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Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims for 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 at least for those 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 U.S. 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 This common practice, called "off-label" prescribing, has raised

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¹ David Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCH. INT. MED. 1021 (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. See Hua Chen et al., *Off-Label Use of Antidepressant, Anticonvulsant, and Antipsychotic Medications Among Georgia Medicaid Enrollees in 2001*, 67 J. CLIN. PSYCH. 972 (2006), reporting that 75% of prescriptions for antidepressants in the study were for off-label uses as were 80% of prescriptions for anticonvulsant medications. See also 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?*, SAN FRAN. CHRON., May 1, 2005, at A1; Maxwell J. Mehlman, *Off-Label Prescribing*, http://www.thedoctorwillseeyounow.com/articles/bioethics/offlabel_11/ (last visited October 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, 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'*

significant concerns over the safety and efficacy of prescribed medications when they are prescribed outside the scope of their approval. A study published in the Journal of the American Medical Association (JAMA) in May, 2006, sharpened these questions when it reported that “most” off-label prescriptions studied had “little or no scientific support.”²

Certainly, concerns over the effectiveness or even the safety of such off-label prescribing are significant, both for the health of individual patients and for the health of the private and public health care budgets. The advent of the Medicare prescription drug benefit has intensified the interest in the phenomenon of off-label prescribing and the relationships between the pharmaceutical industry and practicing physicians.³ Actions taken to constrain off-label prescribing in response to these increasing concerns, however, face a serious risk of error. Counterintuitively, efforts to restrict off-label prescribing categorically will harm individual patients, who will be denied medication that may be uniquely effective though not yet definitively proven so, and upon patients generally by seriously reducing medical innovation and “field discovery”⁴ of important therapeutics.

Prescription Drug Marketing, U.S. NEWS AND WORLD REPORT, Apr. 26, 2004 (stating that about 23% of prescriptions are for off-label uses).

² Radley, *supra* note 1, at 1021.

³ Department 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.” See also, Gardiner Harris, *U.S. Weighs Not Paying for All Uses of Some Drugs*, N.Y. TIMES, Jan. 30, 2004.

⁴ 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 FDA in 2002 after years of off-label use for this purpose. See *infra*, note 216 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, *Increased Governmental Inquiries Elevates Attorneys’ Importance to Pharmaceutical Companies*, 185 NEW J. L. J. 330 (2006). See also Harold J. DeMonaco et al., *The Major Role of Clinicians in the Discovery of Off-Label Drug Therapies*, MIT Sloan Working Paper 4552-05, 3, <http://www.medscape.com/viewarticle/529167> (defining “field discovery” as new applications of drugs that are discovered through “clinical practice that [is] independent of pharmaceutical company or university

Questions concerning the exercise of medical judgment in off-label prescribing certainly reflect rational concerns for individual patients, but they also reflect 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 and practicing physicians as well as researchers as a corrupting influence that pollutes medical judgment. The conflicts-of-interest narrative of off-label prescribing mistakenly assumes that removing the confounding financial self-interest of doctors will result in better decisions. In this purer environment, off-label prescribing, it may be assumed, will be more rational, meaning evidence-based, relying on the at least adequate information that will remain.

At best, the conflicts-of-interest narrative is only a partial 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 (as well as negative effects), 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

research.”); 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 Debacle*, 79 B. U. L. REV. 93, 96 (1999). See also discussion of patients’ heterogeneity *infra* at note 60 and accompanying text.

of serious gaps in research and knowledge. Efforts to seriously restrict this prescribing will also operate without a firm evidentiary foundation for decision making and, thus, will struggle with whether particular incidences or patterns of off-label prescribing are “correct.”⁵ 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-labeling prescribing is not the relationship between the pharmaceutical industry and doctors, or at least not totally so. Rather, the prevalence of off-label prescribing is a manifestation of patterns of learning in the medical profession and deficiencies in the production and dissemination of clinical knowledge. Furthermore, the fraud and abuse litigation strategy currently pursued by the federal government to respond 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 the public health because of limitations in the

⁵ In fact, a significant gap in most research on industry influences on physician prescribing behavior is that 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. RICHARD A. EPSTEIN, *OVERDOSE* 160 (2006); 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 25.

testing performed during the drug approval process.⁶ In spite of the value of Phase IV clinical trials, regulatory requirements for post-approval trials are nearly non-existent; 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 turns the lens and examines the character, quality and volume of clinical research and its limited usefulness for clinical decision making. This Part describes contemporary deficiencies in the production of clinical knowledge that impede efforts by 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 sets up a feedback loop between established patterns of physician learning and the character of contemporary clinical research efforts by demonstrating how efforts to control conflicts of interest in research, especially through disclosure, reinforce the skepticism toward scientific research on the part of practicing physicians.

⁶ See discussion *infra* text accompanying notes 63-64. 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 (2004) for a brief but clear description of the FDA new drug approval process, including clinical trials. The number of individuals on which a drug is tested at a pre-approval stage has increased over the years, from an average of 1,321 subjects in 1981-1984 to 4,237 in 1994-1995. Office of Inspector General, HHS, *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research*, OEI-01-97-00195 (June 2000) at 12.

Finally, the article considers the strongest current regulatory effort to constrain off-label prescribing at this time. In Part III, 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 copycat litigation efforts.⁷

This Part uses the Neurontin litigation, and its aftermath, to sharpen the critique of the limits of conflicts-of-interest dominated approaches 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 taken as an illustration of the centrality of conflicts of interest in the relationships among the pharmaceutical industry, researchers and doctors; it is more richly studied for what it reveals about the nature of clinical knowledge and clinical judgment. The litigation and its aftermath 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,

⁷ See *infra* text accompanying note 204. It remains the largest settlement to date for litigation focusing solely to the marketing, educational, and research activities of a pharmaceutical firm relating to off-label prescribing. Since that settlement, the government has aggressively pursued pharmaceutical firms for these activities, gathering significant settlements. See, e.g., Julie Schmit, *Schering-Plough to Pay \$435 Million Settlement*, USATODAY, Aug. 30, 2006, 1B (reporting settlement of government claims of fraud for promotion of off-label uses leading to submission of false claims against Medicaid as well as pricing violations); DOJ, *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; U.S. *ex rel.* Rost v. Pfizer, 2006 WL 2501454 (D. Mass.), regarding off-label use of human growth hormone. See also Robert Brady, et al., *Crackdown on "Off-Label" Pitches*, National Law Journal, March, 20 2006, S1, reporting on settlements of actions against Serono 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 LAW REPORTER 392 (March 11, 1999). 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 206-207.

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.⁸

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 continuing safety surveillance as well as broader testing of effectiveness for both approved and unapproved purposes, the demand for post-marketing studies is quite weak. A number of factors converge to create a weak demand for such research. As discussed below, the legal framework for drug approval and for prescribing encourages narrow approvals and resultant off-label prescribing. In addition, prescribing physicians themselves do not create a strong demand for 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 .

⁸The 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. The databank may be proprietary to the payer, and the resultant analysis may also be so. Finally, problems regarding creating adequate space for clinical innovation; access to unproven but effective interventions; and the translation of averages to the individual patient will persist. See James Walker, *Electronic Medical Records and Health Care Transformation*, 24 HEALTH AFFAIRS 1118 (2005); Clifford Goodman, *Savings in Electronic Medical Record Systems: Do it For the Quality?*, 24 HEALTH AFFAIRS 1124 (2005). One illustration of potential public-private information partnerships are those newly established between the larger managed care organizations 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. For analysis, see Kristin Madison, *ERISA and Liability for Provision of Medical Information*, 84 N.C. L. Rev. 471, 502-504 (2006), calling for effective accountability for MCO's 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.

State and federal law protect 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” in attempting to treat individual patients, distinguishing this practice from “experimentation,” and the heightened regulatory standards for informed consent required of experimental protocols. Nor does state malpractice law generally require specific disclosure by the physician to the patient that the particular prescribed use is off-label.⁹

The Food, Drug and Cosmetic Act (FDCA)¹⁰ also respects off-label prescribing. The Act, which requires that a drug be approved by the FDA before it is made available to the market, essentially prohibits the FDA from circumscribing physician prescribing of approved medications, including prescribing that differs in indication, population, dose or duration from those approved by the FDA.¹¹ Under the FDCA, the FDA has no authority to “limit or interfere with the authority of a health care practitioner to prescribe” an

⁹ For an overview of liability risks for off-label prescribing, *see* Mehlman, *supra* note 1. *But see* Richardson v. Miller, 44 S.W.3d 1 (Tenn. Ct. App. 2000) (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). 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).

¹⁰ Food, Drug and Cosmetic Act, 29 U.S.C. § 301 (2000).

¹¹ 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 below, in the context of the Neurontin litigation.

approved medication within the context of a legitimate physician-patient relationship.¹²

The intention of this provision is to avoid federal interference with the practice of medicine,¹³ a somewhat quaint notion at this point but alive in this situation nonetheless.¹⁴

Federal drug law, however, does more than merely respect off-label prescribing.¹⁵ The design of the FDCA actually encourages the proliferation of off-label uses and a high frequency of off-label prescribing. 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.¹⁶ The FDA only rarely requires post-approval clinical trials as a condition of approval,¹⁷ and the agency's follow up on required trials has been uneven.¹⁸ Even though there is a simplified approval process for expanded uses of

¹²21 U.S.C. § 396 (2000).

¹³ *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001).

¹⁴ See generally Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. KAN. L. REV. 149 (2004).

¹⁵ Of course, the federal government has other interests, and perhaps countervailing policies and authority as the largest payer of drugs, including off-label prescriptions. As will become apparent in the later discussion of the Neurontin litigation, these interests have not operated as a significant prospective counterweight to the incentives in the FDCA regulatory structure. See discussion *infra* text accompanying notes 220-45.

¹⁶ 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).

¹⁷ The FDA may 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) and 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). 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. Postmarketing Surveillance Programs, <http://www.fda.gov/cder/regulatory/applications/Postmarketing/surveillancepost.htm> (last visited October 8, 2006).

¹⁸ A 2006 GAO study reported that generally the agency's postmarketing surveillance system suffered from a lack of clarity, insufficient oversight, and a lack of clear criteria for decisions. In addition, the GAO

already approved drugs,¹⁹ regulatory incentives to invest in expanded approval are uneven at best.²⁰

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

criticized the FDA's follow up on postmarketing trials that it had required. GAO, *Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process* (March 2006), <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* (Feb. 3, 2006), http://www.kaisernet.org/daily_reports/rep_index.cfm?hint=3&DR_ID=35193.

¹⁹ Oates, *supra* note 16, at 1285.

²⁰ See, *e.g.*, Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002), which created incentives for testing approved drugs in children in terms of extension of patent protection for those drugs. 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 3. Revenue from sales of Neurontin fell 77% when patent protection expired. Hoover's In-Depth Company Records, *Pfizer, Inc.* (March 7, 2007), available at 2007 WLNR 4302915. Of course, 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 doesn't do so, as described below. See discussion *infra* accompanying notes 22-23. The 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.

circumstances. The practice of off-label prescribing, then, would seem to be a rational reaction to the limitations of the formal approval process.²¹

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 trials,²² and the weakness of the regulatory requirements for post-marketing research would become less significant.

²¹ Some have argued that these limitations in the drug approval process argue in favor of dismantling the entire system. *See, e.g.,* Daniel B. Klein and Alexander Tabarrok, *Who Certifies Off-Label?*, REG., June 1, 2004, at 60.

²² Of course, doctors are not the only gatekeepers for prescribed drugs. Most health plans and pharmaceutical benefit management programs, however, do little to confine off-label prescribing, although they are actively engaged in significant efforts to influence physician and patient demand on other fronts, including, for example, shifting from expensive to less expensive substitute formulations (“fail first” requirements) or to generic drugs or creating tiered benefits or increased co-pays or requiring preauthorization, or, in the case of Medicaid programs simply limiting the number of prescription drugs that will be reimbursed for each patient, among other methods. Soumerai, *supra* note 22, describing these methods; J.D. Kleinke, *Access Versus Excess: Value-Based Cost Sharing for Prescription Drugs*, 23 HEALTH AFFAIRS 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 also*, Rachel Christensen Seithi, *Prescription Drugs: Recent Trends in Utilization, Expenditures, and Coverage*, Employee Benefit Research Institute Issue Brief No. 265 (January 2004), <http://www.ebri.org/pdf/briefspdf/0104ib.pdf>, reporting on a general decline in the number of employers using substantive controls. *See also*, the discussion of Medicaid coverage policy *infra* notes 182-190 and 220-240 and accompanying text. Consumer behavior also can create an incentive for postmarketing research and formal approval of an 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. Seithi, *supra* note 22; GAO, *FDA Oversight of Direct-to-Consumer Advertising Has Limitations* (October 2002), <http://www.gao.gov/new.items/d03177.pdf>.

Practicing physicians, in fact, do *not* exert a high demand for convincing scientific proof of effectiveness for off-label uses. They do not create a robust market for scientifically valid information on effectiveness or even safety.²³

The conflicts-of-interest narrative of off-label prescribing implies that doctors' prescribing is simply purchased by the pharmaceutical industry through free lunches, office supplies, travel, speaker's fees, and other more extravagant gifts.²⁴ While the "doctor for sale" story may be true as far as it goes,²⁵ a fuller appreciation of physician prescribing behavior requires examining how physicians actually do learn to alter their practices, in this case to establish a new prescribing pattern for particular 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."²⁶ High valuation of experience²⁷ over studies permeates the observed learning patterns of

²³ Radley, *supra* note 1, at 1021.

²⁴ Troy Brennan, et al., *A Social Science Perspective on Gifts to Physicians From Industry*, 290 JAMA 252 (2003); Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?*, 283 JAMA 373 (2000).

²⁵ See discussion of lack of outcomes research in the conflicts of interest literature *supra* note 5.

²⁶ Rebecca K. Schwartz et al., *Physician Motivations for Nonscientific Drug Prescribing*, 28 SOC. SCI. & MED. 577 (1989), as quoted in Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, at footnote 205 (2002).

²⁷ Even physicians who report that they always or often use evidence-based medicine 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. OF GEN. INT. MED. 236 (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 impact on 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 INT. MED. 260 (2005).

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.”²⁸

There is also evidence that even when physicians do review professional journals for relevant information for clinical decision making that they are likely to fail to distinguish between rigorous studies and preliminary studies;²⁹ may be limited in their ability to assess the strength of any particular study;³⁰ and may in fact rely excessively on abstracts, overlooking instances in which the abstract may overstate results.³¹ 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

²⁸ 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), as quoted in Noah, *supra* note 26 at footnote 205. See also H.B. Slotnick, *How Doctors Learn: Physicians’ Self-directed Learning Episodes*, 74 ACADEMIC MEDICINE, 1106, 1110 (1999) (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.)

²⁹ R.B. Haynes, *Loose Connections Between Peer-Reviewed Clinical Journals and Clinical Practice*, 113 ANN. INT. MED. 724 (1990).

³⁰ 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, *supra* note 27.

³¹ 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).

the quality of information.³² Physicians also may be equally influenced by letters and case reports published in journals, which can be merely anecdotal, as by sound scientific studies.³³ 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.³⁴ While the lack of influence for clinical guidelines may be attributed simply 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.³⁵ 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.³⁶

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

³² Haynes, *supra* note 29.

³³ In one survey doctors reported both that they referred to “review articles” in journals (73%) but that they did not refer to “research studies” (55%). McAlister, *supra* note 27.

³⁴ See, e.g., James Ducharme, *Clinical Guidelines and Policies: Can They Improve Emergency Department Pain Management?*, 31 J.L. MED. & ETHICS 783 (2005).

³⁵ See generally Lars Noah, *Medicine’s Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373 (2002), for an in-depth discussion of practice guidelines. See also 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).

³⁶ Kleinke, *supra* note 22, at 36, detailing the impact of bias in the development of guidelines for the use of pharmaceuticals.

doctor's experience of residency training where the opinion of the attending physician is revered as authoritative.³⁷ Studies document significant influence of peer opinions on clinical decision making,³⁸ although some studies conclude that the context for the transmission of opinions may make a difference in effect on practice.³⁹

Documentation of wide variations in medical practice patterns corroborates the reported reliance on peers and opinion leaders as these same studies on practice variations reveal practice homogeneity as well.⁴⁰ One might expect that if physicians relied on scientific research results for medical decision making, neither the variations among regions nor the homogeneity within regions would be so pronounced.

Journals are not the only tool for formal learning in medical practice, of course. 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.⁴¹ CME, however, is largely ineffective in achieving its ultimate goal of improving practice.⁴²

³⁷ Timmermans, *supra* note 31, at 345–47.

³⁸ See, e.g., Jane M. Young, et al., *Role for Opinion Leaders in Promoting Evidence-Based Surgery*, 138 ARCH. SURG. 785 (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. At the same time, however, surgeons in this survey reported that peer-reviewed surgical literature influenced their practice as well.

³⁹ 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 (2005).

⁴⁰ The classic studies on interregional variations and intraregional homogeneities in practice were done by John E. Wennberg. See, e.g., *Dealing with Medical Practice Variations: A Proposal for Action*, 3 HEALTH AFFAIRS 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. 307, 1310–1314 (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 (94%) than on local colleagues (89.3%). *Id.*

⁴¹ 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*

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.⁴³ Lecture and case-based CMEs, which are the custom of the trade, can change information levels but do not change practice. The authors of this article found that traditional didactic CME “has little or no role to play” in changing practice.⁴⁴ A later analysis confirmed this conclusion and noted that such programs “have little or no beneficial effect in changing physician practice.”⁴⁵ Doctors absorb new information, but do not necessarily incorporate it into their decision making.

Some CME pedagogies can effect change in practice.⁴⁶ 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

Review, 296 JAMA 1094 (2006) (describing CME requirements of state medical licensure bodies, the Joint Commission on Accreditation of Healthcare Organizations, the specialty boards, and others).

⁴² A recent review of the role of CME in improving physician practices concludes that physicians do not accurately assess their own learning needs and that efforts to improve physician competency through continuing education will need to develop other tools to do so. *Id.* at 1094.

⁴³ David Davis, et al., *Impact of Formal Continuing Medical Education*, 282 JAMA 867 (1999). The results of this study were confirmed by a later analysis reported in B.S. Bloom, *Effects of Continuing Medical Education on Improving Clinical Care and Patient Health: A Review of Systematic Reviews*, 21 *INT’L J. TECHNOL. ASSESS. HEALTH CARE* 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 DENT.* 164 (2004).

⁴⁴ Davis, *supra* note 43, at 873.

⁴⁵ Bloom, *supra* note 43.

⁴⁶ 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 *ANN. ALLERGY ASTHMA IMMUNOL.* 237 (2004). See also Paul E. Mazmanian & David A. Davis, *Continuing Medical Education and the Physician as a Learner*, 288 JAMA 1057 (2002).

significant effects than the standard CME.⁴⁷ Most CME, however, is the “standard CME,”⁴⁸ 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. In fact, although survey data indicates that practicing physicians are skeptical about scientific studies, 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 somewhat accurate.⁴⁹ Of course, this may be due to the “free lunch” that comes with the information,⁵⁰ 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.⁵¹ 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

⁴⁷ Davis, *supra* note 43, at 870-871. 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).

⁴⁸ Bloom, *supra* note 43.

⁴⁹ Kaiser Family Foundation, National Survey of Physicians Part II: Doctors and Prescription Drugs (2002) available at <http://www.kff.org/rxdrugs/20020415b-index.cfm>.

⁵⁰ See, e.g., Troy Brennan, *Health Industry Practices That Create a Conflict of Interest*, 295 JAMA 429 (2006); Dana Katz, *All Gifts Large and Small*, 3 AJOB 39 (2003); Wazana, *supra* note 24, 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. Studies of the influence of pharmaceutical detailing do not analyze its impact on patient outcomes. Wazana, *supra* note 24, at 378. Furthermore, some studies recognize specific positive effects, including “improved ability to identify the treatment for complicated illnesses.” *Id.*

⁵¹ See, e.g., Judith K. Hellerstein, *The Demand for Post-Patent Prescription Pharmaceuticals* (December 1994). NBER Working Paper No. W4981. Available at SSRN: <http://ssrn.com/abstract=226580>. See also discussion of Neurontin prescribing patterns, *infra*, text accompanying notes 209-213.

mailings “do not result in changes in prescribing practice . . . that physicians frequently prescribed drugs in violation of warnings, including black box warnings.”⁵² Of 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 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.⁵³

Why are practicing doctors more likely to emulate their peers in their practice decisions, to look to physician opinion leaders, and to trust experience rather than to rely

⁵² Jerry H. Gurwitz, *Serious Adverse Drug Effects – Seeing the Trees Through the Forest*, 354 NEW ENG. J. MED. 1413 (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 also* KE Lasser, *Adherence to Black Box Warnings for Prescription Medications in Outpatients*, 166 ARCHIVES OF INTERNAL MEDICINE 3, 338-44 (2006) (reporting that doctors studied prescribed medications subject to black box warnings to 7 of 1000 outpatients, with female patients and patients over 75 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.”); AK Wagner, *FDA Drug Prescribing Warnings: Is the Black Box Half Empty or Half Full?*, 15 PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 6, 369-86 (2006)(reporting that 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).

⁵³See e.g., American Medical Association, Report 10 on the Council of Scientific Affairs (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 AMA] 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 AMA policy H-115.971 Safety and Efficacy of Selective Serotonin Reuptake Inhibitors (SSRIs) in Children and Adolescents, available at http://www.ama-assn.org/apps/pf_new/pf_online?f_n=browse&doc=policyfiles/HnE/H-115.971.HTM. After reviewing the evidence, the AMA concluded that the association between the antidepressants and rates of suicide was not supported by data. AMA asks FDA to Study Impact of Antidepressant Labeling Changes. AMA Science News. Available at <http://www.ama-assn.org/ama/pub/category/15240.html>.

on published scientific studies or formal FDA approval? To some extent, physicians are simply employing common coping skills to manage 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.⁵⁴ Although Medline and other medical research databases are searchable, doctors report a low confidence level in their ability to do a literature search on a particular question.⁵⁵ Learning preferences and information preferences are common coping tools for massive amounts of information.⁵⁶

Similarly, informal communication networks among peers can transmit information much more quickly than peer-reviewed journals can.⁵⁷ Especially in certain practice areas, including oncology for example, the demand for speed may outpace the demand for scientific verification (for example, through completion of ongoing but incomplete clinical trials) of the quality of information that is being shared.⁵⁸ Furthermore, information gathered from peers comes with an interpretative framework of experience, which is valued in medicine.⁵⁹

We also see in these learning preferences 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

⁵⁴ Noah, *supra* note 35, at 402-403.

⁵⁵ McAlister, *supra* note 27.

⁵⁶ Noah, *supra* note 35, at 402-403.

⁵⁷ *Id.*

⁵⁸ Klein, *supra* note 21, at 60.

⁵⁹ *See supra* notes 26-27.

patient presenting to the individual physician. The problem of heterogeneity extends to individualized responses to medications.⁶⁰

Finally, in a tradition-oriented profession like medicine (like most professions), 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 this learning pattern 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.⁶¹

The observed skepticism of scientific studies as essential supports for prescribing may reflect patterns of learning and practice that are simply resistant to scientific evidence no matter what the quality of information available. Reliance on peers and peer practices may also respond to ineffective dissemination of knowledge through other outlets, including both journal articles and continuing medical education programs. In addition to these considerations, deficiencies in the production and quality of clinical knowledge, which are 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

⁶⁰ Heterogeneity is a particular problem in the responsiveness of patients to particular medications, both in terms of effectiveness and adverse effects. Soumerai, *supra* note 22, at 143. *See also*, EPSTEIN, *supra* note 5, 118-120.

⁶¹ See, e.g., Symposium: Appropriate Management of Pain: Addressing the Clinical, Legal, and Regulatory Barriers, 24 J.L. Med. & Ethics 285-364 (1996).

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,⁶² has produced an insufficient supply of clinical knowledge for off-label prescribing. This gap exists not only in the case of non-approved uses but also the perhaps even more common incidents of off-label prescribing relating to the use of approved medications for patient populations on which the drug has not been tested and where there may be significant disparities in effectiveness and safety (*e.g.*, certain drugs tested only on men but prescribed for women and drugs tested only on adults but prescribed for children) and use of medications for doses or for 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 insufficiency in the production of Phase IV clinical trials extends to all prescribing, including both off-label prescribing and prescribing within the scope of approval. These 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, a number that is too small to reveal uncommon though quite serious adverse effects. 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. Once available for prescribing,

⁶² See Part II *supra*.

however, the approved drug will be used by patients taking any number of other medications; and so, 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 both of effect and safety. These differences are likely to be detected only in the postmarketing phase of research.⁶³ Finally, the FDA does not require proof of comparative efficacy for approval of a new medication, and so trials that compare one drug to another usually take place, if at all, only after a new medication has been approved.⁶⁴

The insufficiency in clinical trials occurs both in terms of the volume of this research as well as in its quality. Understanding the sources of inadequacies in contemporary clinical research for the needs of clinical practice emerges from an examination of the funding for clinical research (and the presumed impact of that funding) as well as limitations in the design of clinical trials.

Randomized clinical trials are expensive. In fact, the larger number of subjects and longer lifespan of Phase IV trials make them particularly expensive. The pharmaceutical industry is not the only source of financing for post-marketing clinical

⁶³ DeMonaco, *supra* note 4.

⁶⁴ Those comparative studies currently conducted can suffer from design flaws relating to whether the appropriate dosage is chosen for the comparable 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); V. Frighi, *Medical Journals, Academia, and Industry-Sponsored Clinical Trials*, 2 PLOS MED.7, e218 (2005); J. Lexchin, et al., *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, 326 BRITISH MED. J. 7400, 1167 (2003), available at <http://www.pubmedcentral.nih.gov/picrender.fcgi?tool=pmcentrez&blobtype=pdf&artid=156458>

research; it's just the biggest by far.⁶⁵ The federal National Institutes of Health (NIH) has been expanding its commitment to clinical research of late, but currently spends only 30% of its budget (approximately \$850 million) on pharmaceutical clinical trials of all types, including Phase I, II, III as well as Phase IV trials.⁶⁶ The federal Agency for Healthcare Research and Quality (AHRQ) spends approximately \$30 million annually on clinical trials, although again not only Phase IV trials.⁶⁷ 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.⁶⁸ 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.⁶⁹ The Medicare program has also begun to "fund" clinical research studies on its own beneficiaries through a condition on payment for "experimental" interventions.⁷⁰ In comparison to the approximately \$950 million of federal money devoted to all phases of clinical trials, pharmaceutical firms spend \$4.1 billion on such research, over four times the government expenditure. Of that, about \$410 million is spent on Phase IV trials alone.⁷¹ While private insurers and pharmacy benefits management programs are beginning an effort to

⁶⁵ EPSTEIN, *supra* note 5, at 145, analyzing data on marketing expenditures and relating those to clinical trial expenditures.

⁶⁶ D.G. Nathan & H.E. Varmus, *The National Institutes of Health and Clinical Research: A Progress Report*, 6 NAT'L MED. 1201 (2000).

⁶⁷ Tunis, *supra* note 35 1628.

⁶⁸ *Id.*

⁶⁹ AHRQ, *Center for Education and Research on Therapeutics*, available at <http://www.ahrq.gov/clinic/certsovr.pdf>.

⁷⁰ Center for Medicare & Medicaid Services, *National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development* (2006). *See also*, Sandra J. Carnahan, *Medicare's Coverage with Study Participation Policy: Clinical Trials or Tribulations*, YALE J. HEALTH POL'Y, L. & ETHICS, forthcoming. *See also*, discussion of data collection by private insurers, *supra* note 8.

⁷¹ K. Getz & S. Zisson, *Clinical Grants Market Decelerates*, 10 CENTERWATCH 4 (2003). The pharmaceutical industry spends more than \$38 billion annually on research and development generally. Nicholas Bakalar, *Review Finds Drug Makers Issue More Positive Studies*, N.Y. TIMES, Feb. 27, 2007.

produce clinical research on approved drugs, this effort is in its infancy and currently is confined largely to collecting data from the pharmaceutical industry itself.⁷² Even if this effort increases, the information produced may be viewed as proprietary.

Pharmaceutical industry support for research, so essential to the production of clinical knowledge in the face of limited public funding, has raised substantial concerns, as described in Part I of this article. The interesting, vigorous and disturbing 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 current credibility crisis may have a nonspecific but pervasive effect on the uptake of clinical research results into medical practice, especially when fed into a model of physician learning and decision making that is already skeptical of the usefulness of scientific studies.⁷³ Finally, the quality of clinical research certainly limits its utility for regulatory and private controls over physician prescribing. If clinical studies are biased, then public and private efforts to control prescribing rely on defective information.⁷⁴

In January 2003, Bekelman and colleagues published a watershed article on the impact of funding source on results of research.⁷⁵ In this article, they performed a meta-

⁷² See, e.g., Peter J. Neumann, Evidence-Based and Value-Based Formulary Guidelines, 23 HEALTH AFFAIRS 124 (2004). Interestingly, the Neurontin settlement, discussed in Part IV, is providing grants to organizations to study prescribing patterns and provide education to doctors and consumers concerning sources of information for prescription drugs. *Attorney General Myers, Kitzhaber Address "1st of Its Kind" Conference in Portland*, U.S. State News, Dec. 4, 2006, available at 2006 WLNR 20971720; *Kaiser Permanente Receives Research Grant to Study Medication Prescribing Practices*, DRUG WEEK, May, 19, 2006, available at 2006 WLNR 8114182.

⁷³ See *supra* notes 26 and 28.

⁷⁴ See *infra* text accompanying note 86.

⁷⁵ 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, James F. Fries and Eswar Krishnan, *Equipose, Design Bias, and Randomized Controlled Trials: The Elusive Ethics of New Drug Development*, 6 ARTHRITIS RESEARCH & THERAPY 3, R250–R255 (2004), available at <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=15142271>; Mohit

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.⁷⁶ Bekelman's study thus examined the aggregation of data over several studies of single drugs or other medical interventions.⁷⁷ Bekelman and colleagues concluded that the sponsorship of a study was very closely associated with the outcome reported, even in the case of random controlled trials. The authors concluded that:

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 to reach conclusions that were favorable to the sponsor than were nonindustry studies.⁷⁸

The pattern of "pro-industry conclusions," as the authors termed the phenomenon, was pronounced in several instances.⁷⁹ 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.⁸⁰ Other studies showed less dramatic differences, but a difference of 20% was most common when comparing the rate of positive and negative outcomes over the aggregated studies of particular drugs or other interventions.⁸¹

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

Bhandari, et al., Association Between Industry Funding and Statistically Significant Pro-Industry Findings in Medical and Surgical Randomized Trials, 170 CAN. MED. ASSOC. J. 4, 477-480; Lexchin, *supra* note 64.

⁷⁶ See Bekelman, *supra* note 75, at 456.

⁷⁷ *Id.*

⁷⁸ *Id.* at 463.

⁷⁹ *Id.*

⁸⁰ *Id.* at 456.

⁸¹ *Id.* at 458.

the part of the industry-funded researcher, influencing the researcher's collection and analysis of data?⁸² 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?⁸³ Or, is the observed bias in the literature 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?⁸⁴ Or, is it possible that 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."⁸⁵

Of course, 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

⁸² The Bekelman article considers several factors contributing to disproportionately positive results, but does not list individual researcher bias among those. Bekelman, *supra*, note 75, at 464. *But see*, Catherine D. DeAngelis, *The Influence of Money on Medical Science*, 296 JAMA 996, 996 (2006), considering this possibility.

⁸³ *See e.g.*, Fries, *supra* note 75. The authors argue that "extensive preliminary data are used to design [industry-funded] studies with a high likelihood of being positive;" and 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 comparables that are likely to provide a positive result for the sponsor and one that is acceptable to the F.D.A.

⁸⁴ 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 with other funding for research. D. Blumenthal, et al., *University-Industry Research Relationships in Biotechnology: Implications for the University*, 232 SCIENCE 1361 (1986); *See also* Richard Smith, *Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies*, 2 PLoS Med 5, e138 (2005), available at <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1140949>, reporting 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, *supra*, note 75, at 463. *See* discussion of Bayh-Dole *infra*, text at notes 134-137.

⁸⁵ Editorial, *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 22, 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 84, 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.

research about a particular drug. Systemic bias has serious implications for the aggregation of published results. Such aggregation of results is often the foundation for the “evidence” for evidence-based medicine – for practice guidelines and consensus statements for treatment decisions.⁸⁶ If published results, in the aggregate, show a bias toward “pro-industry” conclusions, the disutility of published clinical trials becomes apparent, raising issues not only for the practicing physician but also for any gatekeeper, governmental or private, that aims at controlling individual prescribing decisions by reference to published clinical studies.

The Bekelman piece is only an 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.⁸⁷ In a summer 2006, editorial, Dr. Catherine DeAngelis, the editor-in-chief of JAMA, identifies a litany of examples of

⁸⁶The aggregation of study results is filtered through expert opinion in the development of clinical practice guidelines; however, a study of experts involved in the development of published practice guidelines or consensus statements found that 87% had financial connections to pharmaceutical firms. Niteesh Choudhry, et al., *Relationships Between Authors of Clinical Practice Guidelines and the Pharmaceutical Industry*, 287 JAMA 612 (2002). Of course, these relationships may have no effect on the content of the guidelines. See *supra* note 4. See also David G. Duvall, *Conflict of Interest or Ideological Divide*, CURRENT. MED. RES. & OPINION, Sept. 1, 2006, available at 2006 WLNR 18371153. The use of expert opinion in the development of guidelines also illustrates the reliance on peer and leader opinions in medical decisionmaking. See discussion *supra* text accompanying notes 26, 25, 37-40, 54-59, 61.

⁸⁷ While the discussion that follows focuses on the issues arising in the publication of clinical studies, research centers 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. Jordan Cohen, *AAMC Urges Speedy Adoption of NIH Conflict of Interest Reforms* (2004), available at <http://www.aamc.org/newsroom/pressrel/2004/040506.htm>; United States General 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*, (Issued November 2003), available at http://www.eric.ed.gov/ERICDocs/data/ericdocs2/content_storage_01/0000000b/80/2b/f3/c2.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.); Harrington, Peter J, *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). See also, *infra*, text accompanying notes 165-169 for discussion of governmental policies on conflicts of interest.

“research irregularities” in research sponsored by “for-profit companies.”⁸⁸ 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.”⁸⁹ She further details 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.⁹⁰ DeAngelis’ concerns are shared by many,⁹¹ and the behaviors she identifies are well documented.⁹² In addition to JAMA’s adventures, the New England Journal of Medicine dealt with its own controversy with industry-supported research when it published notices stating that they believed that Merck intentionally altered the evidence in clinical trials of Vioxx the results of which were published in the Journal.⁹³

⁸⁸DeAngelis, *supra* note 82.

⁸⁹ *Id.* at 996.

⁹⁰ *Id.*

⁹¹ The most prominent critique of the pharmaceutical industry, including their research efforts, is another medical journal editor Marcia Angell, former editor of the New England Journal of Medicine, author of *The Truth About Drug Companies: How They Deceive Us and What to Do About It* (2004).

⁹² See, e.g., Thomas Bodenheimer, *Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539 (2000) (documenting ghostwriting); See also, U.S. ex rel. McDermott v. Genentech, 2006 WL 3741920 at 3 (D. Maine 2006) (concerning alleged ghostwriting).

⁹³Gregory D. Curfman, et al., *Expression of Concern Reaffirmed*, 354 NEW ENG. J. MED. 1193 (2006). See also Claire Bombardier, et al., *Correspondence, Response to Expression of Concern Regarding VIGOR Study*, 354 NEW ENG. J. MED. 1196 (2006). See also, The Lancet Editors, *Vioxx: An Unequal Partnership Between Safety and Efficacy*, 364 THE LANCET 1287 (2004) (noting that “the real picture of cardiovascular risk has been apparent for some time and Merck’s vigorous defence 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.”); Editorial, *Vioxx, The Implosion of Merck, and Aftershocks at the FDA*, 364 THE LANCET 1995 (2004).

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.⁹⁴ As most critics acknowledge, pharmaceutical industry support for clinical research has significant benefits, and it is highly unrealistic to think that patients would be better off without it.⁹⁵ 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,⁹⁶ has instituted several policies to handle financial conflicts of interest related to articles submitted for publication.⁹⁷ Among those, the requirement of author disclosure of financial interests and the requirement of independent data analysis for industry-supported studies illustrate important points in the limitations of

⁹⁴ 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 (2004).

⁹⁵ Brennan, *supra* note 24; DeAngelis, *supra* note 82.

⁹⁶ JAMA is a member of the International Committee of Medical Journal Editors, 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* <http://www.icmje.org/> (last visited October 8, 2006).

⁹⁷ 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. Editorial, *supra* note 84. One of the most highly publicized instances of alleged suppression of study results indicating that the use of Paxil for adolescents suffering from depression may increase suicide rates for that population. Eliot Spitzer, Attorney General of New York, sued GlaxoSmithKline for its actions in regard to Paxil. As part of the settlement of the litigation, GSK agreed to establish a clinical trials registry on which it would post summaries of all clinical studies within 10 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 Law Reporter 1290 (September 2, 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 Law Reporter 1325 (September 16, 2004).

current responses to financial conflicts of interest in the production of clinical knowledge.⁹⁸

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 1985;⁹⁹ made disclosure mandatory in 1989;¹⁰⁰ began publishing author disclosures in 1990;¹⁰¹ and strengthened its disclosure requirements in 2006,¹⁰² in response to concerns about author non-compliance with the Journal's prior disclosure requirements.¹⁰³

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."¹⁰⁴ 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 provides a launching point for a discussion of how a reader should account for a disclosed relationship between researcher and sponsor in evaluating the article as a source of information to incorporate in practice. In a selection of JAMA issues published in 2005 through the August 2, 2006 issue (selecting every fourth issue published), at least one of the authors for approximately one-third (35 of 106) of articles categorized by the Journal as "Original Contributions" (31 of 90) or

⁹⁸ Editorial, *supra* note 85.

⁹⁹ E. Knoll & George D. Lundberg, *New Instructions for JAMA Authors*, 254 JAMA 97 (1985).

¹⁰⁰ George D. Lundberg & Annette Flanagin, *New Requirements for Authors: Signed Statements of Authorship Responsibility and Financial Disclosure*, 262 JAMA 2003 (1989).

¹⁰¹ DeAngelis, *supra* note 82 at 997.

¹⁰² Annette Flanagin, *Update on JAMA's Conflict of Interest Policy*, 296 JAMA 220 (2006).

¹⁰³ DeAngelis, *supra* note 82 at 997.

¹⁰⁴ *Id.* at 997.

“Reviews” (4 of 16) disclosed financial relationships.¹⁰⁵ Four of the thirty-five instances of reported relevant financial relationships were by authors of Reviews; *i.e.*, meta-analyses of previously published studies. Reviews are among the most influential articles in medical journals.¹⁰⁶ Because “the essence of reviews and 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 NEJM had to relax its prohibition in 2002 because of its inability to secure reviews of drug therapies under the former standards.¹⁰⁷

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 50% were written by authors with disclosable financial relationships. These numbers may actually under-report the proportion of JAMA articles written by authors with relevant

¹⁰⁵ 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. In July 2006, several incidents in which articles of published articles failed to disclose relationships as required by the Journal’s policy came to light. *See* DeAngelis, *supra* note 82.

¹⁰⁶ In one study, 73% of physician respondents reported that they used review articles as an information source. These review articles may be attractive to physicians because they digest 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 on their own and only 46% felt capable of doing a literature search. McAlister, *supra* note 27.

¹⁰⁷ Editorial, *Financial Associations of Authors*, 346 NEW ENG. J. MED. L.J. 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.

financial interests as there have been some reports of authors failing to disclose required information.¹⁰⁸

The editor of JAMA, in an editorial published in the Journal describing implementation of the Journal's disclosure policy, argues that all articles in JAMA have passed "rigorous peer review and careful editorial evaluation."¹⁰⁹ She goes on to say that the fact that authors of several articles published by JAMA in early 2006 failed to disclose required information "does not automatically translate to the article being flawed."¹¹⁰ Still, "[f]or disclosure to be effective, the recipient of the advice must understand how the conflict of interest has influenced the advisor and must be able to correct for that biasing influence."¹¹¹

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, applying its "rigorous peer review" process, and knowing of the financial interests of the author and the source of sponsorship, has published an article, 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.¹¹² If that pattern of skepticism is to be encouraged, then on what should the physician rely in deciding to prescribe medications off-label? Experience? Intuition? Peer opinion leaders? Enlarging the scope just a bit, how should consensus or practice guidelines panels treat the one-third of JAMA articles that are written by authors with financial self-interest?

¹⁰⁸ DeAngelis, *supra* note 82 at 997.

¹⁰⁹ *Id.*

¹¹⁰ *Id.*

¹¹¹ 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 26 and 28.

¹¹² *See supra* notes 26 and 28.

These articles can hardly be eliminated entirely from consideration because they are likely to be the only source of peer-reviewed data and because they may in fact be valid.

Disclosure does not itself remedy concerns with the quality of clinical information. Nor has disclosure of conflicts of interest in medicine produced the desired response in the clinical context. The process of disclosing financial conflicts of interest may encourage the physician to grant himself or herself a “moral license” to behave differently once the disclosure has been made.¹¹³ 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.¹¹⁴ The doctor-reader may behave differently than patients in this regard, however, as doctors tend to believe that they themselves are not influenced by their financial interests but that other doctors may be.¹¹⁵

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. In 2005, JAMA established a policy requiring that the authors of industry-sponsored studies in which data analysis was done “solely 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 for consideration for publication.¹¹⁶ The preference for biostatisticians working at “academic” institutions works from an assumption that the place in which the evaluation is conducted makes a difference. Furthermore, independent, external data analysis is not required of studies

¹¹³ Cain, *supra* 111, at 7.

¹¹⁴ *Id.* at 5.

¹¹⁵ Jason Dana, *A Social Science Perspective on Gifts to Physicians From Industry*, 290 JAMA 252 (2003).

¹¹⁶ 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).

conducted and analyzed in academic institutions working under contract (through a research grant funding the study) with a for-profit industry sponsor. 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 and into contract research organizations (CROs)¹¹⁷ and private physician offices. Although estimates of the magnitude of the shift from academic medical centers (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. Only 40% of the funding of clinical trials is currently being placed with academic medical centers; and 60% is being placed with private practices, a three-fold increase in ten years. Fewer than half of researchers work in academic medical centers, representing an 80% decrease over ten years.¹¹⁸ The number of physicians in private practice who were engaged in protocols tripled to nearly 12,000 physicians between 1990 and 1995.¹¹⁹ Estimates of CRO participation in pharmaceutical research report an annual growth rate of approximately 20% between 1995 and 2000.¹²⁰

¹¹⁷ Contract Research Organizations (CROs) are free-standing, typically for-profit companies that provide research services under contract with pharmaceutical companies as well as 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. 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 AFFAIRS 129, 137-138 (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 78-84 (2002).

¹¹⁸ Jason E. Klein and Alan R. Fleischmann, *The Private Practicing Physician Investigator: Ethical Implications of Clinical Research in the Office Setting*, 32 HASTINGS CTR. REPT. 22, 22 (2002). See also Office of Inspector General, *supra* note, at 12; K. Morin, *supra* note 117.

¹¹⁹ M. Hovde & R. Seskin, *Selecting U.S. Clinical Investigators*, APPLIED CLIN. TRIALS, 34-42. (Feb. 1997).

¹²⁰ Rettig, *supra* note 117.

Research has become a profit center for the physician in private practice.¹²¹ The sponsor typically pays the doctor in private practice a fee of \$2000 to \$7000 per patient enrolled, sometimes with little required beyond the collection of minimal data.¹²² Enrollment payments by NIH for research in AMCs generally have been somewhat lower.¹²³ According to a 2000 OIG study, doctors in private practice engaged in industry-funded studies also tend to receive additional compensation from sponsors in terms of consulting fees, speakers' bureaus, and advisory panels.¹²⁴

It is likely that this trend of moving clinical trials away from academic medical centers and out to private practices will continue. Post-marketing clinical trials require very large numbers of patients, and these numbers might be captured more quickly by paying many private physicians to recruit their own patients rather than by paying an academic researcher to try to recruit individuals from the general population or from teaching hospitals.¹²⁵ Some sponsors believe that the practicing physician researchers and the contract research organizations will be able to complete clinical trials more quickly than will an academic medical center because of additional administrative requirements often found in universities.¹²⁶ Others have argued that the most effective and informative clinical trials must be conducted in a great number of physician offices with a wide range of patients and practitioners with varying skill levels if they are to be useful for medical

¹²¹ Payment for enrollment of patients in clinical trials can substantially exceed the amounts paid by payers for treating those patients. K. Morin, *supra* note 117 at 81.

¹²² K. Morin, *supra* note 117 at 78-84.

¹²³ NIH studies typically pay approximately \$1,000 per enrollee. *Id.* at 81.

¹²⁴ Office of Inspector General, *supra* note 6 at 16.

¹²⁵ *Id.* at 13. See also Department of Health and Human Services, *Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection*, 69 Fed. Reg. 26393 at 26394 (2004).

¹²⁶ For discussion of the perceived advantages of conducting clinical trials in private physician offices, 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).

decision making.¹²⁷ Finally, as is 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.¹²⁸

The JAMA policy requiring university or government analyses of data implies that the academic medical center provides a greater defense against industry behavior that undermines the reliability of clinical studies.¹²⁹ The interests of the academic clinician researcher and the academic medical center, it is thought, will militate against acceptance of publication agreements that allow the sponsor to suppress or permit 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. There may have been an assumption, for example, that academic researchers would be particularly sensitive to financial conflicts of interest. In fact, however, compliance with JAMA's relatively benign disclosure requirements has proven spotty among academic researchers at very well-respected research universities.¹³⁰ Beyond questions of character or understanding¹³¹ that might lie beneath these individual instances of noncompliance, contemporary circumstances challenge the assumed singularity of interests for the academic research endeavor.

¹²⁷ Tunis, *supra* note 35 at 1627. See *supra* note 65 and *infra* text accompanying notes 201-203.

¹²⁸ See *supra* note 65 and *infra* text accompanying notes 201-203.

¹²⁹ 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 JOURNAL OF LAW, MEDICINE & ETHICS 379 (2000).

¹³⁰ DeAngelis, *supra* note 82.

¹³¹ Studies consistently demonstrate that physicians and researchers believe themselves to be "impervious to industry influence" despite the literature that indicates that gifts trigger an "unconscious and unintentional" sense of obligation. See, e.g., David Henry, et al., *Ties That Bind: Multiple Relationships Between Clinical Researchers and the Pharmaceutical Industry*, 165 ARCH. INTERN. MED. 2493, 2495 (2005).

Elite research universities and their medical centers rely primarily on NIH funding to support their research efforts; but even in these institutions, industry-funded research provides opportunities to grow the discretionary budget by providing a margin that remains in the control of the department or the researcher rather than the university fisc.¹³² AMCs other than the research elite may be losing the competition for the now shrinking NIH research dollar; and for these academic institutions, pharmaceutical research contracts are filling the gap.¹³³

In addition, the Bayh-Dole Act of 1980,¹³⁴ which unleashed the entrepreneurial spirit of academic researchers and their employers with the goal of expediting the transfer of academic research to the market, significantly altered the interests of these researchers and universities.¹³⁵ 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.¹³⁶ Start-up companies, like those

¹³² A 1996 study of the 50 universities receiving the highest level of NIH funding reported that 28% of their faculty received industry funding for research. D. Blumenthal, et al., *Participation of Life-Science Faculty in Research Relationships with Industry*, 335 NEW ENG. J. MED. 1734 (1996). More recent data reports that industry funds for research in universities increased by 875% between 1980 and 2000. 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%. Trudo Lemmons, *Leopards in the Temple: Restoring Scientific Integrity to the Commercialized Research Scene*, 32 J.L. MED. & ETHICS 641 (2004), relying on SHELDON KRIMSKY, *SCIENCE IN THE PRIVATE INTEREST: HAS THE LURE OF PROFIT CORRUPTED BIOMEDICAL RESEARCH?* (Rowman & Littlefield) (2003).

¹³³ Reliance on industry funding is not confined to U.S. universities alone. Between 2002 and 2004, for example, industry funding to McMaster University in Canada reportedly nearly quadrupled from \$34 million to nearly \$129 million. In addition, 15.5% of the full-time faculty had “financial connections” to pharmaceutical and biotechnology firms. 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. See Steve Buist, et al., *Risks, Rewards & Research*, HAMILTON SPECTATOR, June, 25, 2005.

¹³⁴ Bayh-Dole Act, Pub. L. No. 96-517, 94 Stat. 3015 (1980).

¹³⁵ See 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); Clovia Hamilton, *University Technology Transfer and Economic Development: Proposed Cooperative Economic Development Under the Bayh-Dole Act*, 36 J. MARSHALL L. REV. 397 (2003).

¹³⁶ L. Pressman. *AUTM Licensing Suvey, FY 1999: Survey Summary*. Northbrook, Ill: Association of University Technology Managers, 2000.

stimulated by Bayh-Dole and often jointly owned by research faculty and their university-employers, in fact have been associated with delays in publication of study results and resistance to sharing results,¹³⁷ mirroring the issues concerning sponsor control of research discussed above. At a minimum, 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.

Industry influence is not the only quality issue affecting the utility of clinical trials for prescribing decisions. Critics of the current state of clinical research focus on faults in the selection and 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. Although these tools are unavoidable in some circumstances such as studies evaluating the effectiveness of pain medication, they tend to suffer from bias.¹³⁸ 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 those trials that are targeted

¹³⁷ Blumenthal, *supra* 132; D. Blumenthal, et al., *Withholding Research Results in Academic Life Science: Evidence from a National Survey of Faculty*, 277 JAMA 1224 (1997); E.G. Campbell, et al., *Data Withholding in Academic Genetics: Evidence from a National Survey*, 287 JAMA 473 (2002).

¹³⁸ Tunis, *supra* note 35 at 1626.

toward producing information needed to make a decision in practice.¹³⁹ PCTs must be designed to respond to clinical decision making. They must “select clinically relevant interventions to compare, include a diverse population of study participants, recruit participants from a variety of practice settings, and collect data on a broad range of health outcomes.”¹⁴⁰ Clinical trials that will be effective in informing prescribing decisions must 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.¹⁴¹ They must also include patients who replicate the typical clinical population in terms of history of medication and medical conditions -- characteristics that are typically treated as excluding factors in clinical trials.¹⁴² In addition, the studies should be designed to compare effectiveness, cost and safety among available drugs and between medications and non-pharmaceutical therapies.¹⁴³ Finally, clinical trials should account for variations in the quality of physician skills as such variations may have a substantial impact on the effectiveness of any therapy.¹⁴⁴ Removing or regulating conflicts of interest in research will not stimulate more clinically-useful design.

Furthermore, off-label prescribing and other treatment decisions also 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

¹³⁹ D. Schwartz & J. Lellouch, *Explanatory and Pragmatic Attitudes in Therapeutic Trials*, 20 J. CHRONIC DIS. 637 (1967); M. Roland & D.J. Torgerson, *What are Pragmatic Trials?*, 316 BRITISH MEDICAL JOURNAL 285 (1998).

¹⁴⁰ Tunis, *supra* note 35 at 1626.

¹⁴¹ *Id.* at 1626.

¹⁴² Office of Inspector General, *supra* note 6, at 14.

¹⁴³ Tunis, *supra* note 35 at 1626.

¹⁴⁴ *Id.* at 1627.

makers.”¹⁴⁵ The lack of clinical research effort reduces the effectiveness of clinical practice guidelines when those guidelines do not include “clear, specific recommendations,”¹⁴⁶ and hampers payers who lack the information necessary to establish scientifically grounded coverage decisions.¹⁴⁷ This insufficiency is certainly not explained by conflicts of interest. In fact, restrictions on industry funding of research is likely to diminish the production of necessary clinical knowledge.¹⁴⁸

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 sets a generic warning flag on the data, a warning flag that is nonspecific and, in the case of peer-reviewed published studies is countered by the peer-review “seal of approval.” Counterintuitively, the warning flag may actually decrease sensitivity to conflicts of interest, by increasing the assumption of trustworthiness, as such disclosures have in the clinical setting,¹⁴⁹ 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 the interpretation of a trial are totally 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 patient safety is at issue. Other options for

¹⁴⁵ *Id.* at 1625. *See also* Soumerai, *supra* note 22, at 142, referencing the gap in timeliness and noting that “drug cost containment policy making often cannot wait for good evidence.”

¹⁴⁶ *Id.*

¹⁴⁷ *Id.*

¹⁴⁸ *See supra* text accompanying notes 65-72 and 95.

¹⁴⁹ *See supra* notes 111-114 and accompanying text.

increasing the volume of post-approval clinical research beyond that required for safety surveillance typically require accounting for the cost of such research somewhere.

Although the conflicts-of-interest tool addresses one aspect of imperfection in information for prescribing, 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 method for distinguishing between appropriate and inappropriate prescribing.

Part III: Through a Glass Darkly: False Claims Act Litigation and Off-Label Prescribing

Over the past two 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.¹⁵⁰ Included among the DOJ's victories is the settlement of \$455 million and guilty plea by the manufacturer of a single drug, Neurontin.

The Neurontin-style litigation, whether hailed as “the best hope for short-term reform”¹⁵¹ or condemned as “inefficient” and “overly-aggressive,”¹⁵² is most often viewed as a dramatization of financial conflicts of interest in research and clinical decision making, fueled by pharmaceutical industry practices relating to prescribing.¹⁵³ It

¹⁵⁰ See *supra*, note 7.

¹⁵¹ David J. Rothman, *Strong Medicine*, THE NEW REPUBLIC (September 27, 2004), available at 2004 WLNR 12846426.

¹⁵² Christopher D. Zalesky, *Pharmaceutical Marketing Practices: Balancing Public Health and Law Enforcement Interests; Moving Beyond Regulation Through Litigation*, 39 J. HEALTH LAW 235, 264 (2006). See also Ralph Hall and Robert Berlin, *When You Have a Hammer, Everything Looks Like a Nail: Misapplication of the False Claims Act to Off-Label Promotion*, 61 FOOD DRUG L. J. 653 (2006).

¹⁵³ 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*, 40 TRIAL 12 (2004).

certainly does that. Although never formally resolved by verdict or final judgment,¹⁵⁴ the evidence strongly suggests that Parke-Davis,¹⁵⁵ the defendant manufacturer of Neurontin, had used both educational and research efforts as vehicles to market the drug aggressively for off-label uses.¹⁵⁶

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 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. The discussion of the case, thus, highlights the deficiencies in current forms of clinical research,¹⁵⁷ both in making prescribing decisions and in regulating those decisions. The case illustrates quite sharply the importance of appreciating the issue of

¹⁵⁴ 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. In fact, in the Neurontin settlement, Parke-Davis pled guilty of violations only for behavior prior to 1996 to avoid exclusion from these reimbursement programs.

¹⁵⁵ 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/pfizer/history/2000.jsp>

¹⁵⁶ Michael A. Steinman, et al., *Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents*, 145 ANNALS OF INTERNAL MEDICINE 284 (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.

¹⁵⁷ See discussion in Part III.

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 research has been weak.¹⁵⁸ Provisions of the Food, Drug, and Cosmetic Act restrict,¹⁵⁹ but do not entirely prohibit,¹⁶⁰ 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.¹⁶¹ Furthermore, the FDA largely relies on voluntary

¹⁵⁸ 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, for example. American Medical Association. 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>; PhRMA Code on Interactions with Healthcare Professionals, available at <http://www.phrma.org/files/PhRMA%20Code.pdf>. See also, American Academy of Family Physicians. (Issued 1998, Revised 2004). AAFP Policies. 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. 62057, 62063 (Oct. 3, 2002). A few private universities also have established their own policies restricting or prohibiting particular marketing and educational activities or 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 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).

¹⁵⁹ 21 U.S.C. § 321(n) (2006); 21 U.S.C. § 352(n) (2004).

¹⁶⁰ The FDCA allows companies to distribute published peer-reviewed studies, for example. 21 U.S.C. § 360(a)(1)(A) (2000).

¹⁶¹ *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51 (1988). 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/default.asp> (Last visited on 9/28/06). See generally 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, 499 (2002); David M. Fritch, *Speak*

compliance with its marketing restrictions and has devoted only limited resources to post-approval marketing surveillance.¹⁶² 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.¹⁶³ 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.¹⁶⁴

Federal agencies also regulate post-approval pharmaceutical research efforts through the mechanisms that govern research with human subjects generally.¹⁶⁵ These 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.¹⁶⁶ 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

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).

¹⁶² See Zalesky, *supra* note 152, describing the FDA's policy of voluntary compliance and limited staff devoted to all advertising and marketing issues of approved drugs.

¹⁶³ 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 151.

¹⁶⁴ *Id.* at 253. See, e.g., D.C. CODE § 48-833.01 (2004).

¹⁶⁵ See, e.g., 45 C.F.R. 46.101 et seq. (regulating research funded by the Department of Health and Human Services); 21 C.F.R. 50.1 et seq. (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 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; CARL H. COLEMAN, ET AL., *THE ETHICS AND REGULATION OF RESEARCH WITH HUMAN SUBJECTS* 107 (LexisNexis (a division of Matthew Bender) 2005).

¹⁶⁶ *Id.* at 106.

sponsors, including sponsors of pharmaceutical research.¹⁶⁷ 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.¹⁶⁸ 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.¹⁶⁹

In contrast to the limitations imposed upon or adopted by the FDA in regulating industry-prescriber interactions, the Department of Justice (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

¹⁶⁷ 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 because research with human subjects must provide benefits that outweigh the risks of the studies. To the extent that conflicts of interest may compromise the validity or usefulness of the results, they may alter the risk-benefit calculus.

¹⁶⁸ 42 C.F.R. 50.604; 68 Fed. Reg. 15456-01 (March 31, 2003). See e.g., 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); United States General Accountability Office, *University Research: Most Federal Agencies Need to Protect against Financial Conflicts of Interest*. Report to the Honorable Richard C. Shelby, U.S. Senate (2003) at.17.

¹⁶⁹ 42 C.F.R. 50.604 (HHS); 21 C.F.R. 54.4 (FDA). The 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 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.”

identified industry-prescriber relationships as a primary target for enforcement efforts.¹⁷⁰ 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,¹⁷¹ such as Medicare and Medicaid, to establish boundaries on post-approval marketing and funding of research by pharmaceutical firms.¹⁷² 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.¹⁷³ Shortly after its approval, physicians were prescribing Neurontin as a 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. In fact, in 1995, one year after approval of Neurontin, 40% of the prescriptions written for the medication were for off-label indications.¹⁷⁴

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

¹⁷⁰ Edward Lansdale, *Use As Directed? How Prosecutors are Expanding the False Claims Act to Police Pharmaceutical Off-Label Marketing*, 41 NEW ENG. L. REV. 159 (2006); Marc J. Scheineson and Shannon T. Klinger, *Lessons From Expanded Government Enforcement Efforts Against Drug Companies*, 60 FOOD & DRUG L. J. 1 (2005); Robert Brady, et al., *Pharmaceutical Companies Have Been Penalized for Pushing Their Products for Unapproved Uses*, NAT'L L.J., March 20, 2006, detailing recent actions and settlements. See also, *supra* note 7.

¹⁷¹ 42 U.S.C. 1320a-7b (anti-kickback statute) and 31 U.S.C. 3729-3733 (false claims act).

¹⁷² 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 (January 24, 2006). See U.S. ex rel. Gilligan v. Medtronic, Inc., 403 F.3d 386 (6th Cir. 2005).

¹⁷³ U.S. ex rel. Franklin v. Parke-Davis, 147 F. Supp. 2d 3945 (D. Mass. 2001). See also, "Neurontin," in Physician's Desk Reference, 2005 WL 1158514.

¹⁷⁴ Darryl Haralson and Thomas Ankner, *Drugmaker Admitted Fraud, But Sales Flourish*, USA TODAY, Aug. 17, 2004, 01A. Prescribing patterns for Neurontin during the litigation and after the settlement are described *infra* at text accompanying notes 209-213.

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. The firm argued that the firm itself filed no false claims as the doctors who prescribed the drug, and thus caused the government programs to make payment, were an "intervening force." It also argued that the False Claims Act could not be used to enforce the FDA's restrictions on promotion of approved drugs for off-label uses. The court rejected each of these arguments as they applied to the relator's claims concerning prescriptions for Neurontin paid for by the Medicare and Medicaid programs.¹⁷⁵

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 physicians who had filed a claim, whether false or not.¹⁷⁶ 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

¹⁷⁵*Franklin*, 147 F. Supp. 2d 39. The court did dismiss the relator's claims relating to Accupril, another drug produced by Parke-Davis for insufficient specificity in pleading. *Id.* 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. U.S. ex rel. *Franklin v. Pfizer*, 2002 WL 32128635 (D. Mass. 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. *Id.* at 49-50. The standards for specificity in pleading false claims actions of this sort may have heightened since this decision. *See, e.g.*, U.S. ex rel. *Rost v. Pfizer*, ___ F. Supp. 2d ___ (D. Mass. 2006). *See also*, U.S. ex rel. *McDermott*, 2006 WL 3741920 at 10-12.

¹⁷⁶ This defense mimics the "learned intermediary" defense that has been available to pharmaceutical manufacturers in products liability suits.

were, in fact, the “intended consequence of the alleged scheme of fraud,” satisfying the requirement of causation.¹⁷⁷

The court also rejected Parke-Davis’ argument that the False Claims Act could not be used to enforce the provisions of the Food, Drug and Cosmetic Act concerning promotion of off-label uses. The court rejected this argument holding that the violation 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.”¹⁷⁸ 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.¹⁷⁹

The court contended with two central issues in applying false claims standards to Parke-Davis’ 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 in its motion to dismiss 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

¹⁷⁷ *Id.* at 53.

¹⁷⁸ *Id.* at 51.

¹⁷⁹ *Id.*

statements about the drug’s performance.¹⁸⁰ The 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 . . .”.¹⁸¹

In considering Parke-Davis’ 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.. 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.¹⁸² 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.¹⁸³

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

¹⁸⁰ *Franklin*, 147 F.Supp.2d at 52.

¹⁸¹ *Id.*

¹⁸² Standards for coverage of prescriptions for off-label uses under Medicaid is discussed *infra* at text accompanying notes 235-238.

¹⁸³ The court’s opinion is somewhat confused about the scope of Medicaid coverage, a not uncommon occurrence; and the court says that it “would appreciate an amicus brief from federal officials” on the question of coverage. Another court took a different view of the key issue in *Parke-Davis*. In *U.S. ex rel. Hess v. Sanofi-Synthelabo, Inc.*, 2006 WL 1064127 (E.D. Mo. 2006), the court interprets the earlier *Parke-Davis* decision (at 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 the information on the drug’s performance for the off-label use was “at most, immature, unreliable and misleading,” but not false. *Id.* at 9. See also, *U.S. ex rel. McDermott*, 2006 WL 3741920 at 13, 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 don’t necessarily diminish the ability of the DOJ to get settlements for government claims regarding the same behaviors, however. See *supra* note 154.

Medicaid is a false claim” in its motion to dismiss the *qui tam* action.¹⁸⁴ 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.¹⁸⁵ 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.”¹⁸⁶ 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.¹⁸⁷ 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.¹⁸⁸ In its later opinion denying Parke-Davis’ 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.¹⁸⁹ 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

¹⁸⁴ *Franklin*, 147 F.Supp.2d at 51.

¹⁸⁵ *See, e.g., Weaver v. Reagan*, 886 F.2d 194 (8th Cir. 1989). *See infra* text accompanying notes 230-237.

¹⁸⁶ 42 U.S.C. 1396b(i)(10)

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

¹⁸⁸ *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 231-234.

¹⁸⁹ *U.S. ex rel. Franklin v. Parke-Davis*, 2003 WL 22048255 (D. Mass.) at 2. 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.

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.¹⁹⁰

The Department of Justice, which had monitored the Neurontin litigation from its filing by the private relator,¹⁹¹ 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.¹⁹² Once it entered the case, the DOJ resurrected the allegation of false claims against the Veterans Administration,¹⁹³ 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.¹⁹⁴

The DOJ characterized Parke-Davis's actions as "a widespread, coordinated national effort to implement an off-label marketing plan."¹⁹⁵ 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

¹⁹⁰ *Id.* at 3.

¹⁹¹ 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.

¹⁹² In the 2003 proceeding, the federal government had filed only a "statement of interest" and had not yet intervened. *Franklin*, 2003 WL 22048255 (D.Mass.) at 1.

¹⁹³ Department of Justice, *supra* note 3.

¹⁹⁴ *See, e.g., Rubel v. Pfizer, Inc.*, 276 F.Supp. 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., Attorney General Myers Announces Prescription Drug Education Grants*, US State News, November, 1 2006, 2006 WLNR 19147009.

¹⁹⁵ Department of Justice, *supra* note 3. *See also*, Steinman, *supra* note 156, in which the authors analyze company documents and conclude that Parke-Davis' educational and research efforts were both part of the marketing plan for Neurontin.

money is. I want you out there every day selling Neurontin” for off-label uses.¹⁹⁶ 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.¹⁹⁷

Particular educational/marketing activities alleged by 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.¹⁹⁸ 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, 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.¹⁹⁹ The DOJ further alleged that Parke-Davis representatives made misleading statements about efficacy of the drug for particular purposes.²⁰⁰

¹⁹⁶ Douglas McLeod, *Lawsuits Mount Over Marketing of Epilepsy Drug*, 38 BUS. INS. 3 (June 14, 2004).

¹⁹⁷ *Neurontin Tactics*, available at <http://dida.library.ucsf.edu/pdf/ida00a10>.

¹⁹⁸ This activity actually may be protected under *Washington Legal Foundation*, 13 F.Supp.2d 51 (1988). See *supra* note 161. See also Greene, *supra*, note 158.

¹⁹⁹ See Steinman, *supra* note 156. See also, EPSTEIN *supra* note 5 at 154, arguing that 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.”

²⁰⁰ The Justice Department singled out the promotion of Neurontin for “bipolar disease” and “monotherapy for epileptic seizure.” Department of Justice, *supra* note 3.

The evidence, as presented by the relator and DOJ, also indicates that the firm’s funding of post-approval clinical research on off-label uses for Neurontin also 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.²⁰¹ 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 1994 Fraud Alert.²⁰² 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.²⁰³

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

²⁰¹ *Franklin*, 147 F.Supp2d at 54.

²⁰² Special Fraud Alert: Prescription Drug Marketing Schemes, 59 Fed. Reg. 65376 (August 1994).

²⁰³ OIG Compliance Program Guidance for Pharmaceutical Manufacturers, 68 Fed. Reg. 237131 (May 5, 2003).

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.²⁰⁴

In all, Parke-Davis paid over \$455 million, the largest settlement for such litigation to that date.²⁰⁵ 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 paid for off-label prescriptions for Neurontin²⁰⁶ as well as products liability and consumer protection claims by patients themselves.²⁰⁷

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. 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 the largest settlement to date 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.²⁰⁸

²⁰⁴ Department of Justice, *supra* note 3.

²⁰⁵ 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. Department of Justice Press Release, *TAP Pharmaceutical Products Inc. and Seven Others Charged with Health Care Crimes; Company Agrees to Pay \$875 Million to Settle Charges*, October 3, 2001 available at <http://www.usdoj.gov/opa/pr/2001/October/513civ.htm> Pricing was not involved in the Neurontin litigation.

²⁰⁶ *In re Neurontin Marketing, Sales Practices and Products Liability Litigation*, 433 F.Supp.2d 172 (MDL 2006), holding that plaintiff private insurers stated a claim against the manufacturer under the federal Racketeer Influenced and Corrupt Organizations Act (RICO).

²⁰⁷ *See The Indictment of Pharma Industry Marketing Practices*, INTERNAL MED. ALERT (Oct. 15, 2006); Jablow, *supra* note 153. *See also* Rubel v. Pfizer, 276 F.Supp.2d 904 (2003); Dellinger v. Pfizer, 2006 WL 2057654 (W.D.N.C.).

²⁰⁸ *See supra* note 154. In addition, the settlement was actually approved by Pfizer, Inc., which had acquired Warner-Lambert/Parke-Davis during the course of this litigation (*see supra* note 155); and Pfizer

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 1995.²⁰⁹ Neurontin sales amounted to \$2.7 billion in 2003, of which nearly \$2.5 billion was for off-label uses.²¹⁰

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.²¹¹ Lehman Brothers estimated that the great bulk of those prescriptions for Neurotin -- 90% of sales, in fact -- were still for off-label uses.²¹² 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.²¹³

deflected fault by stating that the activities “did not involve Pfizer practices or employees.” Kabler, *supra* note 195.

²⁰⁹ Haralson and Ankner, *supra* note 174.

²¹⁰ *Id.*

²¹¹ *Id.*

²¹² *Id.*

²¹³ *Commercial Insight: Neuropathic Pain – A Plethora of Patient Segmentation and Product Differentiation Opportunities*, available at http://www.researchandmarkets.com/product/62cb85/commercial_insight_neuropathic_pain

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.²¹⁴ 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.²¹⁵ 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 Neurontin for the treatment of post-herpetic neuropathic pain, *i.e.*, nerve pain associated with shingles,²¹⁶ in the midst of the Neurontin prosecution.

Neurontin has not been approved for the treatment of neuropathic pain caused by other

²¹⁴ See *supra* note 51.

²¹⁵ See, *e.g.*, Steve Simon, et al., *Breakthrough Pain in Opioid-Treated Patients with Neuropathic Pain*, 2 J. OF OPIOID MANAGEMENT 347, 347 (2006).

²¹⁶ Haralson and Ankner, *supra* note 174. See also, "Neurontin," in Physician's Desk Reference, 2005 WL 1158514.

disease states, and it won't 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.²¹⁷ 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 didn't make the drug effective for treating pain. 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 Justice Department 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, for example.²¹⁸ 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.

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

²¹⁷ See Hoover's, *supra* 20, documenting a 77% decline in revenue from Neurontin after patent expiration; Department of Justice, *supra* note 3, observing that the defendant did not pursue approval of off-label uses because of the impending expiration of the patent on Neurontin.

²¹⁸ Department of Justice, *supra* note 3.

off-label prescriptions of Neurontin for Medicaid beneficiaries.²¹⁹ This payment signals that the government (as purchaser for the program’s beneficiaries) did not get what it paid for when it paid for off-label prescriptions of this drug. Parke-Davis was accused, for example, of “steal[ing] from taxpayers” when it promoted off-label uses of Neurontin.²²⁰ After the settlement, however, Neurontin continued to be the third highest drug cost for some state Medicaid programs.²²¹

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.²²² 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.

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.²²³ The legislation

²¹⁹ *Id.*

²²⁰ *Id.*

²²¹ Haralson and Ankner, *supra* note 174.

²²² 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 22.

²²³ Edmonds v. Levine, 417 F.Supp.2d 1323, 1331 (S.D.Fla. 2006)

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 supporting medical evidence for the off-label use of the drug.”²²⁴

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 seizures²²⁵ 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.”²²⁶ However, the agency decided to reimburse for two unapproved indications for which there were no clinical studies proving the drug effective. These two uses were the prescription of Neurontin for ALS, for which the FDA had formally categorized Neurontin as an “orphan drug,”²²⁷ and for diabetic peripheral neuropathy.²²⁸ 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. It excluded, for example, prescriptions for Neurontin for the treatment of neuropathic pain unless the

²²⁴ *Id.* at 1331.

²²⁵ 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.* at 1331.

²²⁶ *Id.*

²²⁷ 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. *Edmonds*, 417 F.Supp2d at 1332.

²²⁸ *Id.* The state also paid for Neurontin for a particular unapproved treatment for epilepsy. *See supra* note 225.

patient had shingles or diabetes. Patients with neuropathic pain from medical conditions other than shingles or diabetes filed suit.²²⁹

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 citations”²³⁰ in the accepted drug compendia.²³¹ The American Hospital Formulary Service Drug Informant (AHFS) 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.²³² 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.”²³³ All but three of the fifty-four uses listed in this publication were recognized as either “effective” or “possibly effective.” Of the three uses categorized in DRUGDEX as “ineffective,” Florida’s Medicaid program actually covered two: ALS and a specific manifestation of epilepsy.²³⁴

²²⁹ 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.

²³⁰ The federal statute does not define the word “citation.” *Edmonds*, 417 F.Supp.2d at 1331.

²³¹ 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 which would exclude specific drugs and which requires 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. *Edmonds*, 417 F.Supp.2d at 1327-1330. For the adverse impact of these methods of drug utilization controls, see Kleinke, *supra* note 22.

²³² *Id.* at 1333.

²³³ *Id.*

²³⁴ *Id.* See *supra* notes 225 and 227.

The District Court held that the Florida agency’s policy violated the coverage mandated in the federal Medicaid program. 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 for individual patients,²³⁵ but that the method used by the state violated the statutory mandate.

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 “this is the same standard employed for FDA-approved uses” and it “is the equivalent of saying the same thing twice.”²³⁶ 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.²³⁷

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.²³⁸ 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

²³⁵ See *supra* note 231.

²³⁶ *Edmonds*, 447 F.Supp.2d at 1337.

²³⁷ *Id.*

²³⁸ See *supra* note 220.

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 prevented patients in some cases from receiving the only effective care available.²³⁹

Private insurers have fared no better than the State of Florida in their attempts to control individual off-label prescribing decisions, and their challenges have nothing to do with the Medicaid statute. The hesitancy of private payers to involve themselves in reining in off-label prescribing may be a simple matter of administrative convenience. If their primary concern is to control drug costs, there are less expensive methods for doing so. These include shifting costs to consumers through co-pays, tiered benefit systems, prior authorization requirements, and step therapy (“fail first”) mechanisms.²⁴⁰ These are hardly satisfactory as methods for evaluating the appropriateness and effectiveness of an off-label or any prescription for that matter because they erect barriers unrelated to the effectiveness of medications.

²³⁹ Of course, the methods for controlling prescribing that are permitted in the federal Medicaid scheme may also harm patients. Kleinke, *supra* note 22.

²⁴⁰ *Id.*

There are, of course, 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. 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 nearly nonexistent. Moreover, if private insurers and pharmacy benefit managers begin to provide serious funding for clinical trials, who is to say that this funding also won't 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.

V. Conclusion

We can view the Neurontin litigation as catching a bad actor. Certainly, the evidence of Parke-Davis' 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 won't 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; won't improve physician learning, and appears to be reducing educational opportunities as firms react to increased risks; and won't 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 isn't 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 won't get us there. Nor will targeting off-label prescribing as if there were no risks in doing so.