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Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*

Sandra H. Johnson**

INTRODUCTION

Food and Drug Administration (FDA) approval of a drug signals certification of the drug's safety and efficacy for specified purposes, at the dosing level, and for the duration of use examined during the agency's approval process. Some estimates, however, indicate that over half of the prescription medications provided to patients in the United States may be prescribed for a purpose, in a higher or lower dose, over a longer period of time, or for a population (such as children) different from that for which the drug has been approved.¹

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** Tenet Endowed Chair in Health Law and Ethics, Center for Health Law Studies, Saint Louis University School of Law and Saint Louis University Department of Health Care Ethics; Professor of Law in Internal Medicine, Saint Louis University School of Medicine; and Professor of Health Care Administration, Saint Louis University School of Public Health.

1. David Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1025 (2006) (estimating that approximately 21% of prescriptions overall in the medical office setting were off-label solely in terms of the indication or purpose for which the medication was prescribed, although some categories of medications—specifically, cardiac medications and antihistamines for allergies—had much higher rates, approaching or exceeding 50%). Off-label prescribing of medications for psychiatric conditions appears to be higher than that for other medical conditions. *Id.*; see Hua Chen et al., *Off-Label Use of Antidepressant, Anticonfulant, and Antipsychotic Medications Among Georgia Medicaid*

This common practice, called “off-label” prescribing, has raised significant concerns over the safety and efficacy of medications prescribed outside the scope of their FDA approval.² A study published in the Archives of Internal Medicine in May, 2006, sharpened these questions when it reported that “most” off-label prescriptions studied had “little or no scientific support.”³ Concerns over the effectiveness or even the safety of such off-label prescribing are significant for individual patients, for private and public health care budgets, and for the public health. The advent of the Medicare prescription drug benefit⁴ has intensified the interest in the phenomenon of off-label prescribing and in the relationships between the pharmaceutical industry and practicing physicians.⁵

Enrollees in 2001, 67 J. CLINICAL PSYCHIATRY 972, 975 (2006) (“75% of antidepressant recipients and 80% of anticonvulsant recipients received at least one of these medications off label.”); Maxwell J. Mehlman, Off-Label Prescribing, <http://www.thedoctorwillseeyounow.com/articles/bioethics/> (last visited Oct. 2, 2006) (“[E]stimates [of off-label prescribing] run as high as 60% of all drug prescriptions in the United States in a given year.”); David M. Fritch, *Speak No Evil, Hear No Evil, Harm the Patient? Why the FDA Needs to Seek More, Rather Than Less, Speech From Drug Manufacturers on Off-Label Drug Treatments*, 9 MICH. ST. U. J. MED. & L. 315, 356 n.219 (2005) (“One estimate indicated off-label use accounted for 40–50% of the \$216 billion spent on U.S. prescription drugs in 2003.”); cf. Megan Barnett, *The New Pill Pushers: Big Pharma Watches Lawsuit Over ‘Off-Label’ Prescription Drug Marketing*, U.S. NEWS & WORLD REP., Apr. 26, 2004, at 40 (“An estimated 23 percent of prescriptions are written for off-label uses.”).

2. Radley, *supra* note 1, at 1021.

3. *Id.*

4. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (expanding Medicare to cover prescription drugs for beneficiaries).

5. 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* www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm (quoting the Administrator of the Centers for Medicare and Medicaid Services that fraud litigation directed at off-label marketing and prescribing “sends a strong message in advance of the implementation of the Medicare prescription drug benefit that our first priority will be protecting beneficiaries and the programs that serve them”); Nicole Huberfeld, *Pharma on the Hot Seat*, 40 J. HEALTH L. 241, 253 (2007) (“Direct reimbursement by Medicare [through Part D] means that the DOJ will have many more opportunities to regulate the industry through enforcement of the federal False Claims Act.”); *see also* Gardiner Harris, *U.S. Weighs Not Paying for All Uses of Some Drugs*, N.Y. TIMES, Jan. 30, 2004, at C1 (“Federal Medicare officials are close to deciding whether to refuse for the first time to pay for unapproved uses of expensive cancer drugs.”).

Actions taken to constrain off-label prescribing in response to these increasing concerns, however, face a serious risk of error. Counterintuitively, efforts to categorically restrict off-label prescribing will harm individual patients, who will be denied medication that may be uniquely effective though not yet definitively proven so, and seriously reduce medical innovation and “field discovery”⁶ of important therapeutics.

Questions concerning the exercise of medical judgment in off-label prescribing certainly reflect rational concerns for individual patients, but these questions also raise significant public policy issues relating to oversight of medical decision making. Thus far, the dominant public policy response to the phenomenon of off-label prescribing practices addresses the issue as a particular breed of financial conflicts of interest in medicine.

This view constructs a narrative of off-label prescribing that sees the financial relationships between pharmaceutical firms, practicing physicians, and researchers as a corrupting influence that pollutes medical judgment. The conflicts-of-interest narrative of off-label prescribing may mistakenly lead to an assumption that removing the confounding financial self-interest of doctors will itself result in better prescribing practices. It may be assumed that in such a purer environment, off-label prescribing will be more rational, meaning evidence-based, relying on research and information that will be produced and disseminated without the involvement of the pharmaceutical firms.

At best, the conflicts-of-interest narrative is only a partial

6. The off-label use of Neurontin, the subject of the litigation discussed in Part III of this article, for neuropathic pain associated with shingles was approved by the Federal Drug Administration (FDA) in 2002 after years of off-label use for this purpose. See *infra* note 232 and accompanying text. Other notable examples of effective, expanded uses discovered in the context of prescribing for off-label uses include the use of beta blockers for preventive care post heart attack; the use of Viagra for erectile dysfunction; and the use of AZT for AIDS. Jason K. Gross, *Compliance Counsel and ‘Off-Label’ Issues*, N.J. L.J., July 24, 2006, available at <http://www.sillscummis.com/newsroom>; Stephen R. Solbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debauché*, 79 B.U. L. REV. 93, 99–102 (1999); see also Harold J. DeMonaco et al., *The Major Role of Clinicians in the Discovery of Off-Label Drug Therapies* (Mass. Inst. Tech., Sloan Working Paper No. 4552-05, 2006), available at <http://www.medscape.com/viewarticle/529167> (defining “field discovery” as the new applications of drugs that are discovered through “clinical practice that [is] independent of pharmaceutical company or university research”).

accounting of the phenomenon of off-label prescribing. At worst, the conflict-of-interest explanation of off-label prescribing, standing alone, will mislead regulators because it relies on untenable assumptions regarding the production and diffusion of clinical knowledge. In either case, the conflicts-of-interest model cannot contribute to serious efforts to prospectively and substantively control off-label prescribing.

Efforts to address off-label prescribing solely as a matter of conflicts of interest may be important and may have some positive benefits, but, inevitably, public and private regulators will be left with the conundrum that the conflicts-of-interest approach dodges: off-label prescribing decisions usually operate in the face of serious gaps in research and knowledge.⁷ Efforts to seriously restrict this prescribing practice will operate without a firm evidentiary foundation for such limitations and, thus, will struggle with whether particular incidences or patterns of off-label prescribing are “correct,” in terms of effectiveness and an individualized and appropriate risk-benefit analysis for the individual patient.⁸ Furthermore, strident efforts to eliminate certain pharmaceutical industry behaviors that create conflicts of interest may exacerbate this knowledge gap by both depressing the production of clinical research and its assimilation into medical practice.

This paper argues that the core problem in off-label prescribing is not the relationship between the pharmaceutical industry and doctors, or at least not entirely so. Rather, the prevalence of off-label prescribing is a manifestation both of learning patterns in the medical profession and deficiencies in the production and dissemination of clinical knowledge. Furthermore, the fraud and abuse litigation strategy currently

7. Radley, *supra* note 1, at 1021; see RICHARD A. EPSTEIN, *OVERDOSE* 160 (2006) (stating that a restriction on pharmaceutical companies’ involvement in prescribing will likely cause a reduction in the information available for new drugs).

8. In fact, there is a significant gap in most research regarding the industry influences on physician prescribing behavior. The studies that identify the direction of the influence (i.e., increasing prescribing or request for inclusion in formularies) do not identify whether the change in prescribing produces better outcomes or otherwise benefits patients. Paul H. Rubin, *An Uncertain Diagnosis*, REG. Summer 2005 at 34, 35; EPSTEIN, *supra* note 7, at 160. See generally Thomas P. Stossel, *Regulating Academic-Industrial Research Relationships—Solving Problems or Stifling Progress?*, 353 NEW ENG. J. MED. 1060 (2005). See discussion *infra* text accompanying note 26.

pursued by the federal government in response to industry-prescriber interactions around off-label prescribing buries the essential problem in a conflicts-of-interest framework.

Part I of this article analyzes the impact of off-label prescribing patterns upon the market demand for post-approval clinical trials. This Part concerns itself with how physicians learn and how these learning patterns depress the production of new clinical knowledge concerning drugs that have already been approved for release to the market and thus are available for off-label prescribing. Post-approval trials, usually called post-marketing or Phase IV trials, are critical to public health because of limitations in the testing performed during the drug approval process.⁹ In spite of the value of Phase IV clinical trials, regulatory requirements for post-approval trials are nearly non-existent at this point;¹⁰ and the physician-prescriber market exerts only a weak demand for the production of clinical research on approved drugs. Although demands for trials may be strengthening among other players in the health care market, the physician-prescriber market is likely to remain the core determinant of the volume of this research.

Part II of this article examines the character, quality and volume of clinical research and its limited usefulness for individual prescribing decisions as well as current deficiencies in the production of clinical knowledge that impede efforts by

9. See *infra* text accompanying notes 72–73. The FDA approval process for a new drug requires clinical trials of the drug to test its safety and effectiveness. Generally, these trials proceed in three phases. Phase I trials test the metabolic and pharmacological behaviors of the medication in a small group of human subjects, typically between twenty and eighty persons, and are focused primarily on assessing the risks of the drugs. Testing then proceeds to Phase II in which the drug is tested on a larger group of subjects (generally 100 to 300 individuals) and on persons with the particular disease or condition to which the medication is directed. Phase III trials generally are the largest of the trials conducted prior to approval of a drug. Phase III trials usually require 1,000 to 3,000 subjects. Trials that are conducted after or concurrently with the approval of the drug are usually called Phase IV trials. See W. Christopher Matton & F. Scott Thomas, *The Continuing Balance: Federal Regulation of Biotechnology*, 44 JURIMETRICS J. 283, 298–302 (2004) (briefly describing the FDA’s drug approval process, including clinical trials); Office of Inspector General, HHS, *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research*, OEI-01-97-00195, June 2000, at 12 (“An average of 4,237 subjects were used in New Drug Applications from 1994 to 1995, compared with an average of 1,321 subjects from 1981 to 1984.”).

10. See discussion *infra* notes 23–24.

gatekeepers or regulators to move doctors, either by incentive or penalty, toward a stronger reliance on scientific proof of efficacy for off-label prescriptions. This Part also identifies a relationship between established patterns of physician learning and the character of contemporary clinical research by demonstrating how efforts to control conflicts of interest in research, especially through disclosure, reinforce skepticism toward scientific research on the part of practicing physicians.

Finally, this article examines litigation efforts targeted at financial relationships between doctors and pharmaceutical firms relating to off-label prescribing, focusing on federal litigation under the False Claims Act over one particular drug, Neurontin. This prosecution produced a settlement of over \$455 million and has spawned a significant body of similar litigation efforts.¹¹ Part III uses the Neurontin litigation, and its aftermath, to highlight the limitations of the conflicts-of-interest dominated approaches to controlling off-label

11. It remains the largest settlement to date for litigation focusing *solely* on the marketing, educational, and research activities of a pharmaceutical firm relating to off-label prescribing. 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* www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm. Since that settlement, the government has aggressively pursued pharmaceutical firms for these activities, winning significant settlements. *See, e.g.*, United States *ex rel.* Rost v. Pfizer, 466 F. Supp. 2d 6 (D. Mass. 2006) (regarding off-label use of human growth hormone.); Julie Schmit, *Schering-Plough to Pay \$435 Million Settlement*, USA TODAY, Aug. 30, 2006, at 1B (reporting settlement of government claims of fraud for promotion of off-label uses leading to the submission of both false claims against Medicaid as well as pricing violations); Press Release, Dep't of Justice, Eli Lilly and Company to Pay U.S. \$36 Million Relating to Off-Label Promotion (Dec. 21, 2005), *available at* http://www.usdoj.gov/opa/pr/2005/December/05_civ_685.html ("Eli Lilly and Company agreed to plead guilty and to pay \$36 million in connection with its illegal promotion of its pharmaceutical drug Evista."); *see also* Robert Brady et al., *Crackdown on "Off-Label" Pitches*, NAT'L. L.J., Mar. 20, 2006, at S1 (reporting on the settlements of actions against Serono, among other cases, for off-label promotion of a drug to treat AIDS wasting, as well as other cases). Pharmaceutical companies have also filed suit over off-label promotion by competitors. *See, e.g.*, *Off-Label Use: Zeneca, Maker of Nolvadex, Sues Eli Lilly for Claiming Evista Prevents Breast Cancer*, 8 BNA-HEALTH L. REP. 392 (1999) ("Zeneca Group PLC . . . seeks to prohibit Lilly . . . from continuing to market a rival product—Evista—that has not been approved by the Food and Drug Administration."). The impact of the False Claims Act litigation for off-label promotion has also triggered private products liability class actions and suits by private insurers to claim payments made for prescriptions for the drug. *See infra* notes 222–223 and accompanying text.

prescribing and to illustrate the information constraints that challenge efforts to regulate off-label prescribing more directly. Although the Neurontin litigation and similar cases are frequently proffered as an illustration of the centrality of conflicts of interest in the relationships among the pharmaceutical industry, researchers and doctors, this litigation is more richly studied for what it reveals about the nature of clinical knowledge and clinical judgment. The litigation and its aftermath, including the persistence of off-label prescribing of Neurontin, the subsequent approval of certain off-label uses of the drug, and the unsuccessful attempt of the Florida Medicaid program to restrict Neurontin prescribing, also raise questions about the limited impact of this type of litigation on prescribing patterns and illustrate the significant gap between controlling pharmaceutical-prescriber relations through civil and criminal litigation and transforming that effort into prospective, substantive control over prescribing. In addition, viewing the issues addressed in this article through the lens of the Neurontin litigation grounds the analysis in today's reality of inadequate clinical research and limited efforts to disseminate new learning. As off-label prescribing attracts more attention, it is critical that efforts to constrain the practice not outpace the information and dissemination resources that currently exist.¹²

12. The advent of the electronic medical record and the resultant large population databanks promise lower-cost post-approval research as the records can be mined for evidence of adverse effects as well as efficacy for off-label prescriptions. Unfortunately, serious information problems will remain even in the brave new information world. The data may be seriously inadequate for assessing health outcomes and may be inaccurate. Both the databank and the resultant analysis may be proprietary to the payer. Finally, problems in creating adequate space for clinical innovation; access to unproven but effective interventions; and the translation of averages to the individual patient will persist. *See generally* James Walker, *Electronic Medical Records and Health Care Transformation*, 24 HEALTH AFF. 1118 (2005); Clifford Goodman, *Savings in Electronic Medical Record Systems? Do It For the Quality*, 24 HEALTH AFF. 1124 (2005). One illustration of potential public-private information partnerships is the newly established partnership between the larger managed care organizations (MCOs) and federal agencies, including both the federal Agency for Healthcare Research and Quality and the FDA, which to this point focus almost solely on drug safety issues. *See* Kristin Madison, *ERISA and Liability for Provision of Medical Information*, 84 N.C. L. REV. 471, 502-04 (2006) (calling for effective accountability for MCOs as medical information providers. Whether or not these concerns about the usefulness of the research constructed from the aggregation of patient records turn out to be well founded, these data sets are only now emerging).

PART I: WEAK DEMAND FOR POST-MARKETING
CLINICAL RESEARCH

Despite the extraordinary potential value of post-marketing clinical research for approved drugs—in terms of enhancing continuing safety surveillance as well as encouraging broader testing on the effectiveness of medications for both approved and unapproved purposes—the demand for post-marketing studies is quite weak. A number of factors converge to diminish demand for such research. As discussed below, the legal framework for drug approval and drug prescribing encourages narrow approvals and results in broad off-label prescribing. In addition, prescribing physicians themselves do not demand continuing research on approved drugs in part because of learning patterns that tend to minimize the impact of published studies and formal continuing medical education.

State law generally creates a relatively neutral environment for off-label prescribing. State liability standards, for example, generally do not place the physician at significantly increased risk of liability for off-label prescribing *per se*. Doctors are not subject to strict liability for prescribing a medication off-label. In fact, off-label use often becomes the customary standard of care in particular circumstances, with the result that doctors are at risk for malpractice liability for failure to prescribe an approved drug for an off-label use. Furthermore, liability standards typically allow a doctor to engage in off-label prescribing as a matter of “clinical innovation,” as distinguished from “experimentation” (which triggers heightened regulatory standards for informed consent), in attempting to treat individual patients.¹³ Nor does state malpractice law generally require specific disclosure by the physician to the patient that the particular prescribed use is off-label, although products liability suits against pharmaceutical manufacturers related to marketing of off-label uses have seen some success.¹⁴

13. FDA, “Off-label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices, 1998 Update, GUIDANCE FOR INSTITUTIONAL REV. BOARDS, CLINICAL INVESTIGATORS & SPONSORS, available at <http://www.fda.gov/oc/ohrt/irbs/offlabel.html> (noting that IRB review and Investigational New Drug Application is not required).

14. Mehlman, *supra* note 1 (providing an overview of liability risks for off-

The Food, Drug, and Cosmetic Act (FDCA)¹⁵ specifically provides that the FDA has no authority to “limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed [medical] device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.”¹⁶ While the Act does not include a parallel provision for drugs, the FDA adheres to an identical policy for physician prescribing¹⁷ of approved medications including prescribing that differs in indication, population, dose or duration from those approved by the FDA.¹⁸ The intention of this policy is to avoid federal interference with the practice of medicine,¹⁹ a somewhat quaint notion at this point but alive in this situation nonetheless.²⁰

Federal drug law, however, does more than merely permit

label prescribing, but noting that in *Richardson v. Miller* the “court held that the fact that a drug use was off-label could be introduced as evidence that the prescribing physician deviated from the standard of care”); see *Richardson v. Miller*, 44 S.W.3d 1 (Tenn. Ct. App. 2000). Pharmaceutical firms have been found liable for injuries related to off-label uses when they have actively promoted those uses and concealed adverse effects. *Proctor v. Davis*, 682 N.E.2d 1203 (Ill. App. 1997); see also Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L.J. 967 (2007); Bernadette Tansey, *Hard Sell: How Marketing Drives the Pharmaceutical Industry: A Patient’s Right to Know: How Much Should Doctors Disclose About Treatments Not Approved by the FDA?*, S.F. CHRON., May 1, 2005, at A1.

15. Food, Drug and Cosmetic Act, 21 U.S.C. § 301 (2000).

16. 21 U.S.C. § 396 (2000).

17. The FDA, however, does regulate pharmaceutical firms’ behavior in relation to promoting off-label uses. The FDA prohibits pharmaceutical firms from marketing drugs for off-label uses, but allows companies to engage in limited educational and research efforts related to off-label prescribing. The limitations on firm behavior in relation to promotion of off-label uses are discussed in Part III below, in the context of the Neurontin litigation.

18. See 37 Fed. Reg. 16,503 (Aug. 15, 1972); see also 56 Fed. Reg. 67,440-01 (Dec. 30, 1991). More recently, the Food and Drug Administration Modernization Act loosened FDA restrictions on the dissemination of information on unapproved uses of approved drugs by pharmaceutical firms to physicians. Pub. L. No. 105-115 § 401, 11 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C.); James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71 (1998).

19. *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 349–51 (2001) (specifically commenting on the benefits of off-label prescribing of medical devices and the restrictions on the FDA’s authority to interfere).

20. See Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. KAN. L. REV. 149, 192 (2004).

off-label prescribing.²¹ The operation of the FDCA encourages the proliferation of off-label uses. Because a drug approved for a particular purpose is then available to the prescribing physician for any purpose, the regulatory structure incentivizes pharmaceutical firms to seek a narrow approved use, at least initially, in order to minimize the delay to market and reduce the investment in research required to meet FDA standards for approval.²² The FDA only rarely requires post-approval clinical trials as a condition of approval,²³ and the agency's

21. Of course, the federal government has other interests regarding off-label prescriptions, and perhaps countervailing policies and authority as the largest purchaser of drugs. As will become apparent in the later discussion of the Neurontin litigation, these interests have not operated as a significant counterweight to the incentives in the FDCA regulatory structure. *See infra* text accompanying notes 238–270.

22. Mitchell Oates, *Facilitating Informed Medical Treatment Through Production and Disclosure of Research Into Off-Label Uses of Pharmaceuticals*, 80 N.Y.U. L. REV. 1272, 1280 (2005).

23. The FDA has had authority to require post-marketing clinical trials in two circumstances: first, if the drug was approved under the fast-track provision for getting drugs to market in the case of life-threatening diseases; second, in the rarest cases where testing a drug on human beings is unethical, the FDA requires testing when circumstances make such testing feasible and ethical. 21 C.F.R. § 314.510 (2000); 21 C.F.R. § 314.610(b)(1) (2002). In addition, the FDA may require post-marketing clinical trials where testing is needed to assure that particular drugs used by a substantial number of children are safe and effective for pediatric use. 21 U.S.C. 355(c) (2000). The Food and Drug Administration Amendments Act of 2007 (FDAAA), described below, reauthorized the Pediatric Research Equity Act which is the source of this provision and appears to have significantly expanded the pediatric assessment required at submission for approval of a new drug. Pub. L. No. 110-85 § 302, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.). Current FDA regulations do provide for post-marketing surveillance, requiring that the manufacturer report any new information concerning safety and efficacy periodically. These regulations, however, do not require that the drug be submitted to formal clinical trials, but may lead to a reevaluation of the drug's approval. FDA, Center for Drug Evaluation and Research, Postmarketing Surveillance Programs, <http://www.fda.gov/cder/regulatory/applications/Postmarketing/surveillancepost.htm> (last visited Oct. 8, 2006); *see also* INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMIES, THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 155–56 (2007) (“FDA’s statutory authority to require postmarketing studies has been a subject of debate for decades.”). On September 27, 2007, President Bush signed the FDAAA to take effect on October 1, 2007. Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.). The FDAAA expands the authority of the FDA to require post-approval trials, but only where justified by “new safety information.” *Id.* § 801(a). This may be a significant expansion in terms of post-approval drug safety surveillance, but it does not reach the bulk of clinical research required to guide prescription of

follow up on required trials has been lax.²⁴ Incentives to invest in expanded approval²⁵ are uneven at best.²⁶

off-label uses. In addition, the FDAAA establishes a new process in which the FDA may require at initial approval or thereafter that a drug with “serious adverse drug experience” requires a “Risk Evaluation and Mitigation Strategies” (REMS) plan through which the drug would be monitored to assure that the benefits continue to outweigh risks. *Id.* § 901(a). Again, this can be an important addition to drug surveillance and safety, but does not respond to the broader need for post-approval clinical trials addressed in this article. The FDA is required to issue regulations under this provision by fall, 2009, so the impact of this provision is unlikely to be felt for some time. *Id.* § 9019(a); *see also* Charles Steenburg, *The Food and Drug Administration’s Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 FOOD & DRUG L. J. 695 (2006) (suggesting that the FDA has frequently negotiated a requirement of postapproval studies with pharmaceutical firms in the absence of clear authority to require them).

24. A 2006 United States Government Accountability Office (GAO) study reported that generally the agency’s post-marketing surveillance system suffered from a lack of clarity, insufficient oversight, and a lack of clear criteria for decisions. In addition, the GAO criticized the FDA’s follow up on post-marketing trials that it had required. GAO, IMPROVEMENT NEEDED IN FDA’S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS 36 (Mar. 2006), *available at* <http://www.gao.gov/new.items/d06402.pdf>. The problems extend to medical device issues as well as pharmaceuticals. *See FDA Briefing Addresses Problems in Medical Device Postmarket Surveillance System*, KAISER DAILY HEALTH POL’Y REP., Feb. 3, 2006, *available at* http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=3&DR_ID=35193. The FDAAA strengthened post-marketing adverse event surveillance in several respects. *See, e.g.*, Pub. L. No. 110-85, FDAAA § 402 (requiring that all adverse event reports received within one year of a labeling change for pediatric use be forwarded to the FDA’s Office of Pediatric Therapeutics); *id.* § 502(a) (requiring that all adverse events be reported by the applicant where pediatric studies are being conducted under the reauthorized Best Pharmaceuticals for Children Act); *id.* § 901(a) (requiring Risk Evaluation and Mitigation Strategies).

25. 21 C.F.R. § 314.70; Oates, *supra* note 22, at 1285 (describing burdensomeness of supplemental approval process).

26. *See, e.g.*, Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) (creating incentives for testing approved children’s drugs, by, in part, increasing patent protections for those drugs). Congress reauthorized this Act as Title V of the FDAAA and expanded the market exclusivity earned by firms that engage in such research. The intersection of patent law with the FDCA diminishes incentives for seeking approval of expanded uses of an approved drug. In the context of Neurontin, for example, it is possible that approval of expanded uses was not sought because of the anticipated expiration of the patent protection of the drug. Department of Justice, *supra* note 5. Revenue from sales of Neurontin fell 77% when patent protection expired. Hoover’s In-Depth Company Records, *Pfizer, Inc.* 2 (Mar.7, 2007), *available at* 2007 WLNR 4302915. The FDCA limitation on promotion of approved drugs for off-label uses targeted to physician-prescribers could create an incentive for seeking approval, but ordinarily does not do so. *See infra* discussion accompanying notes 28–29. The

Of course, the market could provide incentives for continuing research on approved drugs despite weak regulatory mandates. If physicians in practice refused to prescribe drugs beyond the use, duration, population or dosage for which they have been approved, firms would be incentivized by the prescriber market to seek broader approval expeditiously. The frequency and breadth of off-label prescribing, however, provide strong inferential evidence that doctors do not regard FDA approval as a necessary indicator of effectiveness (e.g., when they prescribe for an unapproved use) and perhaps even safety (e.g., when they prescribe at unapproved dosages or durations or for significantly distinct populations on which the drug has not been tested). In view of the serious constraints of the formal approval process, at least in terms of the time lag and the capacity of the FDA, a practice of awaiting formal approval for each indication is impractical, may harm patients, and actually may violate the standard of care in particular circumstances. The practice of off-label prescribing, then, would seem to be a rational reaction to the limitations of the formal approval process.²⁷

While prohibiting off-label prescribing by requiring formal FDA approval for every indication, dose, duration of therapy, and population for which an approved drug may be prescribed is impractical, practicing doctors could instead, as a general rule, refrain from prescribing medications until they are at least proven effective and safe, even if not formally approved, for the particular prescription contemplated. One may argue that the practice of medicine, to the extent that it relies on a scientific model of knowledge, would demand no less than substantial proof of safety and effectiveness prior to off-label prescribing. If doctors did so, pharmaceutical firms would confront a strong market demand for post-marketing clinical

emergence of pre-emption of state products liability claims, for drugs that are prescribed as approved, may create an incentive for seeking formal approval of expanded uses, but it is too early to tell. *See, e.g.*, Daniel R. Cahoy, *Medical Product Information Incentives and the Transparency Paradox*, 82 IND. L.J. 623 (2007).

27. Some have suggested that these limitations in the drug approval process argue in favor of dismantling the entire system. *See, e.g.*, Daniel B. Klein & Alexander Tabarrok, *Who Certifies Off-Label?*, REGULATION, June 1, 2004, at 60–62.

trials,²⁸ and the weakness of the regulatory requirements for post-marketing research would become less significant.

Practicing physicians, in fact, do *not* exert a high demand for convincing scientific proof of effectiveness for off-label uses. Nor do they create a robust market for scientifically valid information on effectiveness or even safety.²⁹ On what information, then, do doctors rely in making prescribing decisions for off-label uses?

The conflicts-of-interest narrative of off-label prescribing implies that doctors' willingness to prescribe is simply purchased by the pharmaceutical industry through free lunches, office supplies, travel, speaker's fees, and other more extravagant gifts.³⁰ While the "doctor for sale" story may be

28. Of course, doctors are not the only gatekeepers for prescribed drugs. Most health plans and pharmaceutical benefit management programs, however, currently do little to confine off-label prescribing, although they are actively engaged in efforts to influence physician and patient demand on other fronts, including, for example, shifting from expensive to less expensive substitute formulations ("fail first" requirements), switching to generic drugs, creating tiered benefits or increased co-pays, requiring preauthorization, or, in the case of Medicaid programs, simply limiting the number of prescription drugs that will be reimbursed for each patient. Stephen B. Soumerai, *Benefits and Risks of Increasing Restrictions on Access to Costly Drugs in Medicaid*, 23 HEALTH AFF. 135 (2004) (describing these methods); J.D. Kleinke, *Access Versus Excess: Value-Based Cost Sharing for Prescription Drugs*, 23 HEALTH AFF. 34, 42 (2004) (noting that the private insurance sector has "mostly abandoned" the "command-and-control... and other first-generation management strategies" for pharmaceuticals); see Rachel Christensen Seithi, *Prescription Drugs: Recent Trends in Utilization, Expenditures, and Coverage*, EMP. BENEFIT RES. INST. ISSUE BRIEF No. 265 (Jan. 2004), available at <http://www.ebri.org/pdf/briefspdf/0104ib.pdf> (reporting on a general decline in the number of employers using substantive controls). *But see* Peter J. Neumann, *Emerging Lessons from the Drug Effectiveness Review Project*, 25 HEALTH AFF. 262 (2006). Consumer behavior can also create an incentive for postmarketing research and formal approval of an already approved drug for an off-label indication as FDA approval for the off-label use is required if the firms want to advertise directly to consumers. Direct-to-consumer (DTC) advertising of prescription medications increases requests by patients for specific prescriptions, but there is a large gap between request and prescribing. While one survey found that approximately 35% of patients had discussed an advertised drug with their doctor, a 2002 GAO study reported that only 5% of consumers had both requested and received a prescription for a particular drug that had been the subject of DTC advertising. GAO, FDA OVERSIGHT OF DIRECT-TO-CONSUMER ADVERTISING HAS LIMITATIONS 4 (Oct. 2002), available at <http://www.gao.gov/new.items/d03177.pdf>.

29. Radley, *supra* note 1, at 1021.

30. Troyen A. Brennan et al., *A Social Science Perspective on Gifts to Physicians From Industry*, 290 JAMA 252, 252-53 (2003); Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?*, 283

true as far as it goes,³¹ a fuller appreciation of physician prescribing behavior requires examining how physicians actually learn to alter their practices, in this case to establish a new prescribing pattern for particular medical conditions.

The literature on physician learning belies the common view of the practice of medicine as bounded by science. In fact, one student of physician learning observed that doctors “have a deep skepticism about clinical trials, from a belief that clinical experience, rather than the scientific evidence should govern clinical practice.”³² High valuation of experience³³ over studies permeates the observed learning patterns of practicing physicians, including the surprisingly limited influence of published studies and the relative ineffectiveness of didactic continuing medical education.

Peer-reviewed journals are the gold standard for the publication of rigorous medical and scientific research; and journal articles do exert some influence on specific treatment decisions, but not nearly as much as one might anticipate. One researcher on physician decision making, for example, has noted that “the universal skepticism of practicing physicians regarding the utility of the scientific literature is startling.”³⁴

JAMA 373, 373 (2000).

31. See discussion of lack of outcomes research in the conflicts of interest literature *supra* note 7.

32. Rebecca K. Schwartz et al., *Physician Motivations for Nonscientific Drug Prescribing*, 28 SOC. SCI. & MED. 577, 581 (1989).

33. Even physicians who report that they always or often use evidence-based medicine (EBM) in making practice decisions rely instead most heavily on clinical experience. Ninety-three percent of physicians in one study reported relying on clinical experience as an information source, and the rate of reliance did not differ substantially between the group reporting commitment to evidence-based medicine and the group that only sometimes or rarely/never utilized EBM in their practice. Finlay A. McAlister et al., *Evidence-Based Medicine and the Practicing Clinician*, 14 J. GEN. INTERNAL MED. 236, 238–39 (1999). Reliance on clinical experience may be dangerous, of course. A study of data on the impact of clinical experience, in terms of years of practice concluded that, in fact, experience may have an inverse relationship with health outcomes, compliance with screening recommendations, and information base for prescribing. Niteesh K. Choudhry et al., *Systematic Review: The Relationship Between Clinical Experience and Quality of Health Care*, 142 ANNALS INTERNAL MED. 260 (2005).

34. Ann Lennarson Greer, *The State of the Art Versus the State of the Science: The Diffusion of New Medical Technologies into Practice*, 4 INT’L J. TECH. ASSESSMENT IN HEALTH CARE 5, 9 (1988); see also H.B. Slotnick, *How Doctors Learn: Physicians’ Self-directed Learning Episodes*, 74 ACAD. MED.,

There is also evidence that even when physicians do review professional journals for relevant information for clinical decision making, they are likely to fail to distinguish between rigorous studies and preliminary studies;³⁵ may be limited in their ability to assess the strength of any particular study;³⁶ and may in fact rely excessively on abstracts, overlooking instances in which the abstract may overstate results.³⁷ In addition, critics of peer-reviewed journals as a source of guidance for clinical decision making have noted that journals are not focused on the practitioner and often mix reports of a few rigorous trials with many preliminary studies, making it difficult for the practitioner (who may skip the methodology section) to be discriminating in evaluating the quality of information.³⁸ Physicians also may be as influenced by letters and case reports published in journals, which can be merely anecdotal, as by sound scientific studies.³⁹ The reliance on anecdotal, informal reports is consistent with observations of a higher trust level for clinical experience over clinical trials.

Written clinical guidelines standing alone also have proven relatively ineffective in changing practice patterns.⁴⁰ While the lack of influence of clinical guidelines may be attributed simply

1106, 1110 (1999) (stating that when addressing specific, acute needs, doctors tend to rely on readily available literature and discussions with colleagues—they are more likely to refer to medical journals for guidance in addressing general problems).

35. R.B. Haynes, *Loose Connections Between Peer-Reviewed Clinical Journals and Clinical Practice*, 113 ANNALS INTERNAL MED. 724, 725 (1990).

36. Only 34% of physician respondents in one survey reported that they had confidence in their ability to evaluate the methodology of a study on their own, and only 46% felt capable of doing a literature search. McAlister et al., *supra* note 33.

37. One study of how residents learn, for example, observed that even the “librarian residents,” a term used to describe those residents who reported reading as a source of information, were most likely to read only the abstracts and conclusions of articles. Stefan Timmermans & Alison Angell, *Evidence-Based Medicine, Clinical Uncertainty, and Learning to Doctor*, 42 J. HEALTH & SOC. BEHAV. 342, 345–47 (2001).

38. Haynes, *supra* note 35.

39. Lars Noah, *Medicine’s Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373, 397 n.40 (2002). In one survey doctors reported that they referred to “review articles” in journals (73%) but that they did not refer to “research studies” (45%). McAlister, *supra* note 33 at 236.

40. See, e.g., James Ducharme, *Clinical Guidelines and Policies: Can They Improve Emergency Department Pain Management?*, 31 J.L. MED. & ETHICS 783 (2005).

to physician resistance to “cookbook medicine,” the more intractable problem is the quality of most clinical guidelines. For example, guidelines frequently produce only the most general guidance, in part because of the dearth of clinical research required to ground more specific, and perhaps more influential, guidelines.⁴¹ Thus, guidelines often must rely extensively on “expert opinion” or consensus (a.k.a. committee) efforts rather than data. Further, to the extent that specific guidelines rely on the aggregation of published research studies, they may simply incorporate biases in that literature.⁴²

Perhaps because of their trust of experience over controlled studies, doctors may tend to rely on opinions of respected peers and opinion leaders within the profession rather than on clinical studies or clinical guidelines standing alone. Deference to “group think” and to a hierarchy of opinion may be a learned pattern of decision making adopted in the doctor’s experience of residency training where the opinion of the attending physician is revered as authoritative.⁴³ Studies document significant influence of peer opinions on clinical decision making,⁴⁴ although some studies conclude that the context for the transmission of opinions may make a difference in effect on practice.⁴⁵

Documentation of medical practice patterns corroborates

41. See Sean R. Tunis et al., *Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy*, 290 JAMA 1624, 1625 (2003). See generally Noah *supra* note 39 (discussing practice guidelines).

42. Kleinke, *supra* note 28, at 36 (detailing the impact of bias in the development of guidelines for the use of pharmaceuticals).

43. Timmermans, *supra* note 37, at 345–47.

44. See, e.g., Jane M. Young et al., *Role for Opinion Leaders in Promoting Evidence-Based Surgery*, 138 ARCHIVES SURGERY 785, 785, 789 (2003) (reporting that 88% of surgeons surveyed agreed that they had colleagues who would be influential in altering their own practice, and 93.8% reported that clinical opinion leaders in surgery were very or somewhat likely to influence their practice patterns). Surgeons reported that opinion leaders were more influential than clinical audits or clinical practice guidelines. *Id.* At the same time, however, surgeons in this survey reported that peer-reviewed surgical literature influenced their practice as well. *Id.*

45. At least one study indicates that the influence of opinion leaders varies along the same lines as the influence of continuing medical education described below. A. Wadhwa et al., *A Qualitative Study of Interphysician Telephone Consultations: Extending the Opinion Leader Theory*, 25 J. CONTIN. EDUC. HEALTH PROF. 98, 102 (2005).

the reported reliance on peers and opinion leaders as these studies reveal interregional practice heterogeneity as well as intraregional homogeneity.⁴⁶ One might expect that if physicians relied on scientific research results for medical decision making, neither the variations among geographic areas nor the homogeneity within regions would be so pronounced.

Journals are not the only tool for formal learning in medical practice. Continuing medical education (CME) is so highly valued as a vehicle for updating clinical knowledge that it is a routine licensure requirement for practicing physicians and is often used as a rehabilitative mechanism in physician discipline.⁴⁷ CME, however, is largely ineffective in achieving its ultimate goal of improving practice.

A significant study analyzing empirical studies of the impact of CME on practice decision making concluded that studies consistently demonstrated that formal, didactic CME exerts only a weak effect on practice patterns.⁴⁸ Lecture and case-based CMEs, which are the custom of the trade, can change information levels but do not change practice. The authors of one article found that traditional didactic CME “has little or no role to play” in changing practice.⁴⁹ A later analysis confirmed this conclusion and noted that such programs “have little or no beneficial effect in changing physician practice.”⁵⁰

46. The classic studies on interregional variations and intraregional homogeneities in practice were done by John E. Wennberg. See, e.g., John E. Wennberg *Dealing with Medical Practice Variations: A Proposal for Action*, 3 HEALTH AFF. 6 (1984); see also K. McPherson et al., *Small-Area Variations in the Use of Common Surgical Procedures: An International Comparison of New England, England, and Norway*, 21 NEW ENG. J. MED. 1307, 1310–14 (1982). The studies on interregional heterogeneity and local homogeneity of surgical practice may contradict survey data of surgeons’ self-reported higher reliance on peer-reviewed literature than on local colleagues. Young, *supra* note 44.

47. See, e.g., CAL. BUS. & PROF. § 2190; MO. REV. STAT. § 330.160; see also David A. Davis et al., *Accuracy of Physician Self-Assessment Compared with Observed Measures of Competence: A Systematic Review*, 296 JAMA 1094, 1094–95 (2006) (describing CME requirements of state medical licensure bodies, the Joint Commission, the specialty boards, and others).

48. David Davis et al., *Impact of Formal Continuing Medical Education*, 282 JAMA 867, 873 (1999).

49. *Id.* at 873.

50. B.S. Bloom, *Effects of Continuing Medical Education on Improving Clinical Care and Patient Health: A Review of Systematic Reviews*, 21 INT’L J. TECH. ASSESS. HEALTH CARE 380, 380 (2005); see also W. Sohn et al., *Efficacy of Educational Interventions Targeting Primary Care Providers’ Practice Behaviors: An Overview of Published Systematic Reviews*, 64 J. PUB. HEALTH

Doctors absorb new information, but do not necessarily incorporate it into their decision making.

Some CME pedagogies can effect change in practice.⁵¹ In particular, multiple contacts between instructor and student following a learn-work-learn sequence; information provided at the point of an expressed need to know; comparative information on the practice of other physicians; enabling materials that assist in interactions with patients (such as patient education sheets, reminders, and such); mailed materials followed up with personal phone calls; and proctoring and shadowing all show more significant effects than the standard CME.⁵² Most CME, however, is the standard lecture-format didactic CME,⁵³ while most pharmaceutical detailing (one-on-one representative-physician marketing) utilizes the very same pedagogical methods that have been documented as effective in changing practice in the CME context.⁵⁴

A Kaiser Family Foundation survey of doctors found that 74% thought information provided by drug representatives was useful and 81% believed that the information was at least

DENTISTRY 164, 170–71 (2004).

51. A 2004 article, for example, reported that an “interactive, case-based, educational intervention . . . using a series of interactive case-based teleconferences” effected a change in prescribing for asthma even though clinical guidelines recommending such prescribing had been ineffective in changing practice in over ten years. R.S. Davis et al., *Changing Physician Prescribing Patterns Through Problem-Based Learning*, 93 ANNALS ALLERGY ASTHMA IMMUNOLOGY 237, 237 (2004); see also Paul E. Mazmanian & David A. Davis, *Continuing Medical Education and the Physician as a Learner*, 288 JAMA 1057, 1059–60 (2002).

52. Davis, *supra* note 48, at 870–71; see also F. Daniel Duffy & Eric S. Holmboe, *Self-assessment in Lifelong Learning and Improving Performance in Practice*, 296 JAMA 1137, 1138 (2006) (discussing the importance of self-identified learning needs as motivational tools for more effective CME).

53. Bloom, *supra* note 50, at 381.

54. Robert Cohen, “*Unsales Pitches*” *Counter Drug Reps: Program Gives Doctors Alternative Advice, Tips*, STAR-LEDGER (Newark, N.J.) Sept. 9, 2007, at 1 (quoting founder of program that brings academic physicians to doctors’ offices to discuss prescribing: “[d]rug companies are awfully talented and effective in changing doctors’ prescribing behavior People in academia . . . tend to be lousy communicators, and we are not very effective in changing doctors’ prescribing practices.”); Wayne Kondro, *Academic Drug Detailing: An Evidence-Based Alternative*, 176 CAN. MED. ASS’N J. 429, 430 (2007) (describing shift in independent drug education program from written reports to office visits); Scott A. Kale et al., *Teaching Doctors to Fish*, MED. MARKETING & MEDIA, Nov. 1, 2007, at 46 (describing methods of making experts available to doctors and providing materials for patients).

somewhat accurate.⁵⁵ Of course, this may be due to the “free lunch” that comes with the information,⁵⁶ but it may also be due to the more effective pedagogical methods—methods that are responsive to clinical practice—used in this form of CME.

Once established, or once learned, practice and prescribing patterns are hard to alter. Some studies of off-label prescribing reveal habitual patterns among a significant segment of physicians.⁵⁷ Habit may persist even when serious safety concerns emerge. For example, while changes in drug labeling regarding warnings of previously unknown, serious risks are often mailed or faxed directly to physicians, studies indicate that these mailings do not result in changes in prescribing practice—that physicians frequently prescribed drugs in violation of warnings, including black box warnings.⁵⁸ Of

55. KAISER FAMILY FOUND., NATIONAL SURVEY OF PHYSICIANS PART II: DOCTORS AND PRESCRIPTION DRUGS (2002).

56. See, e.g., Troyen A. Brennan, *Health Industry Practices That Create a Conflict of Interest*, 295 JAMA 429 (2006); Dana Katz, *All Gifts Large and Small*, 3 AM. J. BIOETHICS 39 (2003); Wazana, *supra* note 30, at 378 (reporting on studies that document increased prescribing associated with pharmaceutical gifts; a positive disposition toward drug representatives; an increase in physician requests to add a specific drug to the hospital's or insurer's formulary in association with gifting; and doctors' inability to distinguish grounded from ungrounded claims). These studies do not measure patient outcomes subsequent to prescribing changes, however. *Id.* Furthermore, some studies recognize specific positive effects, including “improved ability to identify the treatment for complicated illnesses.” *Id.*

57. See, e.g., Judith K. Hellerstein, *The Demand for Post-Patent Prescription Pharmaceuticals* (December 1994) (Nat'l Bureau of Econ.Res., Working Paper No. W4981), available at <http://ssrn.com/abstract=226580>.

58. Jerry H. Gurwitz, *Serious Adverse Drug Effects—Seeing the Trees Through the Forest*, 354 NEW ENG. J. MED. 1413, 1414 (2006). Black box warnings are the most severe warnings the FDA can issue for a drug that is to remain on the market despite newly discovered adverse effects. See K.E. Lasser, *Adherence to Black Box Warnings for Prescription Medications in Outpatients*, 166 ARCHIVES INTERNAL MED. 338, 338 (2006) (reporting that doctors in the study prescribed medications subject to black box warnings to seven of one thousand outpatients, with female patients and patients over seventy-five-years-old more likely to receive the medications; that fewer than 1% of patients who received such drugs had an adverse drug event; and that “few incidents resulted in detectable harm”); A.K. Wagner, *FDA Drug Prescribing Warnings: Is the Black Box Half Empty or Half Full?*, 15 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 369, 375 (2006) (reporting that more than 40% of patients studied received a medication subject to a black box warning applicable to their situation, including some specifically applicable to pregnancy and that most of the non-compliance observed involved the absence of baseline laboratory monitoring that should have accompanied the drug therapy).

course, part of the paradox in drug approval and post-marketing surveillance is evident in the case of black box warnings in which the particular medication is not removed from the market, but physicians are to be “cautious” in prescribing because of risks discovered post-approval. There may be good reasons for a doctor to continue prescribing a drug with a black box warning, for example, because it is more effective for the particular patient and that gain in effectiveness outweighs the newly discovered risks. Thus, continued prescribing of medication with a black box warning in a particular case may be evidence of inappropriate habitual prescribing, or it may be an exercise of appropriate medical judgment.⁵⁹

The learning and information preferences observed in physicians are common coping tools for managing massive amounts of information.⁶⁰ The inclination to emulate their peers in their practice decisions, to look to physician opinion leaders, and to trust experience rather than to rely on published scientific studies or formal FDA approval all assist physicians in managing the information environment of modern medical practice. The amount of medical information available to a physician is overwhelming: for example, Medline adds 30,000 citations to its database each month.⁶¹ Although Medline and other medical research databases are searchable, doctors report a low confidence level in their ability to do a

59. See, e.g., AM. MED. ASS'N COUNCIL ON SCI. AFF., REPORT 10 (A-05): SAFETY AND EFFICACY OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) IN CHILDREN AND ADOLESCENTS (2005), available at <http://www.ama-assn.org/ama/pub/category/15186.html>.

[The American Medical Association . . .] recognizes that the current product labeling (package insert) of antidepressant drugs, including the Black Box warnings, is a precautionary statement intended to reinforce the need for careful monitoring of patients with depression and other psychiatric disorders during the initiation of treatment. This product labeling should not be interpreted in a way that would decrease access for patients who may benefit from these drugs.

This became American Medical Association (AMA) policy H-115.971 Safety and Efficacy of Selective Serotonin Reuptake Inhibitors (SSRIs) in Children and Adolescents. After reviewing the evidence, the AMA concluded that the association between the antidepressants and rates of suicide was not supported by data. Mark Moran, *AMA Opposes Restrictions on SSRI Use in Youngsters*, 40 PSYCHIATRIC NEWS 1, 1 (2005), available at <http://pn.psychiatryonline.org/cgi/content/full/40/14/1-b>.

60. Noah, *supra* note 39, at 402–03.

61. *Id.*

literature search on a particular question.⁶²

Similarly, informal communication networks among peers allow physicians to transmit information much more quickly than peer-reviewed journals can. Especially in certain practice areas, oncology for example, the demand for access to a drug may outpace the demand for scientific verification (for example, through completion of ongoing but incomplete clinical trials) of the information that is being shared.⁶³ Furthermore, information gathered from peers comes with an interpretative framework of experience that is valued in medicine.⁶⁴

These learning preferences show us a construct of patients as highly variable and medical practice as highly intuitive and reliant on judgment or discretion. The averages produced in scientific studies will not necessarily account for the individual patient presenting to the individual physician, and this problem of heterogeneity extends to individualized responses to medications.⁶⁵

Finally, in a tradition-oriented profession like medicine, there is safety in the herd. Malpractice and professional disciplinary standards, to the extent that they compare an individual doctor's decisions to a national or community custom, reinforce reliance on peer example by rewarding those who assure that their practice is within the mainstream. In some instances, regulatory agencies have used departure from majority prescribing practices as indicia of criminal or licensure violations.⁶⁶

Unwillingness to rely on scientific studies as essential for prescribing may reflect patterns of learning and practice that are simply resistant to scientific evidence regardless of the quality of information available. Reliance on peers and peer practices may also be a response to ineffective dissemination of knowledge through other outlets, including both journal articles and continuing medical education programs. In

62. McAlister et al., *supra* note 33.

63. Klein & Tabarrok, *supra* note 27, at 60.

64. See *supra* notes 33–34 and accompanying text.

65. Heterogeneity is a particular problem in the responsiveness of patients to particular medications, both in terms of effectiveness and adverse effects. Soumerai, *supra* note 28, at 143; see also EPSTEIN, *supra* note 7, at 118–20.

66. See, e.g., Symposium, *Appropriate Management of Pain: Addressing the Clinical, Legal, and Regulatory Barriers*, 24 J.L. MED. & ETHICS 285 (1996).

addition to these considerations, deficiencies in the production and quality of clinical knowledge, discussed in the next section, may actually reinforce clinicians' skepticism of the utility of research studies in their prescribing decisions.

PART II: THE LIMITED UTILITY OF CLINICAL RESEARCH FOR OFF-LABEL PRESCRIBING DECISIONS

If off-label uses of an approved medication are to be tested at all, those tests, by definition, will be conducted after the drug is approved for the market. As discussed earlier, the FDA does not ordinarily require significant post-marketing clinical research as a condition of approval of a particular drug, even though it has some authority to do so. Furthermore, prescribing doctors do not exert strong market demand for post-marketing research for off-label prescribing. Weak demand for post-marketing research, both through regulatory channels and in the prescribing market,⁶⁷ has produced an insufficient supply of clinical knowledge for off-label prescribing. This gap certainly exists in the case of non-approved uses. It also, however, exists in the (potentially more common) incidents of off-label prescribing of approved medications for untested patient populations in which there may be significant disparities in effectiveness and safety of the drug (e.g., certain drugs tested only on men but prescribed for women and drugs tested only on adults but prescribed for children). Additionally, the gap exists when drugs are prescribed for doses or durations (e.g., long-term instead of short-term) that have not been tested in clinical trials prior to approval.

Off-label prescribing is not unique in raising the issue of insufficient clinical research. The negative impact of the insufficiency in the production of Phase IV clinical trials extends to all prescribing, including off-label prescribing and prescribing within the scope of approval. Phase IV studies typically will be the first in which very large numbers of persons are studied. For comparison, Phase III trials, the largest of the pre-approval trials, ordinarily involve only 1,000 to 3,000 people,⁶⁸ a number that is too small to reveal

67. See *supra* Part I.

68. See *supra* note 9.

uncommon, though quite serious, adverse effects.⁶⁹ In addition, the pre-approval trials are time-limited, while post-marketing trials can extend for a much longer time, again increasing the likelihood that adverse events that arise only with very long-term use will be detected. In addition, pre-approval trials generally rely on a “naïve” subject population, one that will not present the risk of drug interactions because these interactions may confound the results for the tested drug.⁷⁰ Once available for prescribing, however, the approved drug will be used by patients taking any number of other medications. Phase IV trials often present the first opportunity for testing the risks of drug interactions. Equally importantly, approved medications are prescribed for individuals, including both the elderly and children as well as individuals with medical conditions such as diabetes, in whom the medication may behave quite differently in terms of both effect and safety.⁷¹ These differences are likely to be detected only in the post-marketing phase of research.⁷² Finally, the FDA does not require proof of comparative efficacy for approval of a new medication, so trials that compare one drug to another usually take place, if at all, only after a new medication has been approved.⁷³

Weak demand for post-marketing clinical trials results in inadequate numbers of these trials to meet the needs of practicing physicians. The problem for clinical decision making

69. Richard Gliklich, *Keeping Approvals on Track*, 14 APPLIED CLINICAL TRIALS 28, 28, 30 (2005).

70. *Id.* at 28–29.

71. Scott Gottlieb, *Opening Pandora’s Pillbox: Using Modern Information Tools to Improve Drug Safety*, 24 HEALTH AFF. 938, 939 (2005) (“There is little chance that [preapproval] trials will ever provide a complete review of how a new treatment will perform when it is used in much broader populations of patients in real-world clinical settings.”).

72. DeMonaco et al., *supra* note 6.

73. See David B. Ross, *The FDA and the Case of Ketek*, 356 NEW ENG. J. MED. 1601, 1601 (2007) (discussing change in FDA policy reducing requirements for noninferiority trials as part of approval processes). Those comparative studies currently conducted can suffer from design flaws relating to whether the appropriate dosage is chosen for the comparable drug and other issues. K.J. Jørgensen et al., *Flaws in Design, Analysis and Interpretation of Pfizer’s Antifungal Trials of Voriconazole and Uncritical Subsequent Quotations*, 7 TRIALS 3 (2006); see Valeria Frighi, *Medical Journals, Academia, and Industry-Sponsored Clinical Trials*, 2 PLOS MED.7, e218 0686, 0686 (2005); J. Lexchin et al., *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, 326 BRIT. MED. J. 1167, 1170 (2003), available at <http://www.pubmedcentral.nih.gov/>.

regarding off-label prescribing is not one entirely of sheer volume but includes quality concerns as well. The quality of current post-approval clinical trials falls short of meeting the needs of prescribers. The first quality concern emerges from the presumed impact of the source of funding for the bulk of clinical trials. The second quality concern arises from the gap between the design of clinical trials and the circumstances of ordinary medical practice.

A. PUBLIC AND PRIVATE FUNDING

Randomized controlled clinical trials are expensive. The large number of subjects involved and long lifespan of Phase IV trials make them particularly expensive. The pharmaceutical industry is not the only source of financing for post-marketing clinical research; but it is the biggest by far.⁷⁴ The federal National Institutes of Health (NIH) has been expanding its commitment to clinical research of late, but in recent years has only spent 30% of its budget (approximately \$850 million) on pharmaceutical clinical trials of all types, including Phase I, II, III and Phase IV trials.⁷⁵ The federal Agency for Healthcare Research and Quality (AHRQ) spends approximately \$30 million annually on clinical trials, although again not only Phase IV trials.⁷⁶ The Veterans' Administration has conducted some significant trials of medical interventions, but its budget for such research is only approximately \$55 million per year, and again not devoted entirely to pharmaceutical research.⁷⁷ The Centers for Education and Research in Therapeutics, a joint FDA-AHRQ effort aimed at improving the production of clinical knowledge, has an annual budget of \$7 million to support clinical trials of drugs.⁷⁸ The Medicare program has also begun to "fund" clinical research studies on its own beneficiaries through a condition on payment for experimental

74. The proportion of public to private dollars for clinical research is likely to move in the direction of decreasing public support. *Researchers Should Rely Less on NIH Grants, More on Industry Funding, Bush Adviser Says*, 6 MED. RES. L. & POL'Y REP., May 16, 2007, at d4.

75. Tunis et al., *supra* note 41, at 1628.

76. *Id.*

77. *Id.*

78. AHRQ, FACT SHEET CENTER FOR EDUCATION AND RESEARCH ON THERAPEUTICS (CERTS) (2004), *available at* <http://www.ahrq.gov/clinic/certsovr.pdf>.

interventions.⁷⁹ In comparison to the approximately \$950 million of federal money devoted to all phases of clinical trials, pharmaceutical firms may be spending as much as \$8 to \$12 billion on post-marketing trials alone.⁸⁰ Although private insurers and pharmacy benefits management programs are beginning to produce clinical research on approved drugs, this nascent effort is confined largely to collecting data from the pharmaceutical industry.⁸¹ Even if this effort increases, the information produced may be viewed as proprietary.

Critics have raised substantial concerns over

79. CTRS. FOR MEDICARE & MEDICAID SERVS., NATIONAL COVERAGE DETERMINATIONS WITH DATA COLLECTION AS A CONDITION OF COVERAGE: COVERAGE WITH EVIDENCE DEVELOPMENT § VI (2006), available at https://www.cms.hhs.gov/pf/printpage.asp?ref=http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8; see also Sandra J. Carnahan, *Medicare's Coverage with Study Participation Policy: Clinical Trials or Tribulations*, 7 YALE J. HEALTH POL'Y L. & ETHICS 229, 231 (2007); see also discussion of data collection by private insurers, *supra* note 12.

80. See, e.g., CUTTING EDGE INFO., MASTERING PHASE IV CLINICAL TRIALS (2007) (estimating expenditures of \$12 billion), available at <http://www.cuttingedgeinfo.com/postmarketingtrials/index.htm?type=GoogleAdWordsContent&gclid=CNPzsKf2to8CFQUsPAodGyBDeA>. The same study said firms spent an average of 14% of their total research and development budgets on post-marketing trials. *Phase 4 Clinical Trials Claim an Average of 14% of R&D Budgets, Study Says*, MARKETWIRE, Nov. 14, 2007, <http://www.marketwire.com/mw/release.do?id=792873>; see also CONG. BUDGET OFFICE, RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 7–8 (2006), available at <http://cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf> (reporting annual industry spending on all R & D of \$38 million, and National Science Foundation estimate that 20% of that is spent on post-marketing research which the NSF excludes from its calculation of pharmaceutical R & D). Some of the expenditure reported by industry in support of post-marketing trials is more appropriately allocated to marketing efforts that may be enfolded in these trials. See EPSTEIN, *supra* note 7, at 145. As with all of the figures for research and development investment by pharmaceutical firms, estimated expenditures come from the industry itself and estimates vary. See, e.g., GAO, NEW DRUG DEVELOPMENT: SCIENCE, BUSINESS, REGULATORY, AND INTELLECTUAL PROPERTY ISSUES CITED AS HAMPERING DRUG DEVELOPMENT EFFORTS, 4, 39 (2006) (reporting that industry spent \$40 billion on all research and development in 2004 but stating that the GAO “did not independently verify these expenditure data; . . . and they represent the best available information at the time of our study”).

81. See, e.g., Peter J. Neumann, *Evidence-Based and Value-Based Formulary Guidelines*, 23 HEALTH AFF. 124 (2004). Interestingly, the Neurontin settlement, discussed in Part III, is providing grants to organizations to study prescribing patterns and provide education to doctors and consumers concerning sources of information for prescription drugs. Press Release, Or. Dep't of Justice, AG Myers & Kitzhaber Address A “1st of Its Kind” Conference in Portland (Dec. 4, 2006), available at <http://www.doj.state.or.us/releases/2006/rel120406.shtml>.

pharmaceutical industry support for research even though it is essential to the production of clinical knowledge due to seriously inadequate public funding. The vigorous debate over industry support of clinical trials challenges the credibility of clinical research on which clinical, management, and regulatory decisions, at least theoretically, should rely. Furthermore, the resulting credibility crisis may have a nonspecific but pervasive effect on the uptake of clinical research results into medical practice, especially if physician learning and decision making is already skeptical of the utility of scientific studies.⁸² Finally, the quality of clinical research limits its utility for public and private controls over physician prescribing. If clinical studies are biased, then public and private efforts to control prescribing rely on defective information.⁸³

B. WHOSE BIAS?

In January of 2003, Bekelman et al. published a watershed article on the impact of funding source on research results.⁸⁴ In this article, they performed a meta-analysis of 37 published quantitative studies that compared the source of funding with the outcomes of 1140 biomedical studies, many of which were drug studies.⁸⁵ The Bekelman study thus examined the aggregation of data over several studies of single drugs or other medical interventions.⁸⁶ The authors concluded that the sponsorship of a study was very closely associated with the outcome reported, even in the case of random controlled trials: “Strong and consistent evidence shows that industry-sponsored research tends to draw pro-industry conclusions. . . . [W]e found that industry-sponsored studies were significantly more likely

82. See *supra* notes 26 & 28.

83. See *infra* text accompanying note 87.

84. Justin E. Bekelman et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review*, 289 JAMA 454 (2003); see also Mohit Bhandari et al., *Association Between Industry Funding and Statistically Significant Pro-Industry Findings in Medical and Surgical Randomized Trials*, 170 CAN. MED. ASS'N J. 477, 477 (2004); James F. Fries & Eswar Krishnan, *Equipoise, Design Bias, and Randomized Controlled Trials: The Elusive Ethics of New Drug Development*, 6 ARTHRITIS RES. & THERAPY 3, R250 (2004), available at <http://www.pubmedcentral.nih.gov/>; Lexchin et al., *supra* note 73, at 1167.

85. See Bekelman et al., *supra* note 84, at 456.

86. *Id.*

to reach conclusions that were favorable to the sponsor than were nonindustry studies.”⁸⁷

The pattern of “pro-industry conclusions,” as the authors termed the phenomenon, was pronounced in several instances.⁸⁸ For example, studies of the results of articles on calcium channel blockers reported that 51% of authors with industry funding reported positive results in trials of the drugs, while 0% of authors of studies that were not sponsored by interested firms reported positive results.⁸⁹ Other studies showed less dramatic differences, but a difference of approximately 20% was common when comparing the rate of positive and negative outcomes over the aggregated studies of particular drugs or other interventions.⁹⁰

It is indicative of this time of turmoil in clinical research that it’s not clear where the blame lies for the observed bias in studies reviewed, accepted and published in medical journals. Does the association of sponsorship with positive results reflect bias on the part of the industry-funded researcher?⁹¹ Or is the bias the result of the pharmaceutical firms’ selectivity in choosing to fund only studies with a high likelihood of positive outcome, thereby strengthening the market for their product?⁹² Or is the bias produced by research contracts or grants in which the sponsor retains the unilateral right to release results for publication or not, allowing the sponsor to control the flow of information through the journals to the medical market?⁹³

87. *Id.* at 463.

88. *Id.*

89. *Id.* at 456.

90. *Id.* at 458.

91. The Bekelman article considers several factors contributing to disproportionately positive results, but does not list individual researcher bias among those. Bekelman et al., *supra* note 84, at 463. *But see* Catherine D. DeAngelis, Editorial, *The Influence of Money on Medical Science*, 296 JAMA 996, 996 (2006).

92. *See, e.g.*, Fries & Krishnan, *supra* note 84. The authors hypothesize that “extensive preliminary data are used to design [industry-funded] studies with a high likelihood of being positive.” *Id.* at R250. They further report that company consultants and staff review “what is known about the drug, its competitors, its potential advantages in terms of toxicity or efficacy, and the potential disease indications” and then design trials that include the “patients, dosages, study duration, end-points, and comparators that are likely to provide a positive result for the sponsor and one that is acceptable to the F.D.A.” *Id.* at R252.

93. In a 1986 survey of research faculty, 24% of those funded by industry reported restrictions on publication of study results compared to 5% of those

Or do the journals themselves contribute to selection bias by rejecting studies that “show that a new treatment is inferior to standard treatment” or “that are neither clearly positive nor clearly negative”?⁹⁴

Any one of these reasons casts doubt on the reliability not only of a single published article, but even more significantly on the entire body of published research about a particular drug. Systemic bias has serious implications for the aggregation of published results. Such aggregation of results supplies the “evidence” for evidence-based medicine for practice guidelines and consensus statements for treatment decisions.⁹⁵ If published results in the aggregate show a bias toward “pro-industry” conclusions, the disutility of published clinical trials becomes apparent and raises a critical issue for the practicing physician. Moreover, any gatekeeper, governmental or private,

with other funding for research. D. Blumenthal et al., *University-Industry Research Relationships in Biotechnology: Implications for the University*, 232 SCIENCE 1361, 1364 (1986); cf. Richard Smith, Essay, *Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies*, 2 PLOS MED. 0364, 0365 (2005), available at <http://www.pubmedcentral.nih.gov/> (reporting that suppression of results is “too crude” a method for influencing the body of published work and reviewing other methods that can achieve the same effect). In fact, Bekelman et al. report that suppression of data is less likely in industry-sponsored studies than in studies in which the researcher is “in the process of bringing their research results to market.” Bekelman et al., *supra* note 84, at 463. See generally *infra* notes 134–37 and accompanying text (discussing the Bayh-Dole Act).

94. *Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors*, 351 NEW ENG. J. MED. 1250, 1250 (2004); see also J.D. Kleinke, *supra* note 28, at 35–36 (discussing the tendency of journals toward publishing articles that expand the use of more aggressive and more expensive drug therapies); Smith, *supra* note 93, at 0365 (describing a strategy of publishing the results of multi-center trials in a number of publications as separate results to produce a body of research that shows a high frequency of positive results, a strategy that directly benefits publishers of medical journals as well as the manufacturer).

95. Experts review the aggregation of study results when developing clinical practice guidelines and consensus statements. A study of such experts, however, found that 87% had financial connections to pharmaceutical firms. Niteesh K. Choudhry et al., *Relationships Between Authors of Clinical Practice Guidelines and the Pharmaceutical Industry*, 287 JAMA 612, 614 (2002). These relationships may have no effect on the content of the guidelines. See Bekelman et al., *supra* note 84, at 463. See generally David G. Duvall, *Conflict of Interest or Ideological Divide*, 22 CURRENT MED. RES. & OPINION 1807 (2006). The use of expert opinion in the development of guidelines also illustrates the reliance on peer and leader opinions in medical decision making. See *supra* text accompanying notes 28–34.

that aims at controlling individual prescribing decisions by reference to published clinical studies must also contend with this suspect reliability.

The Bekelman piece is only one example of the mounting concern over bias in published clinical studies. In the four years since this watershed analysis, the trickle of concern over the validity and purity of research results published in the gold-standard peer-reviewed journals has grown into a torrent.⁹⁶ In a summer 2006 editorial, Dr. Catherine DeAngelis, the editor-in-chief of JAMA, identified a litany of examples of “research irregularities” in research sponsored by “for-profit companies.”⁹⁷ These examples include “refusal to provide all study data to the study team, reporting only 6 months of data in a trial designed to have 12 months of data . . . ; incomplete reporting of serious adverse events; and concealing clinical trial data showing harm.”⁹⁸ She further detailed her concerns that industry sponsorship of clinical studies can “exert inappropriate influence in research via control of study data and statistical analysis, ghostwriting, managing all or most aspects of manuscript preparation, and dictating to investigators the journals to which they should submit their manuscripts,” noting that some companies are rumored to be preventing researchers from publishing in JAMA because of its conflicts-of-interest requirements.⁹⁹ Many share

96. Although the following discussion focuses on the issues arising in the publication of clinical studies, research centers also have established policies to manage conflicts of interest in the conduct of research. For example, the American Association of Medical Colleges has recommended that medical research universities establish conflict-of-interest policies. Press Release, Ass’n of Am. Med. Colls., AAMC Urges Speedy Adoption of NIH Conflict of Interest Reforms (May 6, 2004), *available at* <http://www.aamc.org/newsroom/pressrel/2004/040506.htm>; *see also* U.S. GEN. ACCOUNTING OFFICE, UNIVERSITY RESEARCH: MOST FEDERAL AGENCIES NEED TO PROTECT AGAINST FINANCIAL CONFLICTS OF INTEREST 3 (2003), *available at* http://www.eric.ed.gov/ERICDocs/data/ericdocs2sql/content_storage_01/0000019b/80/1b/9c/c1.pdf (reporting that all of the 171 universities surveyed had conflicts-of-interest policies for their researchers and that 87% of research universities had policies that complied with NIH and NSF guidelines); *infra*, text accompanying notes 162–163 (discussing governmental policies on conflicts of interest). *See generally* Peter J. Harrington, *Faculty Conflicts of Interest in an Age of Academic Entrepreneurialism: An Analysis of the Problem, the Law and Selected University Policies*, 27 J.C. & U.L. 775 (2001) (discussing a variety of conflicts of interest, focusing on those with industry).

97. DeAngelis, *supra* note 91, at 996.

98. *Id.*

99. *Id.*

DeAngelis' concerns,¹⁰⁰ and the behaviors she identifies are well documented.¹⁰¹ In addition to JAMA's adventures, the New England Journal of Medicine dealt with its own controversy with industry-supported research when, after publishing the results of clinical trials of Vioxx, it published notices stating that Merck may have intentionally altered the evidence.¹⁰²

Conflicts-of-interest analysis, which has framed the debate over industry funding of clinical trials, can go only so far in responding to the crisis in the reliability, real or perceived, of clinical research.¹⁰³ As most critics acknowledge, pharmaceutical industry support for clinical research has significant benefits, and it is highly unrealistic to think that

100. The most prominent critique of the pharmaceutical industry, including their research efforts, is by another editor, Marcia Angell, former editor of the New England Journal of Medicine. See generally MARCIA ANGELL, *THE TRUTH ABOUT DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT* (2004).

101. See, e.g., Thomas Bodenheimer, *Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539, 1542 (2000) (documenting ghostwriting); see also United States ex rel. McDermott v. Genentech, No. 05-147-P-C, 2006 WL 3741920, at *3 (D. Me. Dec. 14, 2006) (discussing alleged ghostwriting by pharmaceutical firms).

102. Gregory D. Curfman et al., *Expression of Concern Reaffirmed*, 354 NEW ENG. J. MED. 1193, 1193 (2006); see also Claire Bombardier et al., *Correspondence, Response to Expression of Concern Regarding VIGOR Study*, 354 NEW ENG. J. MED. 1196, 1196-98 (2006) (addressing the concerns of Curfman et al.); Lancet Editors, Editorial, *Vioxx: An Unequal Partnership Between Safety and Efficacy*, 364 LANCET 1287, 1288 (2004) (noting that "the real picture of cardiovascular risk has been apparent for some time and Merck's vigorous defense of this drug in the past was clearly an error" and that "the Vioxx story is one of blindly aggressive marketing by Merck mixed with repeated episodes of complacency by drug regulators"); Richard Horton, Comment, *Vioxx, The Implosion of Merck, and Aftershocks at the FDA*, 364 LANCET 1995, 1995-96 (2004).

103. See William M. Sage, *Some Principles Require Principals: Why Banning "Conflicts of Interest" Won't Solve Incentive Problems in Biomedical Research*, 85 TEX. L. REV. 1413, 1413-18 (2007) (arguing that "conflicts of interest" as a term is used too broadly and thwarts effective responses to incentives in research). Conflicts of interests in research raise other issues, of course, including concerns over the protection of human subjects either because of misunderstandings or miscommunication of the purpose of the intervention or because of enrollment pressures. See, e.g., Kevin W. Williams, *Managing Physician Financial Conflicts of Interest in Clinical Trials Conducted in the Private Practice Setting*, 59 FOOD & DRUG L.J. 45, 68-69 (2004).

patients would be better off without it.¹⁰⁴ Furthermore, conflicts-of-interest regulation has limited usefulness as a tool for controlling for the impact of funding on the quality of clinical research.

JAMA's own response to the credibility crisis illustrates some of the limitations of the conflicts-of-interest response to perceived deficiencies in clinical research. JAMA, like other medical journals,¹⁰⁵ has instituted several policies to handle financial conflicts of interest related to articles submitted for publication.¹⁰⁶ Among those, the requirement of author disclosure of financial interests and the requirement of independent data analysis for industry-supported studies suggest that current responses to financial conflicts of interest in clinical research are imperfect at best.¹⁰⁷

C. DISCLOSURE AND SKEPTICISM

JAMA requires that authors disclose financial conflicts of interest related to the research reported in their submitted article. JAMA began requesting disclosure by authors in

104. Brennan et al., *supra* note 30, at 252–53; DeAngelis, *supra* note 91, at 996.

105. JAMA is a member of the International Committee of Medical Journal Editors (ICMJE), which has established conflict-of-interest policies that each member journal agrees to enforce. Members of ICMJE include the New England Journal of Medicine, The Lancet, Annals of Internal Medicine, and others. See ICMJE—Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, <http://www.icmje.org> (last visited Oct. 20, 2007).

106. For example, journal members of the ICMJE, including JAMA, in response to episodes of suppression of the results of studies, require that clinical trials be posted in a “public trials registry” as a condition of submission for publication. *Id.* One of the most highly publicized instances of alleged suppression involved study results indicating that the use of Paxil by adolescents suffering from depression may increase suicide rates for that population. Eliot Spitzer, the former Attorney General of New York, sued GlaxoSmithKline (GSK) for its actions in regard to Paxil. As part of the settlement, GSK agreed to establish a clinical trials registry on which it would post summaries of all clinical studies within ten months of the completion of the study. At the same time, several other pharmaceutical companies established similar sites. *GSK Will Disclose Clinical Trial Data, Settles Case Brought by New York AG*, 13 HEALTH L. REP. 1290, 1290 (2004). In a settlement just a few days later, Forest Laboratories agreed to establish a registry on which it would list its ongoing clinical trials as well as the results of completed trials. *Forest Laboratories to Create Registry Summarizing Clinical Trials of its Products*, 13 HEALTH L. REP. 1325, 1325 (2004).

107. See DeAngelis, *supra* note 91, at 997.

1985;¹⁰⁸ made disclosure mandatory in 1989;¹⁰⁹ began publishing author disclosures in 1990;¹¹⁰ and strengthened its disclosure requirements in 2006,¹¹¹ in response to concerns about author non-compliance with the Journal's prior disclosure requirements.¹¹² The purpose of publishing financial relationship disclosures, according to the Journal's editor-in-chief, is "so that readers can interpret the article in light of that information."¹¹³ It is not clear exactly how the reader, even the medically-trained reader, is to take the disclosed conflict into account in evaluating whether the article should influence prescribing decisions, however.

A quick look at recent issues of JAMA suggests the complexity of accounting for a disclosed relationship when evaluating an article as a source of information to incorporate in practice. In a selection of recent JAMA issues,¹¹⁴ at least one of the authors for approximately one-third (thirty-five of one-hundred-six) of articles categorized by the Journal as "Original Contributions" (thirty-one of ninety) or "Reviews" (four of sixteen) disclosed financial relationships.¹¹⁵ Four of the thirty-five instances of reported relevant financial relationships were by authors of Reviews, meta-analyses of previously published studies that are among the most influential articles in medical journals.¹¹⁶ Because "the essence of reviews and

108. Elizabeth Knoll & George D. Lundberg, Editorial, *New Instructions for JAMA Authors*, 254 JAMA 97, 97 (1985).

109. George D. Lundberg & Annette Flanagin, Editorial, *New Requirements for Authors*, 262 JAMA 2003, 2003 (1989).

110. DeAngelis, *supra* note 91, at 997.

111. Annette Flanagin, Editorial, *Update on JAMA's Conflict of Interest Policy*, 296 JAMA 220, 220 (2006).

112. DeAngelis, *supra* note 91, at 997 ("[T]here simply is no way to guarantee that all financial relationships and arrangements of all authors are disclosed.").

113. *Id.* at 997.

114. The sample consisted of every fourth issue published between January 5, 2005 and August 2, 2006 for a total of twenty issues.

115. It is likely, however, that more authors than actually disclosed such relationships had financial dealings with sponsors that would be covered by the JAMA disclosure requirement.

116. In one study, 73% of physician respondents reported that they used review articles as an information source. McAlister et al., *supra* note 33, at 236. These review articles may be attractive to physicians because they evaluate a number of articles. In the same survey, only 34% of respondent physicians believed that they were able to evaluate the methodology of a study

editorials is selection and interpretation of the literature,” the New England Journal of Medicine refuses to publish reviews by authors who have a “significant” financial interest relevant to the subject matter of the review, although it had to relax its prohibition in 2002 because of its inability to secure reviews of drug therapies under the former standards.¹¹⁷

Five of the twelve Reviews in JAMA for which no author made a financial disclosure involved review of an issue for which there is no apparent pharmaceutical connection in treatment or diagnosis, while seven Reviews addressed issues with obvious implication for drug therapies or diagnosis. All four of the Reviews written by authors who disclosed financial relationships, however, reviewed pharmaceutical interventions. Thus, of the seven Reviews with apparent pharmaceutical subject matter, more than half were written by authors with disclosable financial relationships. These numbers may actually under-report the proportion of JAMA articles written by authors with relevant financial interests as there have been some reports of authors failing to disclose required information.¹¹⁸

In an editorial published in JAMA describing the implementation of its disclosure policy, the editor-in-chief argued that all articles in JAMA have passed “rigorous peer review and careful editorial evaluation.”¹¹⁹ She went on to observe that the failure of authors of several articles published by JAMA to disclose required information in early 2006 “does not automatically translate to the article being flawed.”¹²⁰ Still, “[f]or disclosure to be effective, the recipient of advice must understand how the conflict of interest has influenced the advisor and must be able to correct for that biasing influence.”¹²¹

on their own and only 46% felt capable of doing a literature search. *Id.*

117. Jeffrey M. Drazen & Gregory D. Curfman, Editorial, *Financial Associations of Authors*, 346 NEW ENG. J. MED. 1901, 1901 (2002) (observing that the Journal had been able to secure only one review article on novel drug therapy over the course of two years under its former prohibition of any financial interest on the part of review authors).

118. DeAngelis, *supra* note 91, at 997.

119. *Id.*

120. *Id.*

121. Daylian Cain et al., *The Dirt on Coming Clean: Perverse Effects of Disclosing Conflicts of Interest*, 34 J. LEGAL STUD. 1, 3 (2005); see *supra* notes 32 and 34.

So, how should the practicing physician or practice guidelines development panel take the disclosed financial support into account and “correct for that biasing influence”? If JAMA publishes an article after applying its “rigorous” peer review process with the reviewers aware of the relevant financial interests, what more would the individual practicing physician be able to bring to the critique of the research? If the practicing physician is simply to be “skeptical,” the advice confirms the pattern of skepticism about scientific journals discussed earlier.¹²² If that pattern of skepticism is to be encouraged, then what should the physician rely on in deciding to prescribe medications off-label? Experience? Intuition? Peer opinion leaders? Enlarging the scope just a bit, how should consensus or practice guideline panels treat the one-third of JAMA articles that are written by authors with financial self-interest? These articles can hardly be eliminated from consideration because they are likely to be the only source of peer-reviewed data and may in fact be valid.

Disclosure does not itself remedy concerns with the quality of clinical information. Disclosure of conflicts of interest has not produced the desired response in the clinical context. The process of disclosing financial conflicts of interest may encourage the physician to grant him or herself a “moral license” to behave differently after making disclosure.¹²³ In addition, disclosure of conflicts of interest by the doctor in a therapeutic relationship may actually increase the patient’s trust level rather than putting them on guard.¹²⁴ The doctor-reader may behave differently than patients in this regard, however, because doctors tend to believe that other physicians may be influenced by their financial interests even while they believe they themselves are not.¹²⁵

D. BLESSED BY ACADEMIA

In an additional response to financial conflicts of interest in research, JAMA has established a special rule for independent statistical analysis for industry-sponsored studies.

122. See generally sources cited *supra* notes 32 and 34.

123. Cain et al., *supra* note 121, at 7.

124. *Id.* at 5–6.

125. Jason Dana, *A Social Science Perspective on Gifts to Physicians From Industry*, 290 JAMA 252, 254 (2003).

In 2005, JAMA began requiring that the authors of industry-sponsored studies in which data analysis was done “only by statisticians employed by the company sponsoring the research” submit an “independent analysis of the data . . . conducted by statisticians at an academic institution, such as a medical school, academic medical center, or government research institute” as a condition of consideration for publication.¹²⁶ The preference for biostatisticians working at an “academic institution” assumes that where the evaluation is conducted makes a difference. Furthermore, JAMA does not require independent data analysis of studies conducted and analyzed in academic institutions working under contract (such as through a research grant) with a for-profit industry sponsor.¹²⁷ By implication, industry sponsorship is less dangerous when the academy is industry’s partner.

In fact, a great deal of clinical research has moved out of the academic medical centers (AMCs) and into contract research organizations (CROs)¹²⁸ and private physician offices. Although estimates of the magnitude of the shift from AMCs to private physician offices or CROs vary, all agree that there has been a landslide in that direction and that it continues to grow. At most, 40% of the funding of clinical trials is currently being placed with academic medical centers; and 60% is being placed with private practices,¹²⁹ a three-fold increase in ten years. Fewer than half of researchers work in academic medical

126. Phil B. Fontanarosa et al., *Reporting Conflicts of Interest, Financial Aspects of Research, and Role of Sponsors in Funded Studies*, 294 JAMA 110, 111 (2005).

127. *See id.*

128. Contract Research Organizations are typically independent, for-profit companies that provide research services under contract with entities including pharmaceutical companies, the government and other groups engaged in clinical research. The CROs conduct basic research and clinical trials and also provide other services, including data and safety monitoring services, for researchers. CARL H. COLEMAN ET AL., *THE ETHICS AND REGULATION OF RESEARCH WITH HUMAN SUBJECTS* 78 (2005). CRO services may also include regulatory compliance support, quality control, and support for marketing. Richard A. Rettig, *The Industrialization of Clinical Research*, 19 HEALTH AFF. 129, 137–38 (2000). CROs also contract with site management service providers to assist doctors in private practice in recruiting patients for research protocols. K. Morin et al., *Managing Conflicts of Interest in the Conduct of Clinical Trials*, 287 JAMA 78, 79 (2002).

129. Morin et al., *supra* note 128, at 78; COLEMAN ET AL., *supra* note 128, at 77.

centers, representing an 80% decrease over ten years.¹³⁰ The number of physicians in private practice engaged in protocols tripled to nearly 12,000 between 1990 and 1995.¹³¹ Estimates of CRO participation in pharmaceutical research suggest an annual growth rate of approximately 20% between 1995 and 2000.¹³²

Research has become a profit center for the physician in private practice.¹³³ The sponsor typically pays the doctor a fee of between \$2000 and \$5000 per patient enrolled, sometimes requiring little beyond the collection of minimal data.¹³⁴ The NIH generally pays somewhat lower enrollment fees for research in AMCs.¹³⁵ According to a study published in 2000, doctors in private practice who engage in industry-funded studies also tend to receive additional compensation from sponsors.¹³⁶

This trend of moving clinical trials from academic medical centers to private practices will likely continue due to the attendant advantages. Post-marketing clinical trials require very large numbers of patients. Researchers may capture these numbers more quickly by paying private physicians to recruit their own patients rather than by paying an academic researcher to recruit individuals from the general population or from teaching hospitals.¹³⁷ Practicing physician researchers

130. Morin et al., *supra* note 128, at 78; see Jason E. Klein & Alan R. Fleischmann, *The Private Practicing Physician Investigator: Ethical Implications of Clinical Research in the Office Setting*, 32 HASTINGS CTR. REPT. 22, 22 (2002).

131. Mark Hovde & Robert Seskin, *Selecting U.S. Clinical Investigators*, APPLIED CLINICAL TRIALS 34, 36 (1997).

132. Rettig, *supra* note 128, at 134.

133. Payment for enrollment of patients in clinical trials can substantially exceed the amounts paid by Medicare or third-party payers for treating those patients. Morin et al., *supra* note 128, at 81; see also Deborah Borfritz, *Can "Phase IV" Trials Work for You?*, 80 MED. ECON. 58, 58 (2003), available at <http://www.memag.com/memag/article/articleDetail.jsp?id=111425> (describing benefits and obligations for research in private practice).

134. Morin et al., *supra* note 128, at 81.

135. NIH studies typically pay approximately \$1,000 per enrollee. *Id.*

136. Physicians engaging in such studies may also be paid consulting fees for giving a presentation, receive an educational stipend, or receive authorship on a journal article reporting the results from the research. Office of Inspector General, *supra* note 9, at 16.

137. See *id.* at 14–15; see also Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection,

and contract research organizations may be able to complete clinical trials more quickly than an AMC because universities often have additional administrative requirements.¹³⁸ In addition, clinical research at physicians' offices may provide better models for medical decision making due to the varying practice settings, patient backgrounds, and practitioner skill levels available in that environment.¹³⁹ Finally, as discussed in Part III of this article, funding post-approval studies in private medical offices may serve other non-research marketing interests for the pharmaceutical firms as well.¹⁴⁰

The JAMA policy requiring university or government analyses of data implies that the AMC provides a greater defense against industry behavior that undermines the reliability of clinical studies.¹⁴¹ The policy implies that the interests of the academic clinician researcher and the academic medical center will militate against acceptance of agreements allowing the sponsor to control publication of results; will more likely demand valid research design; and will be more likely to produce accurate data and reliable statistical analyses and interpretation. The assumption that academic researchers would be particularly sensitive to, and avoid, financial conflicts of interest is challenged by the fact that compliance with JAMA's relatively benign disclosure requirements has proven spotty among academic researchers at very well-respected research universities.¹⁴² Beyond questions of character or understanding¹⁴³ that might lie beneath these individual

69 Fed. Reg. 26,393, 26,394 (May 12, 2004).

138. Susanne Rust & Cary Spivak, *Drug-testing Industry Turns to Private Sector*, MILWAUKEE J. SENTINEL, Apr. 30, 2007, at A17; see Kevin Williams, *Managing Physician Financial Conflicts of Interest in Clinical Trials Conducted in the Private Practice Setting*, 59 FOOD & DRUG L.J. 45, 62-63 (2004) (discussing the perceived advantages of conducting clinical trials in private physician offices).

139. Tunis et al., *supra* note 41, at 1627; see *supra* note 65 and *infra* text accompanying notes 213-215.

140. See *supra* note 65 and *infra* text accompanying notes 213-215.

141. See generally Jesse A. Goldner, *Dealing with Conflicts of Interest in Biomedical Research: IRB Oversight as the Next Best Solution to the Abolitionist Approach*, 28 J.L. MED. & ETHICS 379 (2000).

142. DeAngelis, *supra* note 91, at 996; see also Goldner, *supra* note 141, at 384 (detailing the additional pressures in the academic environment that produce conflicts of interest).

143. See, e.g., David Henry et al., *Ties That Bind: Multiple Relationships Between Clinical Researchers and the Pharmaceutical Industry*, 165 ARCHIVES INTERNAL MED. 2493, 2495 (2005) (noting studies demonstrating that

instances of noncompliance, contemporary circumstances challenge the assumed singularity of interests in the academic research endeavor.

Elite research universities and their medical centers rely primarily on NIH funding to support their research efforts. Even in these institutions, however, industry-funded research enhances the discretionary budget by providing a margin that remains in the control of the department or the researcher rather than the university budget office.¹⁴⁴ AMCs other than the research elite may be losing the competition for the now shrinking NIH research dollar and hence increasingly rely on pharmaceutical research contracts to fill the gap.¹⁴⁵ The Bayh-Dole Act of 1980¹⁴⁶ significantly altered the interests of academic researchers and universities by introducing an incentive for entrepreneurship.

The Bayh-Doyle Act expedited the commercialization of inventions by giving research institutions ownership interests

physicians and researchers believe themselves to be “impervious to industry influence” despite the literature indicating that gifts trigger an “unconscious and unintentional” sense of obligation).

144. See Goldner, *supra* note 141, at 384 (describing budgeting and compensation processes). A 1996 study of the fifty universities receiving the highest level of NIH funding reported that 28% of their faculty received industry funding for research. David Blumenthal et al., *Participation of Life-Science Faculty in Research Relationships with Industry*, 335 NEW ENG. J. MED. 1734, 1734 (1996). More recent data reports that industry funds for research in universities increased by 875% between 1980 and 2000. Trudo Lemmens, *Leopards in the Temple: Restoring Scientific Integrity to the Commercialized Research Scene*, 32 J.L. MED. & ETHICS 641, 645 (2004) (citing SHELDON KRIMSKY, SCIENCE IN THE PRIVATE INTEREST: HAS THE LURE OF PROFIT CORRUPTED BIOMEDICAL RESEARCH? 79–81 (2003)). Elite universities have experienced significant increases. For example, industry funding contributes 31% of the overall budget at Duke University. The University of Texas reported an increase in private funding of 735%, and the University of California at San Francisco, 491%. *Id.*

145. U.S. universities are not alone in relying on industry funding. Between 2002 and 2004, for example, industry funding to McMaster University in Canada reportedly quadrupled from \$34 million to nearly \$129 million. Steve Buist et al., *Risks, Rewards & Research; Blind Faith—Part 1 of 5*, HAMILTON SPECTATOR, June 25, 2005, at A01. In addition, 15.5% of the full-time faculty had “financial connections” to pharmaceutical and biotechnology firms. *Id.* At the same time, pharmaceutical funding for research at the University of Toronto, one of the elite research universities in Canada, declined to less than 10% of the University’s total research funding. *Id.*

146. Bayh-Dole Act, Pub. L. No. 96-517, 94 Stat. 3015 (1980).

in the fruits of their government-funded research.¹⁴⁷ In a 2000 study, 124 of 183 institutions that were members of the Association of University Technology Managers reported that they held equity interests in businesses engaged in research at the university.¹⁴⁸ Start-up companies, like those stimulated by Bayh-Dole and often jointly owned by research faculty and their university-employers, have been associated with delays in publication of study results and resistance to sharing results,¹⁴⁹ mirroring the issues concerning sponsor control of research discussed above. At a minimum, then, rules applicable to “industry” should not be restricted only to large, for-profit pharmaceutical firms, but should also consider the smaller start-ups owned by research faculty and the universities themselves. Moreover, the narrow target of the JAMA policy exemplifies another attempt to make the challenge to clinical research more manageable by drawing boundaries that lack a grounding in reality.

E. THE PRACTICE GAP

Industry influence is not the only issue affecting the utility of clinical trials for prescribing decisions. Critics of the current state of clinical research focus on faults in the design of studies that have little or nothing to do with industry sponsorship and conflicts of interest. For example, current studies of health outcomes in clinical trials frequently suffer from two forms of design flaws. First, many clinical studies rely on observation and self-reporting as the primary tool for evaluating effectiveness.¹⁵⁰ Although these tools are unavoidable in some

147. See generally Clovia Hamilton, *University Technology Transfer and Economic Development: Proposed Cooperative Economic Development Under the Bayh-Dole Act*, 36 J. MARSHALL L. REV. 397 (2003); Gary Pulsinelli, *Share and Share Alike: Increasing Access to Government-Funded Inventions Under the Bayh-Dole Act*, 7 MINN. J.L. SCI. & TECH. 393 (2006).

148. AUTM, AUTM LICENSING SURVEY, FY 1999: SURVEY SUMMARY 17 (Lori Pressman ed., 2000), available at <http://www.autm.net/events/File/Surveys/99AUTMLicSurveyPublic.pdf>.

149. David Blumenthal et al., *Withholding Research Results in Academic Life Science: Evidence from a National Survey of Faculty*, 277 JAMA 1224, 1227 (1997); Eric G. Campbell et al., *Data Withholding in Academic Genetics: Evidence from a National Survey*, 287 JAMA 473, 479 (2002); Joel Lexchin, *The Secret Things Belong Unto the Lord Our God: Secrecy in the Pharmaceutical Arena*, 26 Med. & L. 417, 421 (2007) (reviewing data on suppression of research results in academia).

150. Tunis et al., *supra* note 41, at 1627.

circumstances they tend to suffer from bias.¹⁵¹ Second, most clinical trials are not designed with the clinical decision-making process in mind. In order to remedy this latter problem, some have recommended encouraging “pragmatic” or “practical” clinical trials (PCTs). PCTs are targeted toward producing information needed for clinical decision making.¹⁵² These studies compare clinically relevant interventions, feature a diverse population of study participants, recruit practitioners from a variety of settings, and collect data on a broad range of health outcomes.¹⁵³ PCTs should also include patients from high-risk populations and must use diagnostic indicators that are commonly used in practice, which may be less definitive than other more sophisticated but less available diagnostic tools.¹⁵⁴ Researchers should also select patients who replicate the typical clinical population in terms of history of medication and of preexisting medical conditions, characteristics that are typically excluded in clinical trials.¹⁵⁵ In addition, the studies should compare effectiveness, cost, and safety among available drugs and between medications and non-pharmaceutical therapies.¹⁵⁶ Finally, clinical trials with relevancy for clinical decision making should account for variations in the quality of physician skills, since this may have a substantial impact on

151. See, e.g., Ellen T. Chang et al., *Reliability of Self-Reported Family History of Cancer in a Large Case-Control Study of Lymphoma*, 98 J. NAT'L CANCER INST. 61, 61 (2006) (concluding that recall bias may produce biased results in studies of familial cancer risk), available at <http://jnci.oxfordjournals.org/cgi/content/full/98/1/61>; Y. Fukuoka et al., *Systematic Bias in Self-Reported Annual Household Incomes Among Unpartnered Elderly Cardiac Patients*, 20 APPLIED NURSING RES. 205, 205 (2007) (concluding that there is “potential systematic bias regarding self-reporting of annual household income” with implications for studies of the impact of income).

152. Martin Roland & David J. Torgerson, *What are Pragmatic Trials?*, 316 BRIT. MED. J. 285, 285 (1998); Daniel Schwartz & Joseph Lellouch, *Explanatory and Pragmatic Attitudes in Therapeutic Trials*, 20 J. CHRONIC DISEASE 637, 639 (1967).

153. Tunis et al., *supra* note 41, at 1626.

154. *Id.*

155. Margaret A. Handley et al., *Navigating the Terrain Between Research and Practice: A Collaborative Research Network (CRN) Case Study in Diabetes Research*, 19 J. AM. BOARD FAM. MED. 85, 89 (2006), available at <http://www.jabfm.org/cgi/content/full/19/1/85> (noting need to test “whether research findings from homogenous populations . . . are generalizable to more diverse ones such as those encountered in ‘real world’ practices”); Office of Inspector General, *supra* note 9, at 14.

156. Tunis et al., *supra* note 41, at 1626.

the effectiveness of a therapy.¹⁵⁷

Removing or regulating conflicts of interest in research will not stimulate more clinically-useful design. Furthermore, off-label prescribing and other treatment decisions confront serious quantity and timeliness issues in clinical knowledge. Several experts, for example, have noted that current clinical research endeavors are not producing “an adequate supply of information to meet the needs of clinicians and health policy decision makers.”¹⁵⁸ The lack of a clinically focused research agenda reduces the effectiveness of practice guidelines, which lack clear and specific recommendations,¹⁵⁹ and hampers payers attempting to make scientifically grounded coverage decisions with serious implications for substantive controls on off-label prescribing.¹⁶⁰ One cannot explain this insufficiency by financial conflicts of interest. In fact, restrictions on industry funding of research are likely to diminish the production of necessary clinical knowledge.¹⁶¹

Widespread concern for the credibility and reliability of clinical research in pharmaceuticals is apparent, but the solution is not. The conflict-of-interest framework, especially to the extent that it relies on disclosure, does not effectively respond to the issue of the quality of particular articles. It merely raises a nonspecific warning flag on the data that is often countered by the peer-review “seal of approval” for published studies. Counterintuitively, the warning flag may actually decrease sensitivity to conflicts of interest by creating a false impression of trustworthiness, as such disclosures have in the clinical setting,¹⁶² or conversely by reducing such disclosures to background chatter because of the pervasiveness of industry support for clinical trials. Efforts to assure that pharmaceutical firms do not cook the data or misinterpret the results of a trial are completely justifiable. Exhorting them to voluntarily select and fund studies that do not contribute to or that may undermine their competitive position is probably futile, except in situations where harm to patient safety is at

157. *See id.* at 1627.

158. *Id.* at 1625 (citations omitted); *see also* Soumerai, *supra* note 28, at 142 (referencing the gap in timeliness and noting that “drug cost containment policy making often cannot wait for good evidence”).

159. Tunis et al., *supra* note 41, at 1625.

160. *Id.*

161. *See supra* text accompanying notes 72–81, 104.

162. *See supra* notes 121–124 and accompanying text.

issue and legal, reputational, and even moral concerns are more acute. Other options for increasing the volume of post-approval clinical research beyond that required for safety surveillance typically require accounting for the cost of such research somewhere.¹⁶³

Although the conflicts-of-interest tool addresses one aspect of imperfection in prescribing information, it does so only roughly. In addition, it does not contribute to stimulating the conduct of Phase IV trials, and may instead actually depress the development of post-marketing research. Finally, the conflicts-of-interest approach does not provide a reliable method for distinguishing between appropriate and inappropriate prescribing.

PART III: FALSE CLAIMS ACT LITIGATION AND OFF-LABEL PRESCRIBING

Over the past three years, the Department of Justice (DOJ) has enjoyed tremendous success in pursuing False Claims Act actions against pharmaceutical firms relating to off-label prescribing and post-approval relationships with prescribing physicians.¹⁶⁴ The \$430 million settlement and guilty plea by the manufacturer of a single drug, Neurontin, ranks as one of the most significant DOJ victories.

The Neurontin-style litigation, whether hailed as “the best hope for short-term reform”¹⁶⁵ or condemned as “inefficient” and “overly-aggressive,”¹⁶⁶ is most often viewed as a

163. See, e.g., Daniel Carpenter, *A Proposal for Financing Postmarketing Drug Safety Studies by Augmenting FDA User Fees*, HEALTH AFF., Web Exclusive, Oct. 18, 2005. The FDAAA of 2007 increased user fees. Pub. L. No. 110-85 § 302, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.); see also discussion of the Best Pharmaceuticals for Children Act, *supra* note 24–26, which uses extended market exclusivity to compensate firms for testing approved drugs in post-approval clinical trials with children.

164. See *supra*, note 11; see also Dayna Bowen Matthew, *The Moral Hazard Problem with Privatization of Public Enforcement: The Case of Pharmaceutical Fraud*, 40 MICH. J.L. REFORM 281, 283–84 (2007) (describing magnitude of government litigation efforts in this context).

165. David J. Rothman, *Strong Medicine*, NEW REPUBLIC, Sept. 27, 2004, at 36.

166. Christopher D. Zalesky, *Pharmaceutical Marketing Practices: Balancing Public Health and Law Enforcement Interests; Moving Beyond Regulation Through Litigation*, 39 J. HEALTH L. 235, 264 (2006); see also Ralph Hall & Robert Berlin, *When You Have a Hammer, Everything Looks*

dramatization of financial conflicts of interest in research and clinical decision making fueled by pharmaceutical industry practices relating to prescribing.¹⁶⁷ It certainly is that. Although never formally resolved by verdict or final judgment,¹⁶⁸ the evidence strongly suggests that Parke-Davis,¹⁶⁹ the defendant manufacturer of Neurontin, had used both educational and research efforts as vehicles to market the drug aggressively for off-label uses.¹⁷⁰

Other insights emerge, however, when the course of the litigation and settlement are set parallel to contemporaneous and subsequent patterns of off-label prescribing for Neurontin. Viewed in that context, the difficulties that arise in evaluating whether a particular off-label prescription is itself actually a “false claim” or in some other fashion inappropriate come into a

Like a Nail: Misapplication of the False Claims Act to Off-Label Promotion, 61 FOOD DRUG L.J. 653, 653 (2006).

167. See *The Indictment of Pharma Industry Marketing Practices*, INTERNAL MED. ALERT, Oct. 15, 2006; Valerie Jablow, *Lawsuits Fault Off-Label Use of Neurontin in Suicide Cases*, TRIAL, NOV. 2004 at 12, 12–14.

168. It is unlikely that pharmaceutical defendants in fraud and abuse prosecutions will proceed to trial for a final judgment of violation of the statutes, as a 1996 federal statute provides that a Medicare or Medicaid provider found guilty of such violations must be excluded from those programs. Thomas S. Crane et al., *Congress Strengthens Anti-Fraud and Abuse Juggernaut*, 5 HEALTH L. REP. 37, 37 (Sept. 19, 1996); Edward P. Lansdale, *Used As Directed? How Prosecutors are Expanding the False Claims Act to Police Pharmaceutical Off-Label Marketing*, 41 NEW ENG. L. REV. 159 (2006). In fact, in the Neurontin settlement, Parke-Davis pled guilty of violations only for behavior prior to 1996, apparently to avoid exclusion from these reimbursement programs.

169. Parke-Davis was the named defendant at the initiation of this litigation. This article refers to the defendant firm as Parke-Davis even though Warner-Lambert was the signatory for the settlement. Parke-Davis was a division of Warner-Lambert at that time. Warner Lambert merged with Pfizer in 2000. Pfizer agreed to a corporate compliance program for Warner-Lambert as part of the 2004 settlement agreement. For a lineage of the relationship among these firms, see http://www.pfizer.com/about/history/2000_present.jsp.

170. Michael A. Steinman et al., *Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents*, 145 ANNALS OF INTERNAL MED. 284, 285–88 (2006) (analyzing internal Parke-Davis documents concerning activities relating to prescribing of Neurontin and concluding that continuing medical education and research were used to promote Neurontin but noting that the documents were supplied by the relator’s attorneys). Interestingly, three of the authors of that article served as unpaid expert witnesses in the litigation, a fact that is acknowledged within the text of the article, but is not revealed in the head material for the article. Phil Kabler, *Marketing Predated Firm’s Purchase, Pfizer Says*, CHARLESTON GAZETTE, Aug. 23, 2006, at 3C.

sharper focus. Furthermore, the disreputable connotation of “off-label” as non-scientific or fraudulent is challenged by the subsequent FDA approval of Neurontin for particular indications that had become quite popular while in their “off-label” stage and were, in fact, listed among the uses for which prescriptions were false claims.¹⁷¹ The discussion of the case, thus, highlights the deficiencies in current forms of clinical research,¹⁷² both in making prescribing decisions and in regulating those decisions. The case illustrates quite sharply the importance of appreciating the issue of off-label prescribing as more than simply an issue of inappropriate financial relationships in medicine and the challenge of regulating off-label prescribing in light of medical ways of knowing and learning.

Government regulation of pharmaceutical industry activities in post-approval marketing and funding research has been weak.¹⁷³ Provisions of the Food, Drug, and Cosmetic Act

171. See *infra* text accompanying note 241; see Lansdale, *supra* note 168, at 159.

172. See discussion in Part III.

173. For a comprehensive overview of laws governing post-approval marketing of off-label uses for approved drugs, see Stephanie Greene, *False Claims Act Liability for Off-Label Promotion of Pharmaceutical Products*, 110 PENN. ST. L. REV. 41 (2005). Private efforts to set boundaries on appropriate behavior in relationships between industry and researchers/prescribers have been increasing. In addition to the journal policies discussed earlier, professional medical societies, including the AMA, and the drug industry trade association (PhRMA), have issued guidelines for relationships between prescribers and the companies. AM. MED. ASS'N, CODE OF ETHICS E-8.06: PRESCRIBING AND DISPENSING DRUGS AND DEVICES (2002), available at <http://www.ama-assn.org/ama/pub/category/8483.html>; CODE ON INTERACTIONS WITH HEALTHCARE PROFESSIONALS (PhRMA 2004), available at <http://www.phrma.org/files/PhRMA%20Code.pdf>; see also AM. ACAD. OF FAMILY PHYSICIANS, DISCLOSURE OF CORPORATE TIES AFFECTING FORMULARY CHOICES AND DRUG SUBSTITUTION (1998, revised 2004), available at <http://www.aafp.org/online/en/home/policy/policies/d/drugs.html>. The Office of Inspector General of the Department of Health and Human Services has recommended compliance with the private PhRMA guidelines “as a good starting point for compliance purposes.” 67 Fed. Reg. 62,057, 62,063 (Oct. 3, 2002). A few private universities also have established their own policies restricting or prohibiting particular marketing and educational activities on the part of pharmaceutical firms. Stanford University Medical Center, for example, enacted a new policy on October 1, 2006, which prohibits physicians from accepting industry gifts, including drug samples, anywhere on the medical center campus or at off-site clinical facilities. The policy further bars “pharmaceutical, bio-device and related industry representatives from patient care areas and medical school facilities except for in-service training on

restrict,¹⁷⁴ but do not entirely prohibit, post-approval marketing of approved drugs for off-label uses. In addition, court decisions concerning the constitutional boundaries on the authority of the agency to confine commercial speech have hampered aggressive enforcement of these provisions.¹⁷⁵ Furthermore, the FDA largely relies on voluntary compliance with its marketing restrictions and has devoted only limited resources to post-approval marketing surveillance.¹⁷⁶ Some have argued that the FDA's relative inactivity in this arena is not due to regulatory philosophy or to limitations in resources but rather is due to the influence of pharmaceutical interests.¹⁷⁷ Although some states have enacted statutes to address issues in the marketing of drugs, these efforts are relatively new and undeveloped and rely primarily on disclosure mechanisms.¹⁷⁸

Federal agencies also regulate post-approval pharmaceutical research efforts through the mechanisms that govern research with human subjects generally.¹⁷⁹ These

devices and equipment and by appointment only, as well as allowing industry support of educational activities only under well-regulated conditions." *New Stanford Medical Center Policy Limits Drug Company Access and Gifts*, MED. DEVICES (Oct. 15, 2006), available at http://med.stanford.edu/news_releases/.

174. See 21 U.S.C. § 321(n) (2000); 21 U.S.C. § 352(n) (2000 & Supp. IV 2005).

175. See *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998). The Washington Legal Foundation has established a project called "FDA/DDMAC Watch" through which it challenges FDA interventions in post-approval marketing. See <http://www.wlf.org/Resources/DDMAC/> (last visited 9/28/06); see Nicole Endejann, *Is the FDA's Nose Growing?: The FDA Does Not "Exaggerate Its Overall Place in the Universe" When Regulating Speech Incident to "Off-Label" Prescription Drug Labeling and Advertising*, 35 AKRON L. REV. 491, 505 (2002); David M. Fritch, *Speak No Evil, Hear No Evil, Harm the Patient? Why the FDA Needs to Seek More, Rather Than Less, Speech From Drug Manufacturers on Off-Label Drug Treatments*, 9 MICH. ST. U. J. MED. & L. 315, 334 (2005).

176. See Zalesky, *supra* note 166, at 257 (describing the FDA's policy of voluntary compliance and limited staff devoted to all advertising and marketing issues of approved drugs).

177. David Rothman notes that the OIG, in contrast to the FDA, seems to be "oddly . . . immune to political pressure as they try to rein in drug companies." Rothman, *supra* note 165, at 36.

178. See Zalesky, *supra* note 166, at 253; see, e.g., D.C. CODE § 48-833.01 (2004).

179. See, e.g., 45 C.F.R. § 46.101-409 (regulating research funded by the Department of Health and Human Services); 21 C.F.R. § 50.1-50.56 (regulating research funded by the FDA or which will be submitted to the FDA in relation to agency action). These requirements have a broader reach than

regulations, often called the “Common Rule” because they have been promulgated in similar form by several federal agencies to govern private and public research that arises in the scope of their work, focus on protecting the individuals who participate as subjects in research protocols.¹⁸⁰ These regulations generally delegate enforcement of the protective standards to the private research organization or university itself with only a second front of government oversight that has varied over time in its activity level. Several of the agencies, including the FDA, that share this “Common Rule” have issued guidance or regulations concerning financial relationships between researchers and sponsors, including sponsors of pharmaceutical research.¹⁸¹ Essentially, these conflicts-of-interest regulations rely on the same delegation to private research organizations that characterizes the “Common Rule” generally. The conflicts-of-interest guidance or regulations require that the research organization have a written policy; that researchers disclose conflicts of interest to the research organization; that the organization operate an internal review mechanism; and that the organization manage, reduce or eliminate conflicts of interest, as appropriate.¹⁸² Guidance on conflicts of interest in research from the Department of Health and Human Services is even more general, and consists mostly of questions and points that the institution might consider in implementing an internal conflict-of-interest policy, while the FDA provides for agency evaluation of financial interest disclosures that exceed

indicated in the regulations themselves as research universities typically agree to apply the federal regulations to all research conducted within the university or by university employees. COLEMAN ET AL., *supra* note 128, at 107.

180. See COLEMAN ET AL., *supra* note 128, at 106.

181. See, e.g., 21 C.F.R. § 54.4 (FDA); 42 C.F.R. § 50.604 (HHS). Conflicts-of-interest regulation is justified as an element of protecting the subjects of research for two reasons. First, research with human subjects must provide benefits that outweigh the risks of the studies; and to the extent that conflicts of interest may compromise the validity or usefulness of the results, they may alter the risk-benefit calculus. Second, conflicts of interest may lead to overaggressive enrollment of individuals with inattention to consent or exclusion criteria.

182. 42 C.F.R. § 50.604 (2006); 68 Fed. Reg. 15,456-01 (Mar. 31, 2003); see, e.g., Harrington *supra* note 96, at 793; U.S. GEN. ACCOUNTING OFFICE, UNIVERSITY RESEARCH: MOST FEDERAL AGENCIES NEED TO PROTECT AGAINST FINANCIAL CONFLICTS OF INTEREST, REPORT TO THE HONORABLE RICHARD C. SHELBY, U.S. SENATE 17 (2003).

statutory thresholds.¹⁸³

In contrast to the limitations imposed upon or adopted by the FDA in regulating industry-prescriber interactions, the DOJ and the Office of Inspector General (OIG) of the Department of Health and Human Services have adopted an aggressive litigation strategy to regulate industry post-approval marketing and clinical research funding, especially as these relate to off-label prescribing. In fact, the OIG has identified industry-prescriber relationships as a primary target for enforcement efforts.¹⁸⁴ The DOJ and OIG wield an assault weapon in the form of civil and criminal enforcement of statutes designed to protect the government's financial interests in public programs,¹⁸⁵ such as Medicare and Medicaid, and to establish boundaries on post-approval marketing and funding of research by pharmaceutical firms.¹⁸⁶ This high-profile litigation strategy is currently the primary "regulatory" effort for off-label marketing, industry-funded clinical trials, and prescribing. The Neurontin litigation discussed in this section is the most notable episode in this effort.

The FDA approved Neurontin (gabapentin) in 1994 for use as adjunctive therapy for epilepsy.¹⁸⁷ Shortly after its approval, physicians were prescribing Neurontin as a

183. 42 C.F.R. § 50.604 (2006); 21 C.F.R. § 54.4 (2007). FDA regulations require that applicants for FDA action submit either a certification that investigators of submitted studies do not have conflicts of interest or a disclosure statement that discloses the investigator's financial interests that do exist. For investigators disclosing such financial interests, the FDA evaluates the nature of the interests and the steps that have been taken to eliminate "bias created by a disclosable financial interest."

184. Lansdale, *supra* note 168, at 180; Marc J. Scheineson and Shannon T. Klinger, *Lessons From Expanded Government Enforcement Efforts Against Drug Companies*, 60 FOOD & DRUG L.J. 1, 1 (2005); Robert Brady et al., *Pharmaceutical Companies Have Been Penalized for Pushing Their Products for Unapproved Uses*, NAT'L L.J., Mar. 20, 2006 (detailing recent actions and settlements); *see also supra* note 11.

185. 42 U.S.C. § 1320a-7(b) (2000) (anti-kickback statute); 31 U.S.C. § 3729-33 (2000) (false claims act).

186. Although this article focuses on pharmaceuticals, similar issues have arisen in the promotion of medical devices. *See, e.g.*, Reed Abelson, *Whistle-Blower Suit Says Device Maker Generously Rewards Doctors*, N.Y. TIMES, Jan. 24, 2006, at C1; *see also* United States *ex rel.* Gilligan v. Medtronic, Inc., 403 F.3d 386 (6th Cir. 2005).

187. United States *ex rel.* Franklin v. Parke-Davis, 147 F. Supp. 2d 39, 45 (D. Mass. 2001); *see also* Neurontin, in PHYSICIANS' DESK REFERENCE 2462 (2008).

monotherapy for epilepsy; for pain control for a large number of pain states, including post-herpetic neuropathy; for bipolar disorder; for attention deficit disorder; for ALS; for migraine; for restless leg syndrome; for sleep disorders; and for a variety of other uses.¹⁸⁸ In fact, in 1995, one year after approval of Neurontin, 40% of the prescriptions written for the medication were for off-label indications.¹⁸⁹

The Neurontin litigation began when Dr. David Franklin, a medical liaison employed by Parke-Davis, filed a *qui tam* action in 1996. In his lawsuit, Franklin alleged that Parke-Davis illegally incentivized physicians to write prescriptions for Neurontin which would be paid for by government medical payment programs, including Medicare, Medicaid and Veterans' Administration programs. Franklin argued, among other theories, that these prescriptions amounted to false claims against the government in violation of the False Claims Act.

Defendant Parke-Davis filed a motion to dismiss Franklin's claims on several grounds, but were largely unsuccessful in regard to claims relating to Neurontin.¹⁹⁰ Parke-Davis argued that it had not filed a single claim for reimbursement from any governmental entity for prescriptions for Neurontin. It argued that because only physicians can prescribe, it was only the

188. Lansdale, *supra* note 168, at 159.

189. Julie Schmit, *Drugmaker Admitted Fraud, But Sales Flourish*, USA TODAY, Aug. 17, 2004, at 1A. Prescribing patterns for Neurontin during the litigation and after the settlement are described *infra* at text accompanying notes 225–229.

190. The court did dismiss the relator's claims relating to Accupril, another drug produced by Parke-Davis for insufficient specificity in pleading. *Franklin*, 147 F. Supp. 2d at 50. The court also dismissed the claims relating to violation of the anti-kickback statute. *Id.* at 54. The court in a later opinion denied the relator's motion to amend its pleadings on this particular claim, commenting that the relator's new theory "may well be viable," but that the delay in filing the motion to amend would prejudice the defendant. *United States ex rel. Franklin v. Pfizer*, No. Civ. A. 96-11651, 2002 U.S. Dist. LEXIS 5761, at *4 (D. Mass. Feb. 6, 2002). The court granted the defendant's motion to dismiss the relator's count for false claims against the Veterans' Administration for Neurontin prescriptions for lack of the required specificity in pleading, but denied the motion in relation to the Medicaid program. *Franklin*, 147 F.Supp.2d at 49–50. The standards for specificity in pleading false claims actions of this sort may have heightened since this decision. *See, e.g., United States ex rel. Rost v. Pfizer*, 466 F. Supp. 2d 6, 6 (D. Mass. 2006); *see also United States ex rel. McDermott v. Genentech*, 2006 WL 3741920 at *10–*12 (D. Me. Dec. 14, 2006).

physicians who had filed a claim, whether false or not.¹⁹¹ The doctors, according to Parke-Davis, were an “intervening force” and as such the necessary causal link between its own behavior and the false claims was missing. According to the court, however, the doctors’ actions were foreseeable and were, in fact, the “intended consequence of the alleged scheme of fraud,” satisfying the requirement of causation.¹⁹²

Parke-Davis also argued that the False Claims Act could not be used to enforce the FDCA’s restrictions on promotion of approved drugs for off-label uses. The court rejected this argument holding that violation of the anti-promotion provisions of the FDCA could be pursued under the False Claims Act if the violation of the FDCA “amounts to a material misrepresentation made to obtain a government benefit.”¹⁹³ In the view of the court, the False Claims Act simply provided tools not available to the FDA, including civil money damages and private enforcement, for the enforcement of its restrictions on promotion of off-label uses.¹⁹⁴

The court contended with two central issues in applying false claims standards to Parke-Davis’s marketing efforts. First, while particular activities, such as discussing off-label uses without an initial physician inquiry, may formally violate the FDCA restrictions on marketing, can those communications properly be considered false claims unless the representations themselves are inaccurate or false? Second, if the non-approved indications for which the drug is marketed and prescribed are legitimate uses covered by the federal payment program, can they be false claims by virtue of their status as off-label or by the very fact that the firm had marketed these off-label uses to doctors?

The court rejected the firm’s argument that off-label promotions, even when in violation of the FDCA, are not *per se* false statements within the meaning of the False Claims Act. The court rejected this argument, apparently relying on the relator’s claims in this particular case that the firm knowingly made false statements about the drug’s performance.¹⁹⁵ The

191. This defense mimics the “learned intermediary” defense that has been available to pharmaceutical manufacturers in products liability suits.

192. *Franklin*, 147 F. Supp. 2d at 53.

193. *Id.* at 51.

194. *Id.*

195. *Id.* at 52.

court in this opinion, however, stated that “[a] much closer question would be presented if the allegations involved only the unlawful—yet truthful—promotion of off-label uses”¹⁹⁶

In considering Parke-Davis’s later submission of a motion for summary judgment, however, the court revisited the issue of whether truthful information provided to physicians, but still an illegal promotion under the FDCA, could form the root of a false claim for prescribing.¹⁹⁷ In this later unpublished opinion, the court concluded that defendant’s “non-fraudulent” promotion of Neurontin for off-label uses could, indeed, result in a false claim, but *only* if the Medicaid program did *not* cover the off-label uses at issue.¹⁹⁸ Thus, there would be no false claim in the case of non-fraudulent promotional efforts that nonetheless violated the FDCA if the state Medicaid program covered the specific off-label prescriptions at issue.¹⁹⁹

According to the court’s opinion ruling on the firm’s motion to dismiss, Parke-Davis did *not* “dispute that an off-label prescription submitted for reimbursement by Medicaid is a false claim” in its motion to dismiss the *qui tam* action.²⁰⁰

196. *Id.*

197. United States *ex rel.* Franklin v. Pfizer, No. Civ. A. 96-11651, 2002 WL 32128635, at *1 (D. Mass. Feb. 6, 2002).

198. Standards for coverage of prescriptions for off-label uses under Medicaid is discussed *infra* at text accompanying notes 252–257.

199. United States *ex rel.* Hess v. Sanofi-Synthelabo, Inc., No. 4; 05CV570, 2006 WL 1064127, at *6 (E.D. Mo. Apr. 21, 2006), the court interprets the earlier *Parke-Davis* decision (147 F. Supp. 2d 30) as requiring that the information provided to doctors by the pharmaceutical firm concerning off-label uses be “false information” in order to support a claim under the False Claims Act. In *Hess*, the court dismissed the *qui tam* action against the defendant pharmaceutical firm because the information on the drug’s performance for the off-label use was “at most, immature, unreliable and misleading,” but not false. *Sanofi-Synthelabo, Inc.*, 2006 WL 1064127, at *9; *see also* United States *ex rel.* McDermott v. Genentech, 2006 WL 3741920 at *13 (D. Me. Dec. 14, 2006), dismissing relator’s *qui tam* False Claims Act claim relating to defendant’s promotion of off-label use of a biological product in part because the off-label use was reimbursable under Medicaid as that use was listed in one of the statutory compendia despite evidence that Genentech had pursued an aggressive marketing campaign that included allegations of ghostwriting of journal articles. *Hess* and *Genentech* raise significant questions about the continued viability of *qui tam* actions relating to off-label promotion and certainly challenge the extensive reach of the standards used in *Parke-Davis*. They do not necessarily diminish the ability of the DOJ to get settlements for government claims regarding the same behaviors, however. *See supra* note 168.

200. *Franklin*, 147 F. Supp. 2d at 51.

Even though Parke-Davis apparently did not dispute this proposition at that point in this litigation, it is not an accurate statement of the law. It is well-established that Medicaid programs must cover off-label prescriptions under certain circumstances.²⁰¹ Under the Medicaid program, prescription drugs are not covered if the drugs are prescribed “for a medical indication which is not a medically accepted indication.”²⁰² An off-label or unapproved use, however, can be a “medically accepted indication” under the Medicaid statute if the off-label indication is included in one of the drug compendia listed in the federal statute.²⁰³ The court in its opinion denying the motion to dismiss states that none of the off-label uses at issue in the litigation were listed in any of the compendia during the time covered by the lawsuit.²⁰⁴ In its later opinion denying Parke-Davis’s subsequent motion for summary judgment, however, the District Court further studied the question of whether the off-label uses of Neurontin were covered by Medicaid, at this point viewed by the court as a key question in whether a False Claims Act action for promotion of off-label uses would survive. In its motion for summary judgment, the defendant argued that forty-two state Medicaid programs covered “off-label, non-compendium” prescriptions.²⁰⁵ While the court does not resolve whether states, in fact, have such latitude under the federal Medicaid statute, it concludes that at least eight states did not provide coverage for off-label, non-compendium prescriptions and that, at least as to those states, the False Claims Act claims could survive. The court holds that the defendant’s argument thus goes to the amount of damages rather than to whether there are sufficient facts to support a claim.²⁰⁶

201. See, e.g., *Weaver v. Reagan*, 886 F.2d 194 (8th Cir. 1989); see *infra* text accompanying notes 245–250.

202. 42 U.S.C. § 1396b(i)(10) (2000).

203. 42 U.S.C. § 1396r-8(k)(6) (2000); 42 U.S.C. § 1396r-8(g)(1)(B)(i) (2000).

204. *Franklin*, 147 F. Supp. 2d at 45. Several of the off-label uses at issue in this case were also at issue in subsequent litigation relating to Medicaid coverage of Neurontin for off-label uses. At least at the time of the latter case, the off-label indications were listed in some of the compendia. See *infra* discussion at notes 246–249.

205. *United States ex rel. Franklin v. Parke-Davis*, No. Civ.A. 96-11651, 2003 WL 22048255, at *2 (D. Mass. Aug. 22, 2003). Medicaid is a joint federal-state program in which the federal statute and regulations provide a framework and minimums for coverage, allowing the states discretion on particular items.

206. *Id.* at *3.

The Department of Justice, which had monitored the Neurontin litigation from its filing by the private relator,²⁰⁷ took an active role in the litigation after the District Court's rulings denying the defendant's motion to dismiss and motion for summary judgment.²⁰⁸ Once it entered the case, the DOJ resurrected the allegation of false claims against the Veterans' Administration,²⁰⁹ which had been dismissed by the trial judge. In addition, state attorneys general joined the action to file claims to recover the payments made by their states under the federal-state Medicaid program as well as claims under state consumer protection statutes.²¹⁰

The DOJ characterized Parke-Davis's actions as "a widespread, coordinated national effort to implement an off-label marketing plan."²¹¹ As is often the case in *qui tam* litigation, internal communications provided the interpretive framework or narrative for the government's suit. First, a Parke-Davis marketing executive allegedly told the company's medical liaisons that the FDA-approved use for Neurontin "is not where the money is. I want you out there every day selling Neurontin" for off-label uses.²¹² In addition, an advertising firm working for the company produced a report entitled "1998 Neurontin Tactics" which recommended that the company hold educational programs on the use of Neurontin for bi-polar disorder and other off-label uses of the drug.²¹³

207. The district court notes that the suit was "in limbo" from its filing in 1996 until 1999 "while the United States mulled over its option to intervene." *Franklin*, 147 F. Supp. 2d. at 46.

208. In the 2003 proceeding, the federal government had filed only a "statement of interest" and had not yet intervened. *Franklin*, 2003 WL 22048255, at *1.

209. Department of Justice, *supra* note 5.

210. *See, e.g.*, *Rubel v. Pfizer, Inc.*, 276 F. Supp. 2d 904 (N.D. Ill. 2003). Many of the states that received funds through the settlement agreement used a portion of the proceeds to support programs on physician prescribing practices. *See, e.g.*, Press Release, Or. Dep't of Justice, Attorney General Myers Announces Prescription Drug Education Grants (Nov. 1, 2006), available at <http://www.doj.state.or.us/releases/2006/rel110106.shtml>.

211. Department of Justice, *supra* note 5; *see also* Steinman et al., *supra* note 170 (concluding that Parke-Davis's educational and research efforts were both part of the marketing plan for Neurontin).

212. Douglas McLeod, *Lawsuits Mount Over Marketing of Epilepsy Drug*, BUS. INS., June 14, 2004, at 3.

213. CLINE ET AL., 1998 NEURONTIN TACTICS 5932, available at <http://dida.library.ucsf.edu/pdf/ida00a10>.

Particular educational/marketing activities alleged by the DOJ to be illegal included encouraging sales representatives to pitch off-label use without a prior inquiry from the physician in violation of FDA standards for post-approval marketing.²¹⁴ The Department also challenged the company's sponsorship of continuing medical education. Parke-Davis sponsored "independent medical education" events, as do most pharmaceutical companies. In this case, however, the DOJ alleged that Parke-Davis as sponsor selected the topics, speakers, and content of the programs and planted questions from the floor to assure that the drug would be showcased as it desired. In addition, Parke-Davis conducted teleconferences in which physicians discussed their experience in prescribing Neurontin for off-label uses, with the company paying physician-speakers as well as paying doctors enrolled in the teleconference for their time.²¹⁵ The DOJ further alleged that Parke-Davis representatives made misleading statements about the efficacy of the drug for particular purposes.²¹⁶

The evidence, as presented by the relator and the DOJ, also indicates that the firm's funding of post-approval clinical research on off-label uses for Neurontin was a part of the marketing effort. The government and the relator alleged that doctors participating in study protocols for Neurontin received substantial payments for enrolling their patients in the protocol while having minimal obligations for data collection or analysis.²¹⁷ In addition, the clinical trials often were open label, (where doctor and patient were aware of which drug was being used) a study design generally viewed as inferior to random controlled trials especially where measures of improvement rely on patient self-reporting. The OIG had specifically expressed concerns about these and similar structural practices in post-marketing clinical research in a

214. This activity actually may be protected. *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 74 (D.D.C. 1998); *see also Greene, supra* note 173, at 50.

215. *See Steinman et al., supra* note 170, at 286; *see also EPSTEIN supra* note 7, at 154 ([For doctors,] "time is money, and any hour spent gathering information about new drugs is an hour away from some other part of their practice Many of these promotional efforts at wining and dining are understood in part as efforts to cover the opportunity cost of time.").

216. The Justice Department singled out the promotion of Neurontin for "bipolar disease" and "monotherapy for epileptic seizure." Department of Justice, *supra* note 5.

217. *Franklin v. Parke-Davis*, 147 F. Supp. 2d 39, 54 (D. Mass. 2001).

1994 Fraud Alert.²¹⁸ Finally, Parke-Davis originated the grants and protocols in their marketing department rather than in their research department, a practice that the government identified as “suspect activity” in OIG guidance issued after the initiation of the lawsuit but before the settlement.²¹⁹

In 2004, Parke-Davis entered into a settlement with the federal and state governments. Parke-Davis paid \$152 million plus interest to reimburse both the federal (\$83.6 million) and the state (\$68.4 million) governments for off-label prescriptions for Neurontin paid for by the state-federal Medicaid program. The company also settled state consumer protection claims for \$38 million plus interest. The company also accepted a mandatory corporate compliance program. Finally, the firm pled guilty to the charge that some of its post-approval communications with physicians violated the restrictions of the FDCA and, therefore, violated the False Claims Act. Parke-Davis paid a criminal fine of \$240 million for this violation. The *qui tam* relator recovered an additional \$24.64 million from the firm as part of the settlement as well.²²⁰

In all, Parke-Davis paid over \$455 million to the government parties and to the relator, the largest settlement for such litigation to that date.²²¹ The settlement also spawned several subsequent class action lawsuits against Parke-Davis by private insurers, including Aetna and the Teamsters, and by self-insured employers to recover what the insurance plans had

218. Special Fraud Alert: Prescription Drug Marketing Schemes, 59 Fed. Reg. 65,376 (Aug. 1994).

219. OIG Compliance Program Guidance for Pharmaceutical Manufacturers, 68 Fed. Reg. 237,131 (May 5, 2003).

220. Department of Justice, *supra* note 5; see Matthew, *supra* note 164, at 284 for discussion of *qui tam* relators in pharmaceutical cases.

221. An earlier federal criminal investigation of TAP Pharmaceutical Products, Inc., resulted in a guilty plea and payment of approximately \$875,000,000 by TAP in 2001. The issues in the TAP litigation did not involve off-label prescribing, but focused instead on TAP’s pricing practices for Medicare reimbursement as well as marketing practices. Press Release, Department of Justice, TAP Pharmaceutical Products Inc. and Seven Others Charged with Health Care Crimes; Company Agrees to Pay \$875 Million to Settle Charges (Oct. 3, 2001), *available at* <http://www.usdoj.gov/opa/pr/2001/October/513civ.htm>. Pricing was not involved in the Neurontin litigation. For discussion of subsequent acquittal of TAP executives, see Matthew, *supra* note 164, at 309–14.

paid for off-label prescriptions for Neurontin²²² as well as products liability and consumer protection claims by patients themselves.²²³

The DOJ and Parke-Davis disagreed over whether the firm's activities fell within the ambit of the False Claims Act both as a matter of law and as a matter of fact. The DOJ, however, produced significant evidence that the firm's activities crossed over into suspect practices, including practices that the government had identified earlier as potential fraud; and Parke-Davis admitted to certain violations and paid a notably large settlement for a pharmaceutical case that did not involve pricing or kickback issues, perhaps in part because of the overwhelming risk of exclusion from the Medicare program if the DOJ succeeded in proving its case in court.²²⁴

The "rest of the story" in this instance, however, does not lie in deciding whether the Department's narrative or the defendant's counter story about the company's behavior is true, but rather in what was happening to Neurontin prescribing during the course of the litigation and thereafter. In 2002, 94% of Neurontin prescriptions were for off-label indications, up from 40% in 1995.²²⁵ Neurontin sales amounted to \$2.7 billion in 2003, of which nearly \$2.5 billion was for off-label uses.²²⁶

One might expect that Neurontin prescribing patterns would change as physicians learned of the government's high-profile attack on off-label prescribing of Neurontin and allegations of misleading marketing, but that is not the case. In August, 2004, two years into the state and federal governments' pursuit of the lawsuit and shortly after the attention-grabbing settlement, sales of Neurontin had actually increased by 32% over the same quarter the year before.²²⁷

222. *E.g.*, *In re* Neurontin Marketing, Sales Practices and Products Liability Litigation, 433 F. Supp. 2d 172, 184 (D. Mass. 2006) (holding that plaintiff private insurers stated a claim against the manufacturer under the federal Racketeer Influenced and Corrupt Organizations Act (RICO)).

223. *See, e.g.*, *Rubel v. Pfizer*, 276 F. Supp. 2d 904 (N.D. Ill. 2003); *Dellinger v. Pfizer*, No. 5:03CV95, 2006 WL 2057654 (W.D.N.C. July 19, 2006); *Jablow*, *supra* note 167.

224. *See supra* note 169. In addition, the settlement was actually approved by Pfizer, Inc., which had acquired Warner-Lambert/Parke-Davis during the course of this litigation, and Pfizer deflected fault by stating that the activities "did not involve Pfizer practices or employees." *Kabler*, *supra* note 170.

225. *Schmit*, *supra* note 189.

226. *Id.*

227. *Id.*

Lehman Brothers estimated that the great bulk of those prescriptions for Neurotin—90% of sales, in fact—were still for off-label uses.²²⁸ In fact, only in 2006 did another medication surpass sales of Neurontin for neuropathic pain—which was an off-label use for Neurontin during the course of the litigation until its approval by the FDA (only as to cases in which neuropathic pain is associated with shingles) in 2002—and this was due to the expiration of its patent protection and the resultant entry of generics.²²⁹

The persistence of off-label prescribing for Neurontin even after the eye-popping settlement and guilty plea in this case, could be attributed to the observed persistence of prescribing habits in physicians described earlier.²³⁰ In other words, once brand loyalty has been purchased, it continues even after the flow of money and perquisites stops.

In this case, however, *some* of the off-label prescribing of Neurontin actually was good medicine despite the fact that at the time no rigorous clinical studies supported the uses for which practicing doctors were prescribing the medication. Off-label prescribing decisions, even though stimulated by pharmaceutical detailing, may be justified and may provide essential care for patients. Apparently, this was the case with the off-label use of Neurontin for relief of neuropathic pain.

Neuropathic pain is one of the most treatment-resistant pain conditions that exist. Such pain is chronic and debilitating and does not respond to more common pain medications, including opioids.²³¹ It is not surprising that doctors trying to treat patients with neuropathic pain, and the patients themselves, would be willing to try innovative therapies to get some relief. So it happened that doctors began to use Neurontin for neuropathic pain despite the fact that no rigorous clinical studies supported its use for that purpose. Patients experienced relief with Neurontin, and Parke-Davis apparently spread the word to its own benefit, but also to the benefit of patients in pain. In 2002, the FDA formally approved

228. *Id.*

229. COMMERCIAL INSIGHT: NEUROPATHIC PAIN—A PLETHORA OF PATIENT SEGMENTATION AND PRODUCT DIFFERENTIATION OPPORTUNITIES 80 (2006).

230. *See supra* note 58.

231. *See, e.g.,* Steve Simon et al., *Breakthrough Pain in Opioid-Treated Patients with Neuropathic Pain*, 2 J. OPIOID MGMT. 347, 347 (2006).

Neurontin for the treatment of post-herpetic neuropathic pain (i.e., nerve pain associated with shingles)²³² in the midst of the Neurontin prosecution. Neurontin has not been approved for the treatment of neuropathic pain caused by other disease states, and it will not be. Nor is the drug likely to be subjected to double-blind, random-controlled clinical trials in persons suffering neuralgia from other conditions as the patent for the drug has expired, and generics are taking control of the market.²³³ The absence of clinical trials does not mean that Neurontin (now generic gabapentin) is not effective in treating these highly similar pain states just as FDA approval in 2002 did not make the drug effective for treating pain.²³⁴ Nor was the experience of doctors and patients who observed the pain relieving effect of Neurontin “false” even though it would be categorized as “anecdotal.”

The Neurontin litigation was not solely focused on the use of Neurontin for neuropathic pain, of course. The DOJ specifically referenced the promotion of the drug for bipolar disorder, ALS, attention deficit disorder, migraine, withdrawal seizures, and restless leg syndrome in addition to “various pain states” in its statements describing the settlement.²³⁵ Certainly, Neurontin may not be effective in treating all of these disorders; and surely it is distinctly possible that Parke-Davis representatives exaggerated the evidence regarding these uses. The now-proven effectiveness of Neurontin for neuropathic pain (but only that related to shingles) illustrates one of the challenges in establishing that inappropriate marketing causes inappropriate and ineffective prescribing.²³⁶

Nearly one-third of the amount paid by Parke-Davis (\$152 million plus interest) was paid to the state and federal governments as reimbursement for payments made for off-label

232. Schmit, *supra* note 189; *see also* Neurontin, *supra* note 187.

233. *See* Hoover’s, *supra* note 26 (documenting a 77% decline in revenue from Neurontin after patent expiration); Department of Justice, *supra* note 5 (observing that the defendant did not pursue approval of off-label uses because of the impending expiration of the patent on Neurontin).

234. Steven D. Passik & Kenneth L. Kirsh, Editorial, *Weighing in on the Off-Label Use of Actiq™ for Noncancer-Related Pain: A Recipe for Success or a Recipe for Disaster?*, 8 PAIN MED. 130, 130 (2007) (commenting on the fact that Actiq is approved only for cancer-related pain and not for pain caused by other diseases or conditions).

235. Department of Justice, *supra* note 5.

236. Schmit, *supra* note 189.

prescriptions of Neurontin for Medicaid beneficiaries.²³⁷ This payment signals that the government (as purchaser for the program's beneficiaries) did not get what it paid for (i.e., effective treatment) when it paid for off-label prescriptions of this drug.²³⁸ Parke-Davis was accused, for example, of "steal[ing] from taxpayers" when it promoted off-label uses of Neurontin.²³⁹ After the settlement, however, Neurontin continued to be the third highest drug cost for some state Medicaid programs.²⁴⁰

It would be reasonable for state Medicaid programs to turn the False Claims Act litigation, essentially a damning autopsy of the firm's behavior, into prospective payment regulation. Even a year after the settlement produced "re-payments" to the Medicaid programs for prescriptions written prior to the date of settlement, however, state Medicaid programs continued to pay for off-label use of Neurontin without any significant change in payment standards.²⁴¹ If Parke-Davis was required to repay the Medicaid program for the off-label prescribing it stimulated, because these prescriptions amounted to false claims, then why would the state continue to pay for those same prescriptions after the date of the settlement? The State of Florida decided it would not do so.²⁴²

In 2004, "following news reports that Neurontin was being widely prescribed for off-label uses and that reimbursement for the drug by state Medicaid programs was significant," the Florida legislature acted to encourage the state Medicaid agency to constrain reimbursement for off-label prescriptions of Neurontin.²⁴³ The legislation specifically authorized the agency to implement a prior authorization program for "off-label uses of Medicaid-covered prescribed drugs" that would require doctors "to provide information about the rational and

237. *Id.*

238. *See id.*

239. *Id.*

240. *Id.*

241. In fact, over the course of time, private pharmacy benefit managers also have largely abandoned efforts to restrict off-label prescribing. Nor are private employer-based health insurance plans refusing to pay for off-label uses. *See* discussion *supra* note 27; Matthew, *supra* note 164, at 326 (discussing state laws mandating coverage of off-label prescriptions).

242. *Edmonds v. Levine*, 417 F. Supp. 2d 1323, 1331 (S.D. Fla. 2006).

243. *Id.*

supporting medical evidence for the off-label use of the drug.”²⁴⁴

In July, 2004, the Florida Medicaid agency established a policy under which it would pay for Neurontin *only* for its approved uses (adjunctive therapy for epileptic seizures²⁴⁵ and neuropathic pain associated with shingles) and for off-label uses only when safety and efficacy were proven “by double-blind, placebo controlled, randomized clinical trials.”²⁴⁶ However, the agency decided to reimburse for two unapproved indications for which there were no clinical studies proving the drug effective.²⁴⁷ These two uses were the prescription of Neurontin for ALS, for which the FDA had formally categorized Neurontin as an “orphan drug,”²⁴⁸ and for diabetic peripheral neuropathy.²⁴⁹ Thus, the agency refused to pay for prescriptions of Neurontin for any uses other than adjunctive therapy for epileptic seizures and partial refractory seizures; for post-herpetic neuropathic pain and diabetic peripheral neuropathy; and for ALS.²⁵⁰ It excluded, for example, prescriptions for Neurontin for the treatment of neuropathic pain unless the patient had shingles or diabetes. Patients with neuropathic pain from medical conditions other than shingles or diabetes filed suit.²⁵¹

Florida claimed that its coverage decisions for Neurontin complied with the federal Medicaid requirement that the state cover off-label uses that are “supported by one or more

244. *Id.*

245. Actually, it appears that the agency decided to cover Neurontin for the unapproved indication of “partial seizure refractory” within this category, perhaps mistakenly assuming that it was the same use as that approved by the FDA. *Id.*

246. *Id.*

247. *Id.*

248. An orphan drug has not been proven effective, but is categorized as such because it “might provide a significant benefit” to persons with “serious or life threatening illness” in which the number of people with the disease is relatively small (estimated at under 200,000). One of the compendia approved for use in Medicaid actually reported that Neurontin was “ineffective” for use with ALS. *Id.* at 1332.

249. *Id.* The state also paid for Neurontin for a particular unapproved treatment for epilepsy. *Id.* at 1331.

250. *Id.*

251. Plaintiff Mr. Edmonds, for example, suffered from neuropathy caused by medications required to treat HIV and had found that Neurontin relieved this pain after all other medications had failed. Bob Lamendola, *State Limits 5 Medicaid Drugs to Save Money*, ORLANDO SENTINEL, Aug. 5, 2004, at B5.

citations”²⁵² in the accepted drug compendia.²⁵³ The American Hospital Formulary Service Drug Informant (AHFS), an approved compendium, listed several off-label uses for Neurontin, including its use for neuropathic and neurogenic pain resulting from a variety of medical conditions, but did not provide any citations to studies or journal articles for any of these uses.²⁵⁴ Another of the approved compendia, DRUGDEX, listed fifty-four uses for Neurontin. DRUGDEX classified each use as “effective, possibly effective, or ineffective” and rated the available documentation of effectiveness as “excellent, good, fair, and poor.”²⁵⁵ All but three of the fifty-four uses listed in this publication were recognized as either “effective” or “possibly effective.”²⁵⁶ Of the three uses categorized in DRUGDEX as “ineffective,” Florida’s Medicaid program actually covered two: ALS and a specific manifestation of epilepsy.²⁵⁷

The District Court held that the Florida agency’s policy violated the coverage mandated in the federal Medicaid program.²⁵⁸ The court recognized that the state could have followed other routes within its authority under the federal Medicaid statute to control Medicaid payments for Neurontin prescriptions, which would have required case-by-case review

252. The federal statute does not define the word “citation.” *Edmonds*, 417 F. Supp. 2d at 1335.

253. There are some particular exceptions to this requirement, but the Florida policy did not fall within any of them. For example, as described by the court in *Edmonds*, the state could establish a drug formulary that would exclude specific drugs and which would require a written justification of the exclusion by the agency. Under the Medicaid statute, a state with an exclusionary formulary must have an authorization process in place where a doctor can submit a request to prescribe the drug, and the state will consider such requests on a case-by-case basis. Alternatively, the state could require prior authorization for particular drugs. In such a program, the request is always granted, but the doctor is required to seek prior authorization, which allows the state pharmacist to offer other alternatives. Finally, a state can alert the Secretary of HHS to clinical abuse and overuse of a particular drug; and the Secretary can choose to list the drug as excluded from Medicaid coverage. *Id.* 1327–30. For the adverse impact of these methods of drug utilization controls, see Kleinke, *supra* note 28.

254. *Edmonds*, 417 F. Supp. 2d at 1333.

255. *Id.*

256. *Id.*

257. *Id.*; see *supra* notes 245 and 248.

258. *Edmonds*, 417 F. Supp. 2d at 1343.

for individual patients,²⁵⁹ but that the method used by the state violated the statutory mandate.²⁶⁰

In particular, the court noted that the state's requirement that an off-label use would be covered only if it were supported by "double-blind, placebo-controlled randomized clinical trials" misinterpreted the statute as "the same standard employed for FDA-approved uses" and "the equivalent of saying the same thing twice."²⁶¹ The court said further:

If Congress had intended that "medically accepted indications" must be supported by double-blind, placebo-controlled, randomized clinical trials, it would have said so [Amendments of the statutory provision at issue] over the years substantiate the notion that Congress intended coverage for off-label uses, many of which would obviously not be supported by the same strict criteria required for FDA approval.²⁶²

The core of the injury alleged and recovered for in the Neurontin litigation was that inappropriate marketing corrupted medical decision making with the result that the states paid for unnecessary or ineffective product.²⁶³ Prescription of Neurontin for certain unapproved uses (for example, for neuropathic pain) did not injure the states in this fashion. In fact, Medicaid patients receiving the drug for those purposes received effective and necessary treatment even if the prescription was off-label, and even if their doctors learned of this use through firm-sponsored marketing. Although the FDA has not approved Neurontin for the treatment of neuropathic pain generated by diseases or injuries other than shingles, it seems entirely reasonable for physicians to believe that the drug may be effective for those pain states as well, especially if patients are reporting positive results.

It was also logical for the Florida Medicaid agency to address the forward flow of dollars after the Neurontin settlement. Although the agency was thwarted in this effort by the federal Medicaid statute, its experience is more generalizable. Requiring the completion of "double-blind, placebo-controlled randomized clinical trials" as a prerequisite for covering prescriptions for medications for unapproved uses appeals to the notion of medicine as science, but would have

259. See *supra* note 253.

260. See *Edmonds*, 417 F. Supp. 2d at 1343.

261. *Id.* at 1337.

262. *Id.*

263. See *supra* text accompanying note 238.

prevented patients in some cases from receiving the only effective care available.²⁶⁴

Private insurers have fared no better than the State of Florida in their attempts to control individual off-label prescribing decisions,²⁶⁵ and their challenges have nothing to do with the Medicaid statute.²⁶⁶ The hesitancy of private payers to involve themselves in reining in off-label prescribing may be a simple matter of administrative convenience.²⁶⁷ If their primary concern is to control drug costs, there are less expensive methods for doing so.²⁶⁸ These include shifting costs to consumers through co-pays, tiered benefit systems, prior authorization requirements, and step therapy (“fail first”) mechanisms.²⁶⁹ These are hardly satisfactory as methods for evaluating the appropriateness and effectiveness of an off-label prescription—or any prescription for that matter—because they erect barriers unrelated to the effectiveness of medications.

There are emerging efforts to constrain prescribing, especially off-label prescribing, within a rubric of effectiveness and quality rather than cost control. These efforts face several significant obstacles discussed in this paper.²⁷⁰ First, these efforts must address directly the inadequate quantity and quality of post-approval research on approved drugs and the resulting deficiencies in clinical guidelines. Public funding for such trials is simply inadequate; private funding by pharmaceutical firms has been made suspect; incentives for private funding by private insurers are limited when they can achieve their cost-containment goals through much less expensive means; and incentives for the insurers to share the knowledge they produce on other than a proprietary basis are uncertain. Moreover, if private insurers and pharmacy benefit

264. Of course, the methods for controlling prescribing that are permitted in the federal Medicaid scheme may also harm patients. See Kleinke, *supra* note 28, at 44.

265. See discussion of private efforts *supra* note 28. The Medicare Part D program has established standards similar to those of the Medicaid program. 42 C.F.R. 423.100; 70 Fed. Reg. 4194-01 (Jan. 28, 2005).

266. Kleinke, *supra* note 28, at 41.

267. See *id.*, at 42.

268. *Id.*

269. *Id.*

270. See generally Neumann, *Emerging Lessons from the Drug Effectiveness Review Project*, *supra* note 28; Neumann, *Evidence-Based and Value-Based Formulary Guidelines*, *supra* note 81.

managers begin to provide serious funding for clinical trials, who is to say that this funding also will not be viewed as suspect for the same reasons of self-serving interests that are now recited for pharmaceutical funding? Second, even if a robust program of Phase IV clinical trials of expanded uses for approved drugs does emerge, there will still be the irreducible clinical uncertainties—uncertainties caused by unavoidable temporal gaps between the immediacy of clinical decision making and the slow clock required for trials to be conceived, designed, and executed as well as uncertainties caused by the performance of the drug on individual patients.

CONCLUSION

We can view the Neurontin litigation as catching a bad actor. Certainly, the evidence of Parke-Davis's marketing, educational and research practices provides sufficient support for that view. With that perspective, the litigation simply dramatizes the conflicts-of-interest narrative of pharmaceutical firm-prescriber co-dependencies.

The litigation, the persistence of off-label prescribing post-litigation, and the difficulties encountered in translating the recovery of Medicaid payments into prospective controls raise broader issues than those that will fit under the conflicts-of-interest umbrella, however. Conflicts-of-interest regulation, both public and private, works only at the margins of the issues raised in this situation. While conflicts-of-interest surveillance and management may produce some benefits, this approach can also give a false sense of problem solved even though those interventions do not reach the core issues of the production and dissemination of clinical knowledge. Conflicts-of-interest restrictions may remove one source generating increased distrust of the research enterprise, even though this distrust may be misplaced. Conflicts-of-interest restrictions will not fund post-marketing research, and may actually reduce current resources if the risks of industry funding of post-approval trials include criminal and civil prosecution; will not improve physician learning, and appears to be reducing educational opportunities as firms react to increased risks; and will not fill the knowledge voids within which both doctors and regulators currently practice.

Even if the financial relationships between prescribing doctors and Parke-Davis were inappropriate and perhaps

illegal, the existence of those relationships did not prove that the off-label prescriptions were themselves inappropriate. Off-label prescribing, even where clinical trials proving efficacy for new indications have not yet begun or are not yet completed, can bring great benefit to patients. Of course, such prescribing can also subject patients to ineffective medications with the attendant costs and risks. The real challenge is not detecting and prosecuting the zealous marketing efforts of a Parke-Davis, but rather it is assuring that patients get good care. Raising the risks for pharmaceutical firms in funding Phase IV clinical trials and continuing medical education will not get us there. Nor will targeting off-label prescribing as if there were no risks in doing so.