to align incentives to promote beneficial off-label marketing while discouraging dangerous off-label marketing.

3. Government

Efforts to regulate off-label promotion through FDA rulemaking and guidance have fallen short of what is required to identify and enforce violations. On the one hand, the FDA lacks both the authority and resources to actively police off-label promotion by pharmaceutical companies, even though it is widely practiced. On the other hand, the FDA and the pharmaceutical industry are faced with ambiguous regulation of off-label promotion due to the *WLF I* and *WLF II* litigation. This ambiguity impedes harmonization in marketing practice and fails to deter illegal activity.

Though *qui tam* lawsuits have provided some disincentives regarding illegal off-label marketing practices, they do not adequately protect patient safety because they are reactive, not proactive. Further, *qui tam* whistleblowers may be given perverse incentives to tolerate illegal acts that will result in potentially larger payments under the FCA. Such settlements inadequately deter future efforts at off-label promotion when the high cost of the FDA drug approval process outweighs the cost associated with the risk of enforcement.[166] A system that relies upon reactive self-reporting by industry employees fails to address the ongoing dangers of illegal off-label promotion for public safety and health.

B. Policy Goals

Based on the current policy limitations, the creation of a proactive system that both identifies and provides incentives for appropriate off-label promotion will require substantial reform. This can be accomplished by amending the FDCA to establish a responsible regulatory framework governing off-label promotion. Given historical failures of FDA guidance on the subject, past amendments to the FDCA which address vulnerable populations (such as the Orphan Drug Act, or the ODA) and the broad scope and authority of the act, policy promotion of federal legislation amending the FDCA is the most appropriate course of action to enhance patient and public health safety. Legislative action can meet the essential needs of vulnerable patient populations and

166. *See* Craft, *supra* note 11, at 120–21.

their physicians to obtain information on appropriate off-label treatment under a safety monitoring system. At the same time, a system establishing a responsible regulatory framework to review and assess off-label promotion for all patient populations would provide regulatory clarity for industry actors, government agencies, and courts attempting to determine the scope of appropriate off-label marketing. However, in addition to these carrots, any reform must also include significant sticks to discourage inappropriate off-label marketing, particularly for repeat offenders.

C. Proposed Statute

Below, we propose a federal statute to address these concerns. Statutory reform is desirable because of the relative efficiency of legislation to achieve social change.[167] The following sections provide the text of the proposed bill and an analysis of each provision.

1. General Provisions and Definitions

A BILL

H.R.—

To amend the Food, Drug, and Cosmetic Act to increase vulnerable and orphan disease patient and physician access to appropriate drug treatment information, to establish a responsible regulatory framework to review and assess off-label promotion, to disincentivize inappropriate off-label drug marketing, and for other purposes.

A BILL

Be it enacted by the Senate and the House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This act may be cited as the "Underserved Patient Drug Access and Pharmaceutical Marketing Responsibility Act."

167. *See* Richard A. Epstein, *The Social Consequences of Common Law Rules*, 95 HARV. L. REV. 1717, 1737–38 (1982) (noting that legislation is a more efficient and effective method to achieve social change than common law).

SECTION 2. TO ENSURE ACCESS TO APPROPRIATE DRUG INFORMATION BY UNDERSERVED PATIENTS AND THEIR PHYSICIANS.

(a) Chapter V of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §§ 351–360ccc2.) is amended by inserting after section 528 the following:

"SEC. 529. FDA APPROVED MARKETING PROGRAM TO PROVIDE APPROPRIATE DRUG INFORMATION FOR ORPHAN DISEASE AND OTHER VULNERABLE PATIENTS."

"(a) Findings.—Congress makes the following findings:

(1) Medicines provide significant benefits to the citizens of this country.

(2) However, patients with rare diseases and other vulnerable patients who have not been included in clinical trials often have no FDA-approved drugs to treat them and their condition.

(3) FDA-approved drugs for other disease treatments have been found to appropriately treat these rare disease and vulnerable patients, but cannot be advertised to patients because of the prohibition against manufacturer marketing of unapproved drug uses, known as off-label marketing.

(4) Consequently, these patients and their physicians are uninformed regarding these effective treatments.

(5) Further, advancement of medical knowledge regarding these drugs and these patients is limited because of the low return on investment for manufacturers to obtain FDA approval for these conditions.

(6) However, off-label marketing by drug manufacturers has resulted in safety concerns and prosecutions, but continues despite civil and criminal fines and penalties."

"(b) Definitions.—In this section:

(1) Commissioner.—The term 'Commissioner' means the Food and Drug Administration Commissioner.

(2) Secretary.—The term 'Secretary' means the Secretary of Health and Human Services.

(3) Vulnerable Patient Populations.—The term 'vulnerable patient populations' means patients with limited FDA-approved drug treatment for their specific population or disease, including patients such as pediatric populations, pregnant women, orphan and rare disease patients."

The bill's preamble and Sections 1 and 2 provide the basis and rationale of the Act, and notes that it will amend the FDCA. Section 2 of the proposed bill introduces new FDCA Section 529. Subsection (a) discusses the key aspects of the problem of vulnerable patient access to appropriate, but off-label, pharmaceutical treatment and limited knowledge dissemination to these patients and their physicians due to the ban on off-label marketing. It also notes that there have been abuses by drug companies through off-label marketing. Definitions for the forthcoming substantive sections are given in subsection (b) to provide clarity in understanding the scope of the new provisions.

2. Approved Off-label Marketing Program for Vulnerable Populations

Providing information for physicians and patients on unapproved efficacious drug treatments and emerging off-label clinical interventions for vulnerable patient populations is a need that can be addressed by controlled and monitored use of off-label promotion. To accomplish this goal, a system designed to offer flexibility in approving direct off-label promotion by manufacturers for vulnerable patient populations should be employed.

The FDA's permitting of off-label promotion for certain vulnerable patient populations would be the first step towards such a system.[168] Under the new system, manufacturers would apply for FDA authorization to promote such off-label indications directly to physicians through an application form similar to the request for orphan designation under the Orphan Drug Act.[169]

168. *See* Liang & Mackey, *supra* note 59, at 273.

169. *See* Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.). The Orphan Drug Act provides manufacturers the opportunity to submit drug applications for orphan drug indications. If approved, manufacturers may be eligible for certain incentives including: (a) 7-year market exclusivity; (b) tax credits for clinical trial costs; (c) federal grants to support clinical testing

"(c) Permitted off-label promotion.—

(1) Listing of vulnerable patient populations.—The Commissioner shall create a list of vulnerable patient populations as defined in this Act.

(2) Updating vulnerable patient populations.—The Commissioner shall periodically, but no less often than annually, review and update the list of vulnerable patient populations.

(3) Applicability to vulnerable patient populations.—The provisions of this section shall be applicable only to vulnerable patient population off-label promotion efforts.

(4) Creation of Approved Off-Label Marketing Program.—The Secretary shall direct the Commissioner to—

(A) create an Approved Off-Label Marketing Program for drug companies who wish to market to vulnerable patient populations.

(B) issue regulations announcing and implementing the Approved Off-Label Marketing Program within 180 days of the passage of this Act.

(C) create as part of the Approved Off-Label Marketing Program regulations an application process for drug manufacturer-approved off-label marketing for vulnerable disease populations, which shall include, at a minimum, submission by the drug manufacturer of:

(i) details on the vulnerable patient population and disease to be treated;

(ii) a description of the drug proposed for the approved off-label marketing;

(iii) documentation of the vulnerable patient population and disease prevalence;

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of rare disease treatments; (d) exemption from FDA user fees; and (e) expedited review. *Id.*; Liang & Mackey, *supra* note 59, at 273–74. The purpose of the Act is to incentivize manufacturers to conduct drug development for indications and treatments that might not otherwise be profitable. *See* Orphan Drug Act § 1(b).

(iv) the regulatory and marketing status and history of the product;

(v) any post-market safety or efficacy data concerning the use of the drug for the vulnerable patient population and indication;

(vi) the specific promotional literature and materials, including Internet materials, to be disseminated to physicians for FDA review and approval;

(vii) risk management and pharmacovigilance plans for monitoring and reporting of off-label use, adverse events, other safety concerns, and other events relevant to the clinical treatment and health of the vulnerable patient population, and an affirmation of adequate funds to underwrite these plans;

(viii) any other information that the Commissioner or his/her designee requires; and

(ix) an attestation that all promotion would not be false, misleading, and that all materials would be peer-reviewed and approved by the FDA prior to dissemination.

(D) create an Off-Label Marketing Advisory Committee for Vulnerable Patients, under the terms and conditions of the Federal Advisory Committee Act, 5 U.S.C. §§ 1–16, which shall be comprised of scientific, communications, marketing, health literacy, and other experts, who have specific expertise with vulnerable patient populations.

(i) Responsibilities of the FDA Off-Label Marketing Advisory Committee for Vulnerable Patients.—The Off-Label Marketing Advisory Committee for Vulnerable Patients shall assess and evaluate the accuracy, appropriateness, and nature of proposed drug company off-label marketing materials, and make recommendations to the Commissioner as to the desirability of

allowing the proposed off-label marketing, specifically focusing on any implications for vulnerable patient populations.

(ii) Additional review.—The Off-Label Marketing Review Committee shall also review, as appropriate, applicable literature and other information on the subject beyond that submitted for the proposed off-label marketing and consult with external experts to determine, at a minimum, if:

(A) the available literature on the subject was reliable and reasonably supported that the off-label use is safe and effective, with particular reference to vulnerable patient populations;

(B) the available literature on the subject was reliable and did not support the off-label promotion proposal, with particular reference to vulnerable patient populations; or

(C) there was inadequate information to support the proposed off-label promotion or that there was enough adverse data (including post-marketing data) about the pharmaceutical that a supplemental new drug application is required to support any promotion of off-label uses, with particular reference to vulnerable patient populations.

(E) Application rejection.—An application may be rejected or additional information/data may be requested from the drug manufacturer if the Commissioner or the Commissioner's designee has determined that the risk versus benefit to patients or supporting evidence is not sufficient to allow for the off-label promotion of the drug for the proposed vulnerable patient population."

This section creates the new Approved Off-Label Marketing Program (the Program). It expressly notes that the Program only

applies to vulnerable patient populations, and that the FDA Commissioner must revisit this categorization at least annually to account for changes in the makeup of these populations. It also presents the basic terms of the Program, including the need for the FDA to create an application process that includes specific disclosures about the targeted vulnerable disease population, the makeup of the drug and its regulatory history, the drug's safety profile, the proposed marketing literature (including Internet materials), a risk management plan, and attestations that no inappropriate off-label marketing will occur and that all materials are peer-reviewed and FDA-approved. Importantly, the requirements in this Section create an FDA Advisory Committee, the Off-Label Marketing Advisory Committee for Vulnerable Patients, with appropriate expertise to review applications. FDA Advisory Committees play an important role in supporting the agency by providing independent, expert advice that improves the quality of regulatory decisions made by the FDA.[170] The section also notes that the FDA may reject any drug manufacturer's applications.

Additionally, manufacturers would be required to submit a risk management and pharmacovigilance plan to collect, detect, and report adverse events associated with approved off-label use. Such a strategy, which has been employed in Europe and applied to complex drugs with limited adverse event profiles such as follow-on biologics,[171] can provide rapid information on unanticipated adverse drug events and promote patient safety while also providing information on drug effects in understudied populations. Manufacturers would be responsible for implementing the approved risk management and pharmacovigilance plan to detect these adverse events.[172]

170. *See Advisory Committees: Critical to the FDA's Product Review Process*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143538.htm (last updated Aug. 12, 2011).

171. *See* Bryan A. Liang, *Regulating Follow-On Biologics*, 44 HARV. J. ON LEGISL. 363, 420, 423–24 (2007) (discussing risk management and pharmacovigilance efforts in the EU for new "biosimilar" copies of complex biological molecules on patient populations).

172. The FDA could fund this initiative through user fees for FDA review and approval of direct off-label promotion under this scheme. This amount could be set as other FDA user fees are set. *See generally Prescription Drug User Fee Act (PDUFA)*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm (last updated Aug. 31, 2011) (PDUFA authorizes FDA to collect fees from companies who produce drugs and could be further authorized to collect application fees for a program to consider approval of off-label indications).

3. Limited Enrollment and Required Registration

As a safety matter, because of the lack of full clinical trials and limited knowledge of the drug's complete impact on vulnerable patient populations, it is essential that only a limited group of patients participate initially. Further, to ensure that information is being collected and safety issues are being addressed, a registration program as part of the Program's surveillance and monitoring requirements should also be implemented. These latter components will also provide data and build a knowledge set regarding the approved off-label use in the specific vulnerable patient population.

> "(F) Limited applicability.—Any application for approved off-label marketing shall be limited by the Commissioner to a fraction of the vulnerable patient population under conditions as defined by the Commissioner based upon the vulnerable patient population characteristics, peer reviewed publications, and other information.
>
> (i) Monitoring responsibility.—The drug manufacturer that has obtained approval for a drug under the Approved Off-Label Marketing Program shall be responsible for monitoring the limits of vulnerable patient populations and ensuring that they are not exceeded.
>
> (ii) Fraction exceeded.—If a drug company that has an application in the Approved Off-Label Marketing Program exceeds that as set by the Commissioner, the FDA approval of drug company off-label marketing in the Approved Off-Label Marketing Program may be withdrawn, and the drug company may be directed by the Commissioner to apply for a supplemental new drug application under provisions of 21 C.F.R. § 314.70 for supplemental New Drug Applications. The Commissioner shall have discretion in any withdrawal action.

> (G) Registration.—Any drug company, vulnerable patient population patient who accesses the approved off-label marketing drug, and his or her physician, must register with the FDA and provide clinical information and updates on the treatment experience with the approved off-label marketing drug. The terms and conditions shall be based upon the risk profile, peer reviewed evidence, and other information."

Here, for safety purposes, approved off-label promotion would be limited to a fraction of the applicable diseases population. This is similar to the threshold for FDA Humanitarian Device Exemptions, which promotes the development of medical devices for rare diseases.[173] Further, each physician and patient under the Program would be required to register with the FDA, similar to the process of restricted distribution and patient/provider registration for high-risk drugs.[174]

If off-label prescribing exceeded this threshold, the manufacturer would be required to file a sNDA in order to continue any direct form of off-label promotion. Monitoring off-label prescribing to ensure that the threshold is not exceeded would be the responsibility of the manufacturer; this could be accomplished through active monitoring of physician prescribing practices. The FDA Commissioner would have discretion when the fraction of vulnerable patient population is exceeded to order a sNDA.

4. Clarifying Permitted Off-Label Marketing

While a regulatory framework to encourage positive and needed forms of direct off-label promotion for underserved populations is crucial, regulating inappropriate forms of off-label promotion is equally important. This effort could be accomplished by requiring

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173. *See Humanitarian Device Exemption*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm (last updated Aug. 30, 2010).

174. *See, e.g.*, Robert Shin et al., *Natalizumab (Tysabri®) and VA Healthcare Providers*, U.S. DEP'T OF VETERANS AFF., http://www.va.gov/MS/articles/Natalizumab_Tysabri_and_VA_Healthcare_Providers.asp (last reviewed Dec. 11, 2009). This describes the registration program for Natalizumab, which is a high-risk drug. Requirements in the program include: all patients must be registered and give informed consent; all providers and patients must agree to follow-up evaluations; only registered providers can prescribe the monthly intravenous infusion drug; only registered infusion centers can administer natalizumab; only registered pharmacies can distribute natalizumab; and only enrolled patients enrolled can receive treatment.

all off-label promotion and marketing not associated with vulnerable patient populations to be reviewed and approved by the FDA though a clear policy aimed at assessing whether information is misleading, false, or misbranded.

This could be accomplished by implementing an Advisory Committee for this purpose similar to the Program, by which an off-label marketing review committee would review and provide recommendations to the Commissioner for any proposed off-label promotion.

SECTION 3. TO CLARIFY PERMITTED OFF-LABEL PROMOTION BY AN FDA ADVISORY COMMITTEE.

(a) Chapter III of the Food, Drug, and Cosmetic Act (21 U.S.C. §§ 351–360ccc2) is amended by inserting after section 301 the following:

"SEC. 301A. CREATION OF AN FDA OFF-LABEL PROMOTION ADVISORY COMMITTEE."

"(a) Commissioner may approve drug company off-label marketing.—Subject to the provisions of this Section, the Commissioner is empowered to approve drug company off-label marketing, superseding any other provisions to the contrary.

(b) FDA Off-Label Promotion Advisory Committee.—The Commissioner shall create an FDA Off-Label Promotion Advisory Committee, under the terms and conditions of the Federal Advisory Committee Act, 5 U.S.C. §§ 1–16, comprised of scientific, communications, marketing, health literacy, and other experts, to review proposed drug company off-label marketing, subject to subparagraph (b)(1).

(1) Non-applicability to Approved Off-Label Marketing Program.—The provisions of this Section are inapplicable to off-label marketing materials submitted under the Approved Off-Label Marketing Program, Section 529 of this Act.

(c) Industry application.—Drug manufacturers who wish to engage in off-label marketing, other than that for vulnerable disease populations under Section 529, must obtain approval from the FDA under this Section before initiating such activities. To have its materials reviewed for potential approval, a drug

manufacturer shall submit materials as required by the Commissioner to assess the drug company's proposed off-label marketing materials, including, at a minimum:

(1) studies that support and, as relevant, do not support the off-label use, including identification of the drug, proposed patient populations, regulatory and marketing history, and post-market safety/efficacy data;

(2) Internet materials;

(3) brochures and pamphlets;

(4) all other marketing materials;

(5) risk management and pharmacovigilance plans, and an affirmation of adequate funds to underwrite these plans;

(6) any other information required by the Commissioner; and

(7) an attestation that all materials relevant to the proposed off-label promotion are included, that all promotion would not be false, misleading, and that all materials would be peer-reviewed and approved by the FDA prior to dissemination, prior to any use of any of the proposed off-label marketing materials.

(d) Responsibilities of the FDA Off-Label Promotion Advisory Committee.—The Off-Label Promotion Advisory Committee shall assess and evaluate the accuracy, appropriateness, and nature of proposed drug company off-label marketing materials, and make recommendations to the Commissioner as to the desirability of allowing the proposed off-label marketing.

(1) Additional review.—The Off-Label Promotion Advisory Committee shall also review, as appropriate, applicable literature and other information on the subject and consult with external experts to determine, at a minimum, if:

(A) the available literature on the subject was reliable and reasonably supported that the off-label use is safe and effective;

(B) the available literature on the subject was reliable and did not support the off-label promotion proposal; or

(C) there was inadequate information to support the proposed off-label promotion or that there was enough adverse data (including post-marketing data) about the pharmaceutical that a supplemental new drug application is required to support any promotion of off-label uses."

(e) Enrollment limits.—The Commissioner may, on the basis of an application, Off-Label Promotion Advisory Committee recommendations, and other relevant materials, limit the number of patients who may participate under this off-label promotion approval.

(1) Monitoring responsibility.—The drug manufacturer that has obtained approval for off-label promotion under this Section shall be responsible for monitoring the limits of patient populations are not exceeded if imposed by the Commissioner.

(2) Fraction exceeded.—If a drug company exceeds that fraction of patients set by the Commissioner, the FDA approval for off-label promotion may be withdrawn, and the drug company may be directed by the Commissioner to apply for a supplemental new drug application under provisions of the 21 C.F.R. § 314.70 for supplemental New Drug Application. The Commissioner shall have discretion in any withdrawal action.

(f) Registration.—If the Commissioner creates enrollment limits under subsection (e) of this Section, drug companies that have approved off-label promotion, patient who accesses the promoted drug, and his or her physician must register with the FDA and provide clinical information and updates on the treatment experience with the off-label promoted drug. The terms and conditions shall be based upon the risk profile, peer-reviewed evidence, and other information."

In this situation, like other FDA Advisory Committees, the Off-Label Promotion Advisory Committee would employ technical and nontechnical talent to evaluate the issue at hand: here, the accuracy, appropriateness, and scientific support of off-label drug uses and its marketing proposed by drug companies.[175] In particular, the application for approval of off-label promotion by manufacturers would require submission of any supporting *and* non-supporting studies regarding the proposed off-label marketing. Furthermore, a safety provision that permits unilateral limits on off-label promotion and use by the FDA Commissioner, as well as registration requirements that are similar to the Program, can protect patients while also generating useful data regarding off-label drug uses and outcomes.

5. Authorized Off-Label Promotion Practices

Approval of a manufacturer's ability to promote off-label use for both vulnerable patient populations and other patient populations would also be conditioned on the manufacturer's adherence to certain "authorized off-label marketing practices" as prescribed by the FDA. This is to ensure that off-label promotions would be standardized in such a way that they would be easily recognizable to physicians and patients.

> "(g) Authorized off-label promotion practices.—The Commissioner shall create authorized off-label promotion practices for any approved off-label marketing under this Section and Section 529. At a minimum, such authorized off-label marketing practices shall include:
>
> (1) only promoting the off-label use using approved promotional activities as determined by the FDA;
>
> (2) only disseminating scientific literature that has met FDA criteria for approved promotional materials;

175. To mitigate potential conflicts of interest, the FDA revised its policies and procedures for its Advisory Committees to screen for financial conflicts of interest and has adopted rules and procedures to ensure integrity in the decision-making process. *See Fact Sheet: Improved Policies and Procedures Regarding Transparency, Public Disclosure for FDA Advisory Committees*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/oc/advisory/factsheet080408.html (last visited Dec. 27, 2010).

(3) actively engaging in surveillance and monitoring of the off-label use and periodically reporting to the FDA quality and safety data under its risk management and pharmacovigilence plan; and

(4) including specific labeling on the drugs that they have not been FDA-approved for the off-label use and patients should consult their physicians for more information."

However, beyond the importance of clearly defining approved off-label promoted drugs, whether for vulnerable or other patient populations, there must be penalties for off-label marketing violations. The proposed bill would provide clear guidance to drug companies as to appropriate off-label marketing. Hence, any other off-label marketing would be deemed illegal and penalized as fraud and abuse.

"(h) Penalties for unapproved off-label marketing.—

(1) Any other marketing of drugs by drug companies, their assigns, or representatives, disclosed or undisclosed, shall be prohibited unless in comport with this Act.

(2) Any other marketing of drugs by drug companies, their assigns, or representatives, disclosed or undisclosed, shall be deemed misbranding of drugs.

(3) Any other marketing of drugs by drug companies, their assigns, or representatives, disclosed or undisclosed, that is submitted for, or results in payment by a public healthcare program shall be deemed a false claim, under the False Claims Act, 31 U.S.C. §§ 3729–3733.

(4) Any other marketing of drugs by drug companies, their assigns, or representatives, disclosed or undisclosed, shall be deemed a kickback under the Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b) if payment of any remuneration for referral to the drug result.

(5) If a drug company engages in off-label marketing in violation of this Act greater than one time, that company shall be ineligible for participation in the Approved Off-Label Marketing Program under Section 529 of this

Act and the approved off-label promotion under this Section.

(6) Section 1128(A) of the Social Security Act, 42 U.S.C. § 1320a-7(a) is amended by adding after § 1320a-7(a)(4) the following:

'(5) Conviction of Illegal Off-Label Marketing.—Any individual or entity that has been convicted of illegal off-label marketing related to the delivery of any drug subchapter XVIII of this chapter or under any State healthcare program.'

(7) Nothing in this Act shall limit causes of action or prosecutions for unapproved off-label marketing in federal or state venues against any drug company or individual."

Any off-label promotion outside the context of the statute would create significant risks for drug companies. By providing clear definitions of appropriate off-label promotion, the statute gives drug companies significant guidance about permitted marketing. However, to discourage drug companies from engaging in unapproved off-label marketing, the statute deems off-label marketing outside its framework a misbranding of drugs, a false claim, and a potential kickback. Courts would easily distinguish permitted and prohibited off-label marketing and, using the statutory provisions, deem such actions as fraud and abuse.

Beyond the FCA and potential Anti-Kickback Statute prosecutions, drug companies that violate the statute would also be barred from engaging in any future off-label marketing. The new benefits granted by the statute to companies engaging in appropriate off-label marketing would therefore be eliminated for companies found to have violated the statute, multiplying the penalties for inappropriate marketing strategies. Furthermore, the amendment to the Social Security Act would permit mandatory exclusion of convicted companies from participation in public health programs, including Medicare.[176] Finally, to ensure novel and appropriate penalties are still available against the recalcitrant off-label offender, the provisions of the bill provide expressly that additional prosecutions against individual corporate officers of firms engaged in illegal off-label marketing would not be preempted. This will be a powerful tool for regulators because of the lack of a scienter

176. *See generally* 42 U.S.C. § 1320a-7b (2006) (outlining criminal monetary penalties for acts involving federal health care programs that could include possible disbarment).

requirement to impose penalties on corporate executives and the prohibition of any public program payments to entities that employ excluded persons.[177] Through this series of nonexclusive penalties, appropriate deterrence, particularly of repeat offenders, may be accomplished.

V. POLICY BENEFITS

A. FDA

This approach, beyond improving access and information for vulnerable patient populations and their providers, would enable the FDA to more efficiently identify pharmaceutical products that would benefit from further testing. This builds on efforts to establish an orphan drug database and to encourage manufacturers to conduct clinical trials and seek approval for additional indications, including indications for rare diseases.[178] The FDA could even provide grant funding, similar to the grants provided under the Orphan Drug Act, for clinical research of promising drugs with acceptably low risk profiles for further efficacy testing for the vulnerable patient population and promotion of clinical indication.

This process would promote the development of a knowledge base on off-label uses of such drugs. The mandatory risk management and pharmacovigilance, as well as the prescribing limit and reporting requirements, also provide some assurance that off-label uses would be properly studied and monitored. The resulting data set could be a basis for an FDA assessment of warnings and limitations associated with these drugs and for additional study.

This process would also increase the FDA's situational awareness of off-label drug use and promotion for vulnerable patient popula-

177. *See, e.g.*, Anna Edney, *Drug-Firm Executives Under New Scrutiny in Medicare Fraud*, WASH. POST, Nov. 9, 2010, at A15, *available at* http://www.washingtonpost.com/wp-dyn/content/article/2010/11/08/AR2010110805757.html (discussing the potential prosecution of drug company executives and potential for companies employing such individuals to lose federal reimbursements); Memorandum Report from Stuart Wright, Deputy Inspector Gen. for Evaluation and Inspections to Marilyn Tavenner, Acting Adm'r and Chief Operating Officer, Ctrs. for Medicare & Medicaid Servs. (May 19, 2010), *available at* http://oig.hhs.gov/oei/reports/oei-09-08-00330.pdf; *see also* John W. Lundquist & Sandra L. Convey, *Defending Against Food & Drug Prosecutions*, 21 CHAMPION 20, 22 (1997), *available at* http://www.nacdl.org/CHAMPION/ARTICLES/97jul02.htm ("[I]n providing sanctions which reach corporate agents, the [Food, Drug & Cosmetic Act, 'FDCA'] imposes upon persons exercising authority or supervisory authority not only a positive duty to remedy FDCA violations as they occur, but also a duty to implement policies and practices designed to insure against future violations.").

178. *See* Marcus, *supra* note 65 (describing the FDA's efforts to "repurpose" approved drugs through the creation of an orphan disease database).

tions, while also mandating manufacturer responsibility for monitoring and managing potential adverse events. The FDA could then more proactively remove drugs from the market or require additional testing in a much more nimble way than is currently possible.

By implementing the statute through FDA advisory committees, regulators could better fulfill their mandate to actively monitor and assess off-label promotional activities. At the same time, this method also provides clarity to drug manufacturers regarding acceptable off-label promotion. By centralizing review and decision making within these structures, this reform provides the FDA with a full spectrum of oversight for off-label promotion practices while at the same time providing concrete processes to assess their scientific validity.

This method of implementation would also harmonize legitimate practices of off-label promotion by encouraging adherence to authorized off-label practices, such as appropriate use of scientific literature, post-market surveillance and pharmacovigilance efforts, and adherence to labeling requirements to better inform patients. Using this multi-tiered approach, the FDA would ensure that approvals of off-label marketing included benefits for patient safety and increased transparency, with extension to off-label uses supported by reliable evidence-based literature. Further, by empowering the FDA to reassess and withdraw approval of off-label promotion, this system would create a dynamic post-market surveillance regime to collect patient safety data on off-label uses common in medical practice.

In addition, enforcement mechanisms available under this policy would enable active identification and enforcement against illegal off-label promotion that fall outside of the parameters of acceptable practices. This enforcement framework also puts manufacturers on notice regarding the severity of penalties for continued illegal off-label promotion activities. Furthermore, extending additional penalties beyond misbranding to fraud and abuse would enable the FDA to coordinate enforcement action against rogue manufacturers and their individual officers and directors. Enforcement could be more efficiently initiated against actors who engaged in illegal off-label promotion before approval of an application, after application denial, or after approval has been revoked. Such a stringent penalty set would encourage voluntary adherence to responsible off-label promotion as adopted and continuously monitored by the FDA.

B. Patients and Physicians

Allowing for this regulated form of limited off-label promotion can, importantly, address physician knowledge limitations about the range of treatment options available to vulnerable patient populations. Of course, the opportunity for patients to understand the clinical options available to them is also an important benefit. This information will allow for more informed decisions by patients and increased adoption of advances in clinical treatment by physicians, while also providing transparency of their off-label status. This outcome is especially important given that only approximately 300 approvals for orphan disease indications have been given since enactment of the ODA out of an identified 6800 rare diseases, and that physicians generally lack knowledge about orphan disease treatments.[179]

Further, the system would broaden the spectrum of safety and efficacy information for off-label prescribing through mandates for a risk management and post-market surveillance system, while also ensuring that physicians are provided only scientific literature that has been vetted and approved by the FDA. Patients would gain greater access to innovative clinical treatments that would otherwise take years to gain FDA approval, and physicians would be armed with a growing body of safety and efficacy information to help guide them in their decisions to prescribe off-label. Both patients and physicians would benefit from increased enforcement mechanisms that would make it more difficult for bad actors to engage in illegal off-label promotion that had not been subject to FDA regulatory review. Indeed, standardization of approved off-label marketing practices would also serve to inform patients and physicians as to appropriate, approved off-label promotion.

C. Manufacturers

Drug manufacturers also benefit from the provisions of the proposed statute. These reforms clarify the requirements and limits of off-label promotion, the benefits to the responsible manufacturer, and the penalties for the bad actor. Practically speaking, the reforms provide manufacturers with a set of clear off-label promotion policies and procedures while also creating incentives for manufacturers to develop databases of safe and effective off-label uses. Manufacturers would be encouraged to explore additional re-

179. *See* Liang & Mackey, *supra* note 59, at 273.

search of off-label uses to support potential future sNDAs and even full approval. They may also limit potential future off-label liability by acting in a responsible and guided manner.

Importantly, the proposed bill would lower the cost barrier faced by pharmaceutical companies to investing in treatments for vulnerable patient populations, which may otherwise have been deemed an unprofitable effort. The gained experience with these populations in the context of post-market surveillance and other activities will provide a clear picture of the potential for further efforts with the specific drug, the specific vulnerable patient population, or both. It would also provide production and distribution cost information that may identify potential profitable drugs without having to endure full FDA marketing approval or a sNDA. This may lead companies to consider either sNDA or full FDA marketing approval that heretofore they would not have considered.

Responsible manufacturers would also be at a competitive advantage. Those who participate in the proposed system may obtain data more quickly and can move towards vulnerable patient population markets that have not yet been entered. Further, exclusivity incentives can work in concert with this approach. For example, manufacturers with unapproved drugs could take advantage of ODA incentives to develop approved drugs for the orphan indication and then identify and develop other vulnerable patient population markets using the off-label system. This would maximize returns for promising drugs, which is particularly needed for the small companies who often develop these drugs. Indeed, as a general matter, this could also lead to increased competition and lower costs by facilitating market entry of additional manufacturers without the need for exclusivity incentives like the ODA's.[180]

Reimbursements for drugs may also be enhanced. Off-label promotion and information sharing for vulnerable patient populations may also increase the chances of off-label federal and state reimbursement approval. This would lead to both increased patient access as well as increased revenues for manufacturers as these forms of treatments become common and accepted as valid methods of treatment, similar to recent Medicare action on particular cancer drugs.[181]

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180. *See* Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.) (listing ODA provisions including exclusivity benefits and clinical trial support for FDA-designated orphan drugs).

181. *See* Reed Abelson & Andrew Pollack, *Medicare Widens Drugs It Accepts for Cancer*, N.Y. TIMES, Jan. 27, 2009, at A1 (discussing the impact of Medicare expanding coverage to include cancer treatments not yet approved by the FDA).

CONCLUSION

Off-label marketing creates both risks and opportunities for health policy and patient care. It is abundantly clear that off-label marketing by unscrupulous entities creates risks to public health and patient safety that have not been adequately addressed. Yet, prohibiting all off-label marketing creates its own problems. For example, vulnerable patient populations and their physicians are left unaware of appropriate off-label treatment. Hence, current regulatory rules are either overinclusive, because they create information vacuums for vulnerable patient populations and their physicians, or are underinclusive because of the continued and repeat violations of off-label prohibitions. Reform is needed.

Using a legislative approach to address the information gap of vulnerable patient populations and penalizing repeat offenders in off-label promotion can address these concerns. This approach provides an important comprehensive solution to the multi-faceted issue of off-label promotion. This will eliminate the overinclusive nature of off-label marketing to improve information flow to patients and also addresses the underinclusive nature of current regulatory limitations that place patients and public health at risk. Such a comprehensive policy solution will allow benefits to inure to patients, the government and manufacturers through sharing of common benefits.

To ensure that the benefits associated with pharmaceuticals are fully realized, information on their usefulness must be appropriately disseminated but not mischaracterized. Through a coordinated approach, agencies such as the FDA can be empowered to provide relevant and evidence-based review, responsible manufacturers can be encouraged to provide information and promote clinical indications appropriately, and poorly-acting entities can be penalized and eliminated from off-label activities. Such a process can advance health and healthcare access to the individual patient while fulfilling the important social goals of patient safety, public health, and potential expansion of innovation.