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Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information

John E. Osborn

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Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information

John E. Osborn*

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REGULATING OFF-LABEL INFORMATION

“We have met the enemy and he is us.”

Walt Kelly, creator of Pogo.

I. INTRODUCTION

American pharmaceutical manufacturers are under siege. Even casual observers of this sector recognize the severe challenges to the prevailing business model: declining research productivity; heightened regulatory focus on safety and comparative outcomes with a correspondingly low number of new product approvals; decreasing market capitalization of mature companies; increasing product liability claims; evolving price restraints in the face of increasing managed care market power; and the looming uncertainty of the effects of federal health care reform. But, in fact, the single greatest threat to the pharmaceutical industry may be the policy environment within the United States, which is restricting the ability of companies to speak truthfully with physicians about their products.¹

During the past decade drug companies have endured intrusive government investigations of their business practices, particularly with respect to the marketing and promotion of their products. Firms face extraordinary civil and criminal liability if they discuss or otherwise attempt to influence prescribing other than for the indications approved by the U.S. Food and Drug Administration (FDA). There are now well more than one hundred ongoing civil and criminal investigations involving the U.S. Department of Justice (DOJ) and units of the U.S. Department of Health and Human Services (HHS), as well as associated investigations run by state attorneys general.² Billions of dollars in

1. This article addresses the public policies associated with the regulation of pharmaceutical manufacturers' communications with physicians. This includes discussions between field sales representatives, who work for a manufacturer and seek to promote or "detail" the manufacturer's product, and physicians and their office staff. This article is not concerned with so-called "direct to consumer" advertising, in which manufacturers attempt to communicate directly with current or prospective patients about the benefits of using a drug.

2. In a recent speech at the National Health Care Fraud Summit, U.S. Attorney General Eric Holder noted that "[i]n 2009, the Justice Department reached an all-time high in the number of health care fraud defendants charged, more than 800. We also obtained more than 580 convictions.

civil and criminal penalties have been paid to date for alleged wrongdoing,³ and

And on the civil enforcement front, our health care fraud recoveries last year under the False Claims Act exceeded a stunning \$2.2 billion dollars.” Eric Holder, U.S. Attorney Gen., Address at the National Summit on Health Care Fraud (Jan. 28, 2010) (transcript available at <http://www.justice.gov/ag/speeches/2010/ag-speech-100128.html>). See also *infra* note 21 and accompanying text.

3. Publicly disclosed civil settlement and criminal plea agreements have outlined in great detail allegations against nearly all of the major pharmaceutical companies, including Abbott (which paid \$622 million in 2003 to settle a federal investigation into its sales and marketing practices), AstraZeneca (\$355 million in 2003 and \$520 million in 2010), Bayer (\$97.5 million in 2008), Bristol-Myers Squibb (\$499 million in 2006), Cephalon (\$425 million in 2007), Eli Lilly (\$1.415 billion in 2009), Merck (\$670 million in 2008), Pfizer (\$2.3 billion in 2009), Pfizer/Warner-Lambert (\$430 million in 2004), Schering-Plough (\$345 million in 2004), Serono (\$704 million in 2005), and Takeda/Abbott Pharmaceuticals joint venture (\$875 million in 2001). See Gardiner Harris, *Abbott To Pay \$622 Million To End Inquiry Into Marketing*, N.Y. TIMES, June 27, 2003, at C1; Press Release, Dep’t of Justice, AstraZeneca Pharmaceuticals LP Pleads Guilty to Healthcare Crime; Company Agrees To Pay \$355 Million To Settle Charges (June 20, 2003), http://www.justice.gov/opa/pr/2003/June/03_civ_371.htm; Eric Holder, U.S. Attorney Gen., Remarks at the AstraZeneca Settlement Announcement (Apr. 27, 2010) (transcript available at <http://www.justice.gov/ag/speeches/2010/ag-speech-100427.html>); Press Release, Dep’t of Justice, Bayer Healthcare To Pay U.S. \$97.5 Million To Settle Allegations of Paying Kickbacks to Diabetic Suppliers (Nov. 25, 2008), <http://www.justice.gov/opa/pr/2008/November/08-civ-1050.html>; Barnaby J. Feder, *Bristol Says U.S. Inquiry Is Settled*, N.Y. TIMES, Dec. 22, 2006, at C1; Press Release, Dep’t of Justice, Biopharmaceutical Company, Cephalon, To Pay \$425 Million & Enter Plea To Resolve Allegations of Off-Label Marketing (Sept. 29, 2008), <http://www.justice.gov/civil/ocl/cases/Cases/Cephalon/Cephalon%20Press%20Release.pdf>; Press Release, Dep’t of Justice, Eli Lilly and Company Agrees To Pay \$1.415 Billion To Resolve Allegations of Off-label Promotion of Zyprexa (Jan. 15, 2009), http://www.justice.gov/civil/ocl/cases/Cases/Eli_Lilly/Lilly%20Press%20Release%20Final%2009-civ-038.pdf; Press Release, Dep’t of Justice, Merck Agrees To Pay \$399 Million To Resolve Allegations of Improper Medicaid Billing and Improper Inducements to Healthcare Professionals (Feb. 7, 2008), <http://www.justice.gov/usao/pae/News/Pr/2008/feb/steinkrelease.pdf>; Press Release, Dep’t of Justice, Justice Department Announces Largest Health Care Fraud Settlement in Its History (Sept. 2, 2009), <http://www.justice.gov/usao/ma/Press%20Office%20-%20Press%20Release%20Files/Pfizer/Pfizer%20-%20PR%20%28Final%29.pdf>; Press Release, Dep’t of Justice, Warner-Lambert To Pay \$430 Million To Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion (May 13, 2004), http://www.justice.gov/opa/pr/2004/May/04_civ_322.htm; Press Release, Dep’t of Justice, Schering-Plough To Pay \$345 Million To Resolve Criminal and Civil Liabilities for Illegal Marketing of Claritin (July 30, 2004), http://www.justice.gov/opa/pr/2004/July/04_civ_523.htm; Press Release, Dep’t of Justice, Serono To Pay \$704 Million for the Illegal Marketing of AIDS Drug (Oct. 17, 2005), http://www.justice.gov/opa/pr/2005/October/05_civ_545.html; Press Release, Dep’t of Justice, TAP Pharmaceutical Products Inc. and Seven Others Charged with Health Care Crimes; Company Agrees To Pay \$875 Million To Settle

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many billions more surely will be paid in the coming years, on top of the costs of the investigations themselves and the potential further liability that may stem from related private class actions brought by plaintiffs' counsel. The concomitant media and political scrutiny has irreparably harmed the reputation of the industry.⁴ If the history of Western civilization may be seen as one long battle pitting order against freedom, the government's effort to curtail off-label speech might be dismissed as a minor skirmish on the outskirts of town. However, this issue is anything but minor in policy terms. The eventual outcome will have significant implications for the practice of medicine, the development of new drugs, and the public health.

Physicians may prescribe FDA-approved drugs and biological products for any therapeutic use that is appropriate in their medical judgment.⁵ While the prevalence of off-label prescribing is difficult to estimate, there is little doubt that in oncology⁶ and pediatrics⁷ off-label prescribing is exceedingly common. Off-

Charges (Oct. 3, 2001), <http://www.justice.gov/opa/pr/2001/October/513civ.htm>.

4. A recent survey indicated that the industries that the greatest numbers of people believe should be "more regulated" are oil, pharmaceutical and drug, health insurance, managed care, and tobacco companies. THE HARRIS POLL, BANKS SEEN AS NEEDING MORE REGULATION FOR SECOND YEAR 1 (2009), available at <http://news.harrisinteractive.com/profiles/investor/NewsPDF.asp?b=1963&ID=34987&m=r>.

5. The Food, Drug and Cosmetic Act does not limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

Use of Approved Drugs for Unlabeled Indications, 12 FDA DRUG BULL. 4 (1982).

6. See Am. Soc'y of Clinical Oncology, *Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications*, 24 J. CLINICAL ONCOLOGY 3206, 3206 (2006); see also Daniel B. Klein & Alexander Tabarrok, *Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements?*, 67 AM. J. ECON. & SOC. 743 (2008) (for a recent survey of physician perspectives on the arguably anomalous dichotomy that exists between the FDA's regulation of unapproved products and the absence of regulation of unapproved indications or uses of approved products); Bryan Cote, *Compendia: The Bridge Between FDA Approved Indications and Off-Label Usage*, ONCOLOGY BUS. REV., Jan. 2008, at 10, 11, available at http://www.oncbiz.com/documents/OBR_0108_Compendia.pdf (estimating that approximately 60% of cancer drugs are used off-label); Richard A. Epstein, *Cancer Patients Deserve Faster Access to Life-Saving Drugs*, WALL ST. J., May 2-3, 2009, at A11.

7. See Alicia T. F. Bizzano et al., *Off-Label Prescribing to Children in the United States Outpatient Setting*, 9 ACAD. PEDIATRICS 81 (2009).

label prescribing often is driven by factors beyond the control of the manufacturer,⁸ such that in some therapeutic areas off-label uses are the customary, preferred treatments and are publicly declared to be such on patient advocacy group websites and elsewhere.⁹ Some arms of the government, such as the military, actively encourage off-label use by purchasing and providing drugs specifically intended for off-label use.¹⁰ Moreover, the Centers for Medicare and Medicaid Services (CMS) authorize government reimbursement of products for off-label uses based upon the submission by manufacturers of medical information about such use.¹¹ Indeed, many drugs appear to have legitimate off-label uses that only become evident over time through physician practice and post-approval clinical studies.¹²

Off-label prescribing¹³ has engendered passionate debate in recent years.

8. See *infra* text accompanying notes 109, 110, 113, 116, and 118.

9. Even though no drugs have been expressly approved for the treatment of multiple sclerosis (MS)-related fatigue, Cephalon's Provigil (modafinil) is one of the "medications commonly used in the treatment of MS," according to the National Multiple Sclerosis Society. The MS Society's website notes that the clinical experience of some physicians treating patients with MS has shown "significant benefit [of Provigil] for many patients with MS-related fatigue." National Multiple Sclerosis Society, About MS, <http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/medications/modafinil/index.aspx> (last visited Mar. 29, 2010).

10. For example, the U.S. military conducted a number of clinical studies examining aviator performance and pilot sustained alertness while taking Provigil (modafinil). See Memorandum from the U.S. Dep't of the Air Force (Dec. 2, 2003) (stating that "[m]odafinil, a 'Go Pill', is now approved for management of aircrew fatigue"), available at <http://www.hep.af.mil/HEPF/Policy/modafinil.pdf>.

11. See DEP'T OF HEALTH & HUMAN SERVS., CHARTER: MEDICARE EVIDENCE DEVELOPMENT & COVERAGE ADVISORY COMMITTEE (Nov. 12, 2008), available at <http://www.cms.hhs.gov/FACA/Downloads/medcaccharter.pdf>.

12. See discussion of Cephalon's Provigil (modafinil) in text associated with footnotes 101-108.

13. The term "off-label" includes new, un-FDA-approved indications or uses for a product, potential side effects or safety concerns, dosing regimens to enhance efficacy in certain circumstances, or any other product-related information that was not known or fully developed and appreciated at the time of product approval. See generally Scott D. Danzis, *Off-Label Communications and Prescription Drugs*, in ETHICS AND THE PHARMACEUTICAL INDUSTRY 184 (Michael A. Santoro & Thomas M. Gorrie eds., 2005). "Off-label use may originate from a presumed drug class effect, extension to milder forms of an approved indication, extension to related conditions (the use of the antiasthmatic montelukast [Singulair] for chronic obstructive pulmonary disease), expansion to distinct conditions sharing a physiological link (the use of the antidiabetic drug metformin to treat polycystic ovarian syndrome), or extension to conditions whose symptoms overlap with those of an approved indication." Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008).

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Some have suggested that the government adopt policies to limit physician prerogative to prescribe for unapproved uses. They argue that, at least in certain cases, the risks associated with off-label prescribing are unacceptable, and that the integrity of the drug regulatory system is undermined if there are effectively two different regimes under which some uses are authorized only after rigorous testing and approval while others are wholly unregulated.¹⁴ Others fear that increased scrutiny would signal a marked shift toward federal oversight, away from the longstanding practice of state regulation of the practice of medicine.¹⁵ Indeed, some have said that off-label prescribing should be encouraged to advance public health in the face of a moribund agency approval process that is underfunded, overwhelmed, and incapable of timely reviewing and approving new indications at a pace consistent with medical developments.¹⁶ Regardless of one's perspective, it is undeniable that off-label prescribing is a critical component of the practice of medicine in America.¹⁷

Yet under current law, drug manufacturers may not *promote* their products for off-label uses. The enforcement of off-label promotion restrictions has precipitated far more controversy and consternation than off-label *prescribing*. Although the commercial motivations of drug manufacturers are readily apparent, some believe there is no need to restrict off-label promotion as manufacturers ultimately are deterred from advertising off-label uses by the threat of substantial tort liability for misrepresentation and harm to patients. Others point out that while labeling may be amended to include new information about a drug, invariably there will be occasions in which the company is in possession of truthful, non-misleading scientific and medical information that

14. See Muriel R. Gillick, *Controlling Off-Label Medication Use*, 150 ANNALS INTERNAL MED., 344, 345-46 (2009) (arguing that the costs and risks inherent in prescribing certain biotechnology products suggest the government should limit physicians' discretion to prescribe off-label and instead apply the national cost determination method used by the CMS); see also Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476 (2009).

15. See Federation of State Medical Boards, FSMB Mission, Vision, Core Values and Goals, <http://www.fsmb.org/mission.html> (last visited Mar. 29, 2010) (providing background information on the state regulation of physicians in the United States).

16. At least one former senior FDA official contends that the agency cannot possibly approve proposed modifications to existing labeling, let alone keep labeling current on all approved products, at the pace required to keep up with scientific advances and changes in medical practice. See Scott Gottlieb, *Stop the War on Drugs*, WALL ST. J., Dec. 17, 2007, at A21.

17. See U.S. GEN. ACCOUNTING OFFICE, OFF-LABEL DRUGS: INITIAL RESULTS OF A NATIONAL SURVEY 22, 23-26 (Feb. 1991), available at <http://www.dtic.mil/cgi-bin/GetTRDoc?AD=ADA270395&Location=U2&doc=GetTRDoc.pdf>.

will not be included in the current, approved labeling.¹⁸ The most extreme position contends that the current ban on off-label promotion should be modified substantially or even scrapped, since it significantly increases the cost of drug development, inhibits the rate of adoption of effective new uses of approved products, and limits the full dissemination to prescribing physicians of useful medical information.¹⁹ Others contend that restricting off-label promotion ensures public safety by preventing pharmaceutical companies from spreading false or misleading information about their products in the pursuit of profits.²⁰

These perspectives and practices serve to demarcate the wide bounds of a vigorous policy debate over the significance and validity of truthful medical and scientific information that is not included in the FDA-approved label. Notwithstanding this backdrop of widespread, prevailing medical practice and the importance of new medical and scientific information, the FDA and the DOJ have increased dramatically their enforcement activities in this area, and apparently will continue to do so in the coming years.²¹ What should we make of

18. See *infra* text accompanying notes 97-100.

19. See Alexander T. Tabarrok, *Assessing the FDA via the Anomaly of Off-Label Drug Prescribing*, 5 INDEP. REV. 25, 26-27 (2005), available at http://www.independent.org/pdf/tir/tir_05_1_tabarrok.pdf.

20. See Stafford, *supra* note 13; see also Donna T. Chen et al., *U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey*, 18 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1094 (2009).

21. See Mike Scarcella, *DOJ Ready to Launch Fraud Attack*, NAT'L L.J., Aug. 10, 2009, at 1; see also Carrie Johnson, *A Backlog of Cases Alleging Fraud: Whistle-Blower Suits Languishes at Justice*, WASH. POST, July 2, 2008, at A1 (reporting that over 900 cases are pending with about one-half concerning health care companies); John R. Wilke, *Cases, Fines Soar in Fraud Probes of Drug Pricing*, WALL ST. J., June 7, 2005, at A1 (quoting then Assistant Attorney General Peter Keisler to the effect that there were then more than 150 outstanding investigations involving approximately 500 products); Michael K. Loucks, First Assistant U.S. Attorney, Address from the 2007 Medical Device Congress: Trends in Prosecutions and So-Called Off-Label Promotion Issues (Nov. 26, 2007) (PowerPoint presentation accompanying comments available at <http://www.ehcca.com/presentations/pharmaaudio20071126/loucks.pdf>). In the presentation, Mr. Loucks summarized various factors that he examines in determining whether a prospective case brought to the attention of his office might be worth further inquiry, including the extent of the total product market for FDA-approved uses; whether sales representatives promote the product to physicians who do not treat patients having the FDA-approved condition; whether the company otherwise "targets" such doctors by paying bonuses to sales representatives that take into account sales outside of the FDA-approved uses; or whether such sales are included in company annual objectives. In summary, any drug that has apparent off-label utility could trigger an investigation. This perspective led a leading health care lawyer to observe, "I don't think that a company that has legitimate off-label sales has a safe harbor anymore." Michael McCaughan, *Off-Label Sales in Jeopardy: Rx Industry Fights for Clarity*, RPM REP., Dec. 2007, at 4, 13 (quoting Scott Bass, Sidley Austin LLP).

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this phenomenon? Where off-label prescribing is ineffective or ill-advised, the FDA has a legitimate, compelling interest in protecting the public health by ensuring that companies do not transmit false or misleading information, or otherwise encourage off-label prescribing when there is no underlying medical basis. But where the challenged off-label information is truthful, what is the public interest in forbidding it? The billions of dollars in corporate fines flowing into government coffers or absorbed by legal fees, which might otherwise be put to good use in discovering new medicines, compel us to question the wisdom of government policy in this area. What regulatory scheme will best ensure that physicians are fully informed, yet minimize the potential for exaggeration or embellishment so that the public health is not harmed? How should government regulators best respect the recognized constitutional rights of companies to speak truthfully about their medical discoveries, while ensuring that they speak accurately and fairly?

This article contends that the government's de facto policy of limited rulemaking and broad enforcement by threat of criminal prosecution is not the optimal way in which to develop an appropriate regulatory equilibrium: ideally, one that is efficient, effective, and equitable. The article begins with a summary of the law and public policy concerning off-label prescribing and promotion in the United States. After a brief discussion of the regulatory norms that judges and scholars have long recommended as important in establishing an appropriately balanced regulatory enforcement framework, it evaluates the current regulatory environment in the United States and concludes that there are significant deficiencies related to the absence of clarity, transparency, judicial review, and policy congruity. The article then presents several product-specific case studies that illustrate especially anomalous outcomes or challenging quandaries engendered by prevailing government policy. Following this critique of U.S. policy, the article summarizes the alternative approach of self-regulation now prevailing in the United Kingdom. Finally, it considers which model is likely to be more effective in facilitating appropriate, ethical business behavior by industry, and to that end it makes a number of policy recommendations for changes in U.S. regulatory policy and practice. The animating theme of this article and its policy recommendations is that while pharmaceutical companies have a profoundly important duty to act in a manner that is medically and ethically appropriate, communicating truthful, non-misleading scientific and medical information supports sound medical practice and should not subject companies to civil or criminal liability.²²

22. To be clear, this article is not primarily about commercial free speech and the tension between the First Amendment to the U.S. Constitution and FDA regulations that limit companies

In considering this subject, I am reminded of the stone statue at the apex of the Federal Triangle district in Washington, D.C. The statue is meant to portray a heroic figure—government authority—who restrains with every ounce of strength a wild stallion—unbridled capitalism—poised to break free at any moment and gallop down the boulevard. Unquestionably, there is a vital role for government in preventing the worst excesses of business, but where is the line across which excess occurs; who should make the determination; and what should be the penalty for crossing that line?

II. REGULATING OFF-LABEL SCIENTIFIC AND MEDICAL INFORMATION IN THE UNITED STATES: A CONCISE HISTORY

The Food, Drug and Cosmetic Act of 1938, as amended (the “FDCA” or the “Act”)²³ provides the statutory framework under which the FDA regulates the sale and marketing of drugs in the United States. The Act does not address directly the communication of off-label information. Instead, a series of statutory provisions, as interpreted by the FDA, serve to proscribe off-label promotion and marketing. Specifically, the Act grants the FDA substantial authority to determine the safety and efficacy of all “new” drugs prior to marketing, and to regulate a new drug’s proposed “labeling” to ensure that it is not false or misleading.²⁴ Labeling is defined under the Act to include all tangible material that accompanies a drug.²⁵ Once a drug has been approved by the FDA, the Act specifies that the drug’s labeling may not “suggest” that it be used for any new condition that has not been approved by the FDA.²⁶ FDA regulations restrict company activities in this area to a much greater extent than the FDCA’s statutory scheme. For example, the FDA defines “labeling” to include virtually anything that a company or its employees might produce or present,²⁷ even if the material in question does not accompany the drug. As such, the Act’s prohibition of false or misleading labeling is transformed by the agency into an effective prohibition on any advertisement, promotional message, or discussion that is not “consistent with” the approved product labeling,²⁸ or otherwise concerns any use

from communicating truthful and non-misleading scientific and medical information. Much has been written on this subject, and although the commercial free speech issue is relevant here, the primary focus of this article concerns regulatory policy.

23. Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 301-399 (2006).

24. § 352(a).

25. § 321(m), (p).

26. §§ 321(p), 355(a), (b), (j). The agency also must approve any new uses prior to marketing by the company.

27. Food and Drugs, 21 C.F.R. § 202.1 (2009).

28. The FDA interprets its various regulations to prohibit any communication to physicians or

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that has not been approved expressly by the FDA,²⁹ regardless of whether it is truthful or accurately reflects good medical practice.

The FDCA also makes it a crime to introduce into interstate commerce a drug that is “misbranded.” The Act defines misbranding as making false or misleading statements in the labeling, or failing to include in the labeling “adequate directions for use.”³⁰ This regulation makes eminent sense on its face; if a manufacturer includes demonstrably false information in the label, it certainly is mislabeled or “misbranded” in common parlance. However, FDA regulations have extended this seemingly straightforward statutory provision by introducing the concept of “intended use.” A manufacturer’s intended use includes all uses objectively intended by the drug manufacturer based upon statements made in labeling, in advertisements, or in written or oral statements by company representatives, and if the FDA-approved labeling does not cover each “intended use” then a drug also is deemed to be misbranded.³¹

The collective effect of these regulations is as follows: a drug is approved by the FDA for a specific use; if there is to be a new intended use or if the intended

other health care providers by drug company representatives of information that is not “consistent with” the approved product labeling. *See* FDA Response to Comments on Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074, 64085 (Dec. 3, 1997) (“Under the act, the regulated industry cannot promote its products for unapproved uses, or . . . in ways not consistent with approved labeling.”); *see also* FDA Warning Letter from Thomas W. Abrams, Dir., Div. of Drug Mktg., Adver. & Commc’n, FDA, to Cary Rayment, President and Chief Executive Officer, Alcon, Inc. (Oct. 20, 2006) *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm053637.pdf>; FDA Warning Letter from Michelle Safarik & Jialynn Wang, Regulatory Review Officers, Div. of Drug Mktg., Adver. & Commc’n, FDA, to Elizabeth M. Zola, Assoc. Dir., Regulatory Affairs, Ross Products Div., Abbott Laboratories (July 15, 2005), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm054809.pdf>; FDA Warning Letter from Thomas W. Abrams, Dir., Div. of Drug Mktg., Adver. & Commc’n, FDA, to Adrain Adams, President, Kos Pharmaceuticals, Inc. (July 13, 2001), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM166441.pdf>.

29. As suggested above, this broad prohibition is not set forth in any single regulation, but effectively stems from reading the combination of 21 U.S.C. § 355(a) (2006) (requiring that the FDA approve a product and its labeling prior to introducing it into interstate commerce) and the regulation found at 21 C.F.R. § 202.1(e)(4) (limiting the marketing and promotion of drugs in a manner inconsistent with their approved uses).

30. 21 U.S.C. § 352(f)(1) (2006).

31. 21 C.F.R. § 201.128 (2009).

use otherwise changes, then a manufacturer must demonstrate safety and efficacy for that new intended use and obtain FDA approval for modified labeling that properly reflects this new intended use; if a manufacturer provides information to physicians or other health care providers that is not consistent with the existing, approved product labeling, then the manufacturer has established a new intended use without obtaining FDA approval, and therefore is unable to provide to physicians and consumers the requisite instructions for using the product for this unapproved indication; the company therefore has violated the law by introducing a “misbranded” product into interstate commerce. Many regard this interpretation as awkward at best and untenable at worst.³²

A company may be liable not only under the FDCA but also under the federal False Claims Act (FCA).³³ The FCA makes it unlawful to file a false claim with the government, or to make a false statement that leads to making a false or fraudulent claim paid or approved by the government.³⁴ Liability under the FCA is determined on the basis of the labeling in effect at the time the off-label speech occurs. This appears to be the case even if the information is truthful, and even if the FDA subsequently approves the promoted indication. The interpretation and application of the FCA to off-label promotion challenges are particularly interesting as they go directly to the relevance of the truthfulness of the medical or scientific information: drug companies do not themselves file claims for payment with the government; instead, manufacturers sell their

32. In fact, the actual labeling may be entirely accurate with respect to the directions of use for the product as it is commonly used, but manufacturers may be charged with misbranding if they are *aware* of substantial off-label use, and are unable to unilaterally modify the labeling to correct the situation. See Memorandum of Law in Support of Motion for Preliminary Injunction at 10-11, *Allergan, Inc. v. United States*, No. 09-1879 (D.D.C. Oct. 1, 2009). *But see* *Smoking Everywhere, Inc. v. U.S. FDA*, No. 09-771, -- F. Supp. 2d --, 2010 WL 129667, at *9 (D.D.C. Jan. 14, 2010) (rejecting the FDA’s contention that product testimonials established the manufacturer’s broader intended use to treat nicotine withdrawal symptoms, when the overwhelming focus of the promotional materials was to support the use of the product only as a nicotine substitute).

33. See 31 U.S.C. § 3729 (2006). The False Claims Act imposes liability of three times the government’s loss plus civil penalties for each false claim presented. In response to evidence of substantial fraud in defense contracting, health care, and other areas involving government payments, Congress in 1986 modified a Civil War-era statute to enhance the law’s whistleblower—or *qui tam*—features. In so doing, Congress enabled citizens with evidence of fraud with respect to government contracts and programs to sue, on behalf of the government, in order to recover the funds. As an incentive to file a *qui tam* case, the citizen whistleblower or “relator” may be awarded a portion of the funds recovered, typically between 15-25%. A *qui tam* suit initially remains under seal for at least sixty days during which time government determines whether to join the action. 31 U.S.C. § 3730 (2006).

34. 31 U.S.C. § 3729(a)(2).

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products to wholesale distributors, who in turn sell to pharmacies and other providers, who in turn file claims with the government. Therefore, one might reasonably conclude that liability under the FCA for drug manufacturers would follow only if they make a false statement. However, at least one federal court has found otherwise, ruling that a violation of the FDCA for off-label promotion is sufficient to establish liability under the FCA, whether or not the underlying promotional statements were false.³⁵

This regulatory framework establishes the FDA's fundamental authority in determining the flow of information from drug companies to physicians and patients.³⁶ But this authority is not unlimited. The *Washington Legal Foundation* cases of the late 1990s³⁷ established that the Constitution limits the FDA's ability to control the dissemination of truthful, non-misleading scientific and medical

35. United States *ex rel.* Franklin v. Parke-Davis, 147 F. Supp. 2d 39 (D. Mass. 2001). The court's ruling that the FCA does not require both a false statement and a false claim also is significant for construction of the statute. *But see infra* text accompanying note 88.

36. In the early 1990s, it was common to hear drug company executives say to the firm's commercial group (without a trace of shame or irony): "If you don't get one or two warning letters a year, then you really aren't doing your job." It is difficult to imagine that FDA officials were unaware of this cavalier attitude, and over time it seems they became determined to do something about it. Many observers trace the heightened attention on the problems of off-label promotion to the reign of former FDA Commissioner, Dr. David A. Kessler, who was appointed to the post in 1991. During his time at the agency, he opposed legislation that would have modified labeling for an approved product if a particular off-label use was common practice among clinicians for at least five years, and he generally expressed concerns about physician prescribing decisions that were based on anecdotal experience. *See Protecting and Promoting Public Health: Hearing on S. 1477 Before the S. Comm. on Labor and Human Resources*, 104th Cong. (1996) (statement of Dr. David A. Kessler, Comm'r, FDA), available at <http://www.fda.gov/NewsEvents/Testimony/ucm115101.htm>. These sentiments may have influenced many of those still at the agency or working in policy positions in HHS. Regardless, the FDA's focus on preserving its institutional prerogatives is evident in multiple court filings and public statements. Agency officials have made clear that they are extremely reluctant to acknowledge the truthfulness of safety and efficacy claims without final approval to that effect, and that, in its view, manufacturer dissemination of off-label information is "inherently misleading," even though that same information is not misleading when others do the disseminating. *See Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998), *vacated on other grounds*, *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000). However, courts have not always agreed. "In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe." *See id.*

37. *See Friedman*, 13 F. Supp. 2d at 51; *Wash. Legal Found. v. Henney*, 128 F. Supp. 2d 11 (D.D.C. 2000), *dismissed and vacated in part*, 202 F.3d 331 (D.C. Cir. 2000).

information, at least in the form of peer-reviewed journal articles, medical textbooks, and sponsorship of continuing medical education programs. In this line of cases, an FDA guidance that would have limited the dissemination of peer-reviewed journal articles and medical textbook reprints (so-called enduring materials) were struck down as an unconstitutional infringement of commercial free speech under the Supreme Court's test articulated in *Central Hudson v. Public Service Commission of New York*.³⁸ Subsequently, the FDA avoided a permanent injunction against enforcement of the guidance by stipulating that the ruling merely established "safe harbors" under which manufacturers could be assured that their activities would not be challenged, and that "nothing in [the Food and Drug Administration Modernization Act of 1997 (FDAMA)] provides the FDA with independent authority to regulate manufacturer speech."³⁹

Despite the agency's wide authority, some critics have faulted the FDA for failing to more aggressively enforce the off-label promotion rules and limit abuses by drug manufacturers.⁴⁰ Consequently, the government has increased significantly the number of enforcement actions in this area in recent years, which may be traced to a seminal case involving the Parke-Davis unit of Warner Lambert and its drug Neurontin (gabapentin). Neurontin was approved by the FDA in 1994 as an adjunctive treatment for seizures associated with epilepsy. However, Parke-Davis was accused of developing and executing a promotional campaign to spur prescriptions for the treatment of pain and a series of psychiatric disorders, including anxiety and depression. To accomplish this, Parke-Davis employed a legion of technical medical writers who penned prospective journal articles in support of the purported off-label utility, and then paid physicians to put their names on the articles as authors.⁴¹ Parke-Davis also

38. 447 U.S. 557 (1980). In *Central Hudson*, the U.S. Supreme Court established a four-part test to determine the constitutionality of allowing government regulation of commercial speech: whether the commercial speech to be regulated is lawful and not misleading; whether there is a substantial government interest at stake; if so, whether the proposed regulation advances the asserted substantial government interest; and whether the proposed regulation is more extensive than necessary to serve the interest. *See id.*

39. *Henney*, 202 F.3d at 336.

40. *See* U.S. GOV'T ACCOUNTABILITY OFFICE, *PRESCRIPTION DRUGS: FDA'S OVERSIGHT OF THE PROMOTION OF DRUGS FOR OFF-LABEL USES* 16 (July 2008), available at <http://www.gao.gov/new.items/d08835.pdf>. This report found that between 2003 and 2007 the FDA received approximately 277,000 submissions of promotional material as required under the law, but the agency could not provide data on the number of pieces actually reviewed, the extent to which they identified regulatory violations, the length of the review process, or the status of reviews. To date, there is no systematic means by which the FDA determines which promotional pieces will be reviewed thoroughly.

41. *See* Natasha Singer, *Medical Papers by Ghostwriters Pushed Therapy*, N.Y. TIMES, Aug.

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hired “medical liaisons” as an adjunct sales force to solicit doctors to prescribe off-label, one of whom subsequently brought a *qui tam* action against the company alleging violations of the False Claims Act. Particularly damning were excerpts from a sales presentation in which a manager equated off-label prescriptions to “money,” dismissed alleged safety concerns as unworthy of consideration, and directed sales representatives to promote off-label.⁴² Pfizer, having acquired the Parke-Davis unit through its acquisition of Warner-Lambert, eventually settled these allegations for \$430 million.⁴³ In this matter, the government effectively announced⁴⁴ its intention to focus on off-label promotion as a separate, actionable violation of the FDCA and the FCA. The case is notorious in that its salacious details show the industry at its worst in employing aggressive sales tactics and adopting marketing messages that diverge not only

4, 2009, at A1 (regarding recent allegations related to this practice).

42. John Ford, a Parke-Davis marketing manager, reportedly encouraged the company’s medical liaisons to promote Neurontin for off-label uses for which there was no apparent scientific or medical basis:

I want you out there every day selling Neurontin. . . . We can’t wait for them to ask, we need to get out there and tell them up front. . . . That’s where we need to be, holding their hand and whispering in their ear, Neurontin for pain, Neurontin for monotherapy, Neurontin for bipolar, Neurontin for everything.

DISCLOSURE OF INFORMATION BY RELATOR DAVID P. FRANKLIN PURSUANT TO 31 U.S.C. § 3730 B(2), 11 (1996), *available at* <http://dida.library.ucsf.edu/pdf/rab00a10>.

43. *See* Press Release, Dep’t of Justice, Warner-Lambert To Pay \$430 Million To Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion (May 13, 2004), http://www.justice.gov/opa/pr/2004/May/04_civ_322.htm. In a more recent case, Eli Lilly was accused of illegally promoting its drug Zyprexa (olanzapine). Zyprexa, the first in a new class of so-called atypical antipsychotics, was approved by the FDA in 1996 for the treatment of schizophrenia and in 2005 for the treatment of bipolar disorder. Following FDA approval of the second indication, the record suggests that Eli Lilly shifted its marketing strategy such that its sales representatives would indicate to general practitioners that Zyprexa was appropriate for elderly patients suffering from depression or dementia. In announcing its settlement, the government emphasized the primacy of the FDA’s role, suggesting that any information provided by companies outside of the FDA-approved message would necessarily “undermine the integrity of the doctor-patient relationship and place innocent people in harm’s way.” Eli Lilly settled these allegations in early 2009 for \$1.415 billion. Press Release, Dep’t of Justice, Eli Lilly and Company Agrees To Pay \$1.415 Billion To Resolve Allegations of Off-label Promotion of Zyprexa (Jan. 15, 2009), http://www.justice.gov/civil/oclc/cases/Cases/Eli_Lilly/Lilly%20Press%20Release%20Final%2009-civ-038.pdf.

44. *See* Press Release, Dep’t of Justice, Warner-Lambert To Pay \$430 Million To Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion, *supra* note 43.

from the information contained in the approved label, but also from established medical science.

Since the Parke-Davis settlement, the federal government's policy in this area has been that significant off-label prescribing will be regarded with suspicion, and any discourse with physicians about pharmaceutical and biological drug characteristics not included in the FDA-approved labeling will lead, at the least, to a very intrusive and expensive investigation. Key government prosecutors have confirmed that it does not matter whether or not the questionable speech is truthful or misleading, so long as it is "off-label."⁴⁵

III. THE PUBLIC POLICY IDEAL AND REGULATORY NORMS

Government regulates the behavior of business by developing rules, and then monitoring and enforcing compliance with those rules, preferably in a fair and consistent manner.⁴⁶ American courts acknowledge that agencies have broad discretion to engage in *ad hoc* enforcement actions should they wish to make an example of a firm or an industry in order to affect policy, but they also emphasize the benefits inherent in the development of clear rules under a transparent rulemaking process.⁴⁷ In fact, courts have long preferred this extensive, explicit

45. When asked at an industry sponsored panel if he regards it significant that the off-label information in question is truthful, Assistant U.S. Attorney Loucks replied: "I would say this from an investigator's or prosecutor's perspective, I don't know that it matters much that the off-label promotion activity might be entirely truthful and accurate, it's still off-label." Michael Loucks, Assistant U.S. Att'y in the Dist. of Mass., National Pharma Audioconference: Lessons of Bristol Myers-Squibb's \$515 Million Settlement for Off-Label Promotion, Kickbacks and Drug Pricing (Nov. 26, 2007) (transcript on file with author).

46. There is an extensive academic literature concerning the effectiveness of regulation and choices involving rulemaking and enforcement. In a leading law and economics analysis, Fenn and Veljanovski conclude that economic efficiencies result, and corresponding harm is minimized, when government agencies use their discretion to negotiate with firms rather than applying across-the-board enforcement sanctions. P. Fenn & C.G. Veljanovski, *A Positive Economic Theory of Regulatory Enforcement*, 98 ECON. J. 1055 (1988); see also William M. Landes & Richard A. Posner, *The Private Enforcement of Law*, 4 J. LEGAL STUD. 1 (1975); A. Mitchell Polinsky, *Private Versus Public Enforcement of Fines*, 9 J. LEGAL STUD. 105 (1980); see generally A READER ON REGULATION (Robert Baldwin, Colin Scott & Christopher Hood eds., 1998). Of course, rulemaking and enforcement do not necessarily represent a choice of one form of regulation over another. By definition, there must be rules before there can be enforcement, and even under the most elaborate set of rules there will be those who do not adhere to them who must be subject to enforcement actions as a result. In some areas of U.S. law (for example, securities law) there is relative emphasis placed on clear articulation of rules, and in others there is relative emphasis on selective enforcement.

47. See, e.g., *Am. Mining Cong. v. Mine Safety & Health Admin.*, 995 F.2d 1106, 1112 (D.C.

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rulemaking process as one that at once is consistent with due process and rule of law principles, and provides more effective notice to, and engagement with, the regulated industry in question.⁴⁸

An optimal regulatory regime is fair to the regulated parties, accomplishes the government interests at stake while being sensitive to related legal and policy interests, and minimizes the costs for government and industry. Scholars are quick to praise those normative values that they believe to be associated with proper rulemaking and enforcement, such as clarity, including what some have referred to as accessibility (meaning that the rules are easily interpreted and applied to concrete, real world situations without excessive difficulty or effort); transparency of the rulemaking process; congruity of the rules with other, related legal and regulatory policy preferences and values; and adherence to due process principles, including notice to, and engagement with, the regulated party.⁴⁹ On this point, prominent regulatory theorists have proposed thinking about regulation and optimal regulatory strategy as a cascading series of choices, perhaps as a pyramid, where enforced self-regulation (industry rules with government oversight) would be employed, and only where this approach has failed demonstrably should government resort to state regulation with discretionary or mandatory punishment.⁵⁰

On the other hand, legal scholars and social scientists in Britain and America have written extensively in recent years about the problems associated with rules and rulemaking. In this regard, there is near unanimity that much of the trouble lies in the challenge inherent in the ambiguity of the English language.⁵¹ Beyond

Cir. 1993) (notice and comment to affected parties of proposed rules is preferable to “ad hocery” of enforcement actions).

48. See, e.g., *Whisenhunt v. Spradlin*, 464 U.S. 965, 969 (1983) (Brennan, J., dissenting from denial of certiorari) (arguing that the due process clause demands “that government articulate its aims with a reasonable degree of clarity”); *Morton v. Ruiz*, 415 U.S. 199, 231 (1974) (“[T]he agency must, at a minimum, let the standard be generally known so as to assure that it is being applied consistently”); *SEC v. Chenery Corp.*, 332 U.S. 194 (1947) (holding that the SEC may pursue enforcement actions, but must allow for notice, participation, and transparency).

49. See generally ROBERT BALDWIN & MARTIN CAVE, *UNDERSTANDING REGULATION: THEORY, STRATEGY, AND PRACTICE* (1999); BRONWEN MORGAN & KAREN YEUNG, *AN INTRODUCTION TO LAW AND REGULATION: TEXT AND MATERIALS* (2007); ANTHONY OGUS, *REGULATION: LEGAL FORM AND ECONOMIC THEORY* (1994) (regarding normative values associated with rulemaking and enforcement). On the importance of accessibility, see Colin S. Diver, *The Optimal Precision of Administrative Rules*, 93 *YALE L.J.* 65 (1983).

50. See IAN AYRES & JOHN BRAITHWAITE, *RESPONSIVE REGULATION: TRANSCENDING THE DEREGULATION DEBATE* (1992).

51. Regulation can fail because of the nature of rules and the nature of language. JULIA BLACK,

this, the American inclination for the heavy hand of law enforcement and criminal sanction, combined with the prospective application of mandatory exclusion from federal reimbursement programs, has fostered a regulatory environment that largely fails to meet the critical norms praised by courts and commentators.

IV. THE AMERICAN EXPERIENCE

In the United States, the regulation of off-label medical and scientific communication is inconsistent with the ideals outlined above. In recent enforcement actions, the government has appeared unable or unwilling to distinguish among lawful off-label prescribing by physicians, the communication by companies to physicians and health care providers of truthful and non-misleading speech, the communication by companies of false or misleading information, and clear financial impropriety that may be associated with that communication. Prosecutors have interpreted ambiguous rules to develop innovative but untested legal theories to compel breathtaking settlements and plea agreements. The political and legal dynamic at work here effectively ignores important free speech rights that have been recognized by American courts and the FDA, and threatens the prerogative of doctors to practice medicine by limiting access to the most recent scientific and medical developments. Although there are standards for determining whether corporate malfeasance should be treated as a civil or criminal matter, the process is far from transparent and the standards and associated calculation of financial penalties are not interpreted consistently.

A. The Absence of Clear Rules

With so much at stake, the laws and regulations applicable to the promotion and marketing of drugs and devices ought to be very clear. Companies understand that drug advertisements and other promotional material and statements must be truthful and not misleading. Company sales representatives understand that they may not tell doctors that an approved drug is good for a particular condition unless the FDA approves its use based upon the submission of valid scientific and medical information.

RULES AND REGULATORS 5-45 (1997). "Transparency is usually bought at the price of incongruity . . ." Diver, *supra* note 49, at 91. Diver suggests that the dilemma for the rule maker and the enforcer is how best to strike the proper balance between specificity or transparency, and the discretion that must be applied under varying factual circumstances to reach fair and consistent enforcement. For a discussion of rules and their role in limiting government discretion, see ROBERT BALDWIN, RULES AND GOVERNMENT (1995).

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But beyond these broad guidelines, not much else is clear.⁵² Under current FDA regulations and the agency's interpretation of them, it remains unclear where to draw the line between impermissible off-label promotion and the ostensibly permissible exchange of scientific information. One might say ostensibly, because the FDA has acknowledged several well-known "exceptions" over the years that allow manufacturers to speak about off-label use in certain limited circumstances. For example, manufacturers commonly respond to unsolicited requests for information on off-label uses from health care professionals,⁵³ announce the results of clinical studies concerning a new use for an approved drug,⁵⁴ and provide financial support for scientific and educational activities, provided that they do not influence the content of such activities.⁵⁵ Yet the FDA has never outlined its perspective on these matters in a definitive, comprehensive way. Moreover, at times the agency has suggested that it may not continue to recognize these exceptions.⁵⁶ The only certainty is that the FDA will

52. *But see The View from FDA: An Interview with Robert Temple on Off-Label Promotion*, RPM REP., Dec. 2007 (quoting Dr. Robert Temple) ("No, I don't think [the rules are] confusing. They're not always followed, but I don't think there's any confusion about it. Companies aren't allowed to do it. It is as clear as it could be."). However, in the interview, Dr. Temple did acknowledge some ambiguity and confusion related to companies' sponsorship of and influence over content presented in medical education programs. *Id.*

53. *See* Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994) (indicating that FDA policy allows companies to disseminate information in response to unsolicited requests).

54. 21 C.F.R. §§ 312.2(a), 312.7(a), 812.7 (2009).

55. *See* Decision in *Washington Legal Foundation v. Henney*, 65 Fed. Reg. 14,286 (Mar. 16, 2000) (stating that manufacturers may provide resources for continuing medical education if they comply with statutory provisions).

56. In fact, some of the exceptions specified are not true "safe harbors" in that "[g]uidance documents do not establish legally enforceable rights or responsibilities." 21 C.F.R. § 10.115(d)(1) (2009). The agency's perspective is evinced in its recent attempt to balance First Amendment and public health concerns. *See* Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices; Availability, 74 Fed. Reg. 1,694 (Jan. 13, 2009), *available at* <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm> (Draft Guidance). (The author was a member of an industry working group that advocated for the development and adoption of this guidance.) The Draft Guidance was criticized by prominent members of Congress and consumer advocates for permitting companies to distribute off-label information that will put "the public at risk for ineffective and dangerous uses of drugs." Letter from Henry A. Waxman, Chairman, House Comm. on Oversight & Gov't Reform, House of Representatives, to Andrew C. von Eschenbach, Comm'r, FDA (Nov. 30, 2007),

consider company efficacy claims to be truthful and not misleading if they are found to be such by the agency and are included in approved labeling.⁵⁷

Even if the rules were comprehensive, practical, and clearly articulated, the situation is complicated considerably by the potential application of the First Amendment and its explicit protection of speech. However, following the *Washington Legal Foundation* cases, no federal appellate court and very few other federal district courts have had the occasion to opine on the question of whether the FDA's policy of prohibiting the dissemination of truthful, non-misleading off-label scientific and medical information is unconstitutional. As such, it is not clear whether the views set forth in the *Washington Legal Foundation* cases will be adopted broadly, or whether the First Amendment will be applied to protect other forms and manners of speech related to off-label information.⁵⁸

available at http://online.wsj.com/public/resources/documents/waxmanletter_113007.pdf.

The Draft Guidance also was criticized by industry for reneging on earlier "safe harbor" commitments. See Letter from Daniel J. Popeo, Chairman, Wash. Legal Found., and Richard A. Samp, Chief Counsel, Wash. Legal Found., to FDA (Apr. 21, 2008), available at <http://www.wlf.org/upload/Reprints%20Guidance-%20WLF%20Comments.pdf>. In its comments, the Foundation criticized the agency for failing to address broadly the underlying First Amendment commercial free speech prerogative. "It is inexplicable for FDA to be issuing a Draft Guidance in this area without any explanation regarding what it views as the extent of manufacturers' First Amendment rights." *Id.* at 5. Some of these criticisms were addressed by the FDA in the final guidance. For example, although the Draft Guidance purported to offer manufacturers a bona fide safe harbor for the dissemination of peer-reviewed journal articles, it limited its application to cases where there has not been any unlawful promotion of the product. However, in the final guidance, the agency modified its language; while it may challenge companies that promote illegally, it will not hold companies responsible for the contemporaneous dissemination of journal articles. Finally, the Draft Guidance required that any journal articles disseminated under the safe harbor be limited to those that summarize "adequate and well-controlled clinical investigations." The FDA's final guidance does not contain this limitation.

57. See Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices; Availability, 74 Fed. Reg. 1,694. Some viewed the Draft Guidance as a distinct "relaxation" of the prior level of FDA scrutiny of drug company promotion, especially in comparison with the core principles of the FDA Modernization Act of 1997. This statute allowed for dissemination of journal articles, but only where manufacturers were communicating about drugs as to which they were seeking label expansion and had submitted the article to the agency in advance. See Stafford, *supra* note 13, at 1429. Conversely, others noted that the guidance, even in final form, was relatively narrow in that it only allowed the dissemination of materials that were "written, edited, excerpted, or published specifically for, or at the request of" the manufacturer. See *supra* Good Reprint Practices.

58. In *United States v. Caputo*, 288 F. Supp. 2d 912 (N.D. Ill. 2003), the district court

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The quandary for industry executives and their counsel can be reduced to one word: accessibility. The rules are not reasonably well appreciated and susceptible to practical application. How should companies apply the broad commandment that forbids off-label promotion to the daily routine of interacting with prescribing physicians? Consider a few concrete business situations that illustrate the inadequacy of current FDA rules and regulations: may sales representatives present their message to any physician, so long as it is consistent with the approved labeling, or must all physicians to whom the message is presented have patients who suffer from the on-label indication? Is it “consistent with” the approved labeling to discuss the likely mechanism of action of the active compound if the mechanism is not disclosed in the labeling? May companies sponsor what have been known as “independent” continuing medical education programs, and if so how should they be structured? May a company engage a physician as a bona fide consultant without being seen as improperly influencing prescribing decisions, and if so how should it determine fair market value compensation for the services rendered? May a company offer advice on reimbursement for off-label uses, either to a physician, to a physician office staff,

considered whether the First Amendment shielded defendants from liability for promoting a medical device in a form that had never been approved by the agency. In finding that it did not, Judge Castillo distinguished *Washington Legal Foundation* by noting that the communication at issue in that case was limited to the dissemination of peer-reviewed journal articles and the sponsorship of continuing medical education programs, while accepting defendants’ First Amendment argument in *Caputo* would necessarily allow much greater leeway for manufacturers to promote off-label. “[P]ermitting Defendants to engage in *all* forms of truthful, non-misleading promotion of off-label use would severely frustrate the FDA’s ability to evaluate the effectiveness of off-label uses.” *Id.* at 922. As another data point, Judge Saris of the U.S. District Court in Boston had occasion in 2007 to express her views at a hearing in which the drug manufacturer Schering-Plough Corporation was sentenced for violating the Food, Drug and Cosmetic Act for, among other things, promoting off-label and misleading the FDA. In contrast to Judge Castillo, Judge Saris explicitly rejected the *Washington Legal Foundation* principles. “I do not accept that there is a First Amendment right to market something that does not get FDA approval,” she said. Michael K. Loucks, First Assistant U.S. Attorney, Address from the 2007 Medical Device Congress: Trends in Prosecutions and So-Called Off-Label Promotion Issues (Nov. 26, 2007), *available at* <http://www.ehcca.com/presentations/pharmaaudio20071126/loucks.pdf> (quoting Judge Saris in Schering Sales Corporation sentencing hearing). *See also* *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002) (ban on advertising of compounded drugs is unconstitutional because it did not satisfy Central Hudson test); *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999); *United States v. Caronia*, 576 F. Supp. 2d 385, 394 (E.D.N.Y. 2008) (noting “unsettled” constitutional law, and despite the fact that the speech in question was not inherently misleading, a pharmaceutical sales representative is not entitled to dismissal on First Amendment grounds of case alleging FDCA violations for “misbranding” based upon improper off-label promotion).

to a private payer, or to a state pharmacy and therapeutics committee? May a company express any level of ambition or prospect for an unapproved use lest it be accused of embracing an off-label marketing strategy? FDA regulations simply do not address these and other questions associated with the promotion and sale of prescription pharmaceuticals.

Some cases are rather stark and unsympathetic. In the Neurontin matter, there does not appear to be any valid contention that the company's sales and marketing efforts were predicated on the communication of truthful, non-misleading information that just happened to be outside the FDA-approved labeling. Many cases are not so straightforward, however. The complexities of medicine, health care practices, and the contemporary commercial enterprise suggest that in many situations, FDCA violations may or may not have occurred depending upon the subjective interpretation of myriad factors. The FDA has an obligation to develop and promulgate comprehensive guidance on promotional activities, medical education, and physician consulting engagements. Instead, the agency has issued a series of warning letters in response to complaints and its own observations as to apparent violations. The alleged infractions range from the outrageous (lying about efficacy, denying safety issues) to the sublime (the height or boldness of typefaces used in a marketing brochure makes it misleading). The letters are specific to the facts of each case and are a poor substitute for a general regulatory framework or code of conduct of the sort that has been promulgated by other federal government agencies.⁵⁹ Moreover, the FDA's approach has facilitated a cynical approach by many companies that choose to employ intellectual gymnastics to distinguish their practices from many a narrowly crafted warning letter.

FDA warning letters would be more useful if they were issued with reference to a broad but detailed code of conduct. For example, the U.S. Securities and Exchange Commission (the "SEC" or the "Commission") promulgates detailed regulations and provides further guidance to companies on disclosure issues through its "No Action" letters. No Action letters necessarily are fact-specific as well, but they are intended to supplement a comprehensive framework of securities laws, rules, and regulations. As the Commission notes:

An individual or entity who is not certain whether a particular product, service, or action would constitute a violation of the federal securities law may request a "no-action" letter from the SEC staff. Most no-action letters describe the request, analyze the particular facts and circumstances involved, discuss applicable laws and rules, and, if the staff grants the request for no action,

59. The FDA publishes its warning letters to the public. See U.S. Food and Drug Administration, Warning Letters, <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm> (last visited Mar. 29, 2010).

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concludes that the SEC staff would not recommend that the Commission take enforcement action against the requester based on the facts and representations described in the individual's or entity's original letter. The SEC staff sometimes responds in the form of a no-action letter to requests for clarification of the legality of certain activities.⁶⁰

The FDA deserves credit for issuing its recent—albeit belated—guidance which attempts to address in a comprehensive manner the practice of disseminating reprinted articles from peer-reviewed journals.⁶¹ The agency has characterized the guidance as the FDA's "current thinking" on the topic and notes that the guidance was made necessary due to the expiration of Section 401 of the Food and Drug Administration Modernization Act of 1997 (FDAMA), which had previously provided a safe harbor for the industry on reprint practices.⁶² However, unlike the previously existing FDA Notice clarifying that FDAMA and its implementing regulations merely constituted a safe harbor,⁶³ the most recent guidance explicitly permits the dissemination of off-label scientific and medical information under certain circumstances, regardless of whether the company is pursuing a new indication and without requiring that companies submit the material to be disseminated in advance for review.⁶⁴ Many appreciate the guidance as an initial, if halting, step toward enhanced regulatory clarity to better guide industry practice, inform physicians, and enhance compliance.

B. The Lack of Transparency in the Rulemaking and Enforcement Process

In addition to enacting rules and regulations that are comprehensive and reasonably clear, government should ensure that the process for both the adoption and the enforcement of rules is transparent. The U.S. government has failed on both accounts. In its adoption of rules and regulations, the FDA largely has failed to address forthrightly the evident tension between the First Amendment and its regulations proscribing the communication of truthful and non-misleading information not contained in approved labeling. Moreover, as the DOJ has assumed a higher degree of involvement in developing cases alleging civil and

60. U.S. Securities and Exchange Commission, No Action Letters, <http://www.sec.gov/answers/noaction.htm> (last visited Mar. 29, 2010).

61. *See* Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices; Availability, 74 Fed. Reg. 1,694.

62. *See id.*

63. *See* Decision in *Washington Legal Foundation v. Henney* 65 Fed. Reg. 14,286 (Mar. 16, 2000).

64. *See id.*

criminal violations under the FDCA and the FCA, the investigation, consideration, and resolution of these cases also have become less transparent.

With respect to the development of rules, the FDA has shied away from engaging in an open process in which it attempts to reconcile the competing interests of commercial free speech and regulatory prerogative. Perhaps the best example concerns the agency's response to the *Washington Legal Foundation*⁶⁵ opinions. The nearest the agency came to providing comprehensive rules on the dissemination of off-label scientific and medical information was its 1996 policy guidance, which sought to limit the use by companies of peer-reviewed journal articles and medical textbooks.⁶⁶ This guidance subsequently was found to be unconstitutionally broad in a preliminary ruling issued by a federal district court in the *Washington Legal Foundation* cases.⁶⁷ The FDA was presented with a clear choice: it could have contested the ruling on appeal, or it could have modified and reissued its guidance in reaction to the decision. As noted above, until very recently the agency did neither, instead declaring that its guidance (as well as similar statutory language) merely provided a safe harbor for companies.⁶⁸ As such, any failure by companies to follow the guidance was not necessarily a violation of the law. However, the agency retained its general authority under which it could challenge manufacturers. Absent the adoption of a bona fide safe harbor for companies to rely upon in disseminating these kinds of materials, manufacturers still face potential civil and criminal liability. In light of this revised posture, the appellate court had no legal basis to provide its opinion on the underlying question, thereby ensuring that the law in this area would remain ambiguous. Based upon deposition and other testimony offered by FDA officials in the course of the litigation, it seems evident that the agency was displeased with the court's decision, yet there was no public attempt to address the important policy issues raised by the case.

In 2002, shortly after the Supreme Court's decision in *Thompson v. Western*

65. See *Wash. Legal Found. v. Henney*, 128 F. Supp. 2d 11 (D.D.C. 2000), *dismissed and vacated in part*, 202 F.3d 331 (D.C. Cir. 2000).

66. See Advertising and Promotion; Guidances, 61 Fed. Reg. 52,800 (Oct. 8, 1996).

67. See *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 72-74 (D.D.C. 1998), *vacated on other grounds*, *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000); *Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999), *dismissed and vacated in part*, 202 F.3d 331 (D.C. Cir. 2000).

68. See Decision in *Washington Legal Foundation v. Henney*, 65 Fed. Reg. 14,286. The FDA subsequently published a Request for Comment on First Amendment Issues several years after the *Washington Legal Foundation* cases concluded, and though it received numerous comments it has not yet taken action in response. See Request for Comment on First Amendment Issues, 67 Fed. Reg. 34,942 (May 16, 2002).

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States Medical Center,⁶⁹ which held that the FDA's proposed ban on advertising of compounded drugs was unconstitutional because it did not satisfy the *Central Hudson* commercial free speech test, the FDA published a notice⁷⁰ requesting public comments on the First Amendment issues raised by this and other cases, and how it might properly regulate commercial speech within the bounds permitted by the Constitution. The agency's request suggested it might well be prepared to engage with industry and commentators on a more transparent basis. The questions themselves were important: how can the agency advance public health with fewer restrictions on speech? What can the FDA do to limit speech on off-label uses of approved drugs? Does industry practice lead to over-prescribing? Does the First Amendment allow for more limits on claims made in labels than those made in advertisements?⁷¹ There were a large number of responses to this request. Some were critical of the agency, but others praised it for soliciting views and prompting public debate. Yet despite the public response, the FDA failed to take action, publish its views, or otherwise seek to resolve the questions raised by *Thompson*.

With respect to enforcement, the process has become less transparent over time, particularly with the increased involvement of the DOJ. The DOJ has long been involved in the investigation and prosecution of possible violations of the FDCA through the Civil Division and its Office of Consumer Litigation. However, in recent years certain U.S. Attorneys' Offices, notably those in Boston and Philadelphia, have developed innovative legal theories on misbranding and the FCA premised on the primacy of FDA regulatory authority and the impropriety of drug company off-label communication. These offices have managed their cases without any apparent policy coordination. Accordingly, there is an absence of transparency in terms of ascertaining standards as to whether there has been wrongdoing by a company, whether a case is treated as a criminal or civil matter, and what level of financial penalty should be levied if there has been wrongdoing. Additionally, it is unclear whether and to what extent a company's history of alleged wrongdoing or, conversely, its record of cooperation and good behavior, will lead to greater or lesser penalties. Absent judicial review and without a comprehensive code of written standards, companies are left to digest and interpret the implications of the most recent civil settlement and criminal plea agreements. These periodic pronouncements effectively constitute silent or implicit rulemaking, in which an agency acts as

69. 535 U.S. 357 (2002).

70. Request for Comment on First Amendment Issues, 67 Fed. Reg. 34,942.

71. See Lester M. Crawford, Jr., *Commercial Speech and Public Health: Request for Comment*, 288 JAMA 36 (2002).

both rule maker and adjudicator.⁷²

While the Department's prosecution guidelines are set forth in the United States Attorneys' Manual,⁷³ it has resisted extending these general guidelines to provide written policy direction with respect to off-label promotion cases. In correspondence between the Washington Legal Foundation (WLF) and the DOJ occurring in 2004 and 2005, WLF urged senior Department officials to develop such guidelines related to the investigation and disposition of cases involving the communication of truthful, non-misleading speech.⁷⁴ WLF argued that more precise standards would serve two important purposes: they would inform the industry as well as guide prosecutors. The Department declined the invitation and rejected the notion that any additional policy guidelines were needed. Then Assistant Attorney General for the Civil Division Peter D. Keisler responded that "the Department does not have theoretical views regarding off-label promotion of products subject to regulation by the Food and Drug Administration The Department applies the law to the facts of actual cases and, as a result, there is no need for pure analysis of off-label promotion."⁷⁵

Further, while the DOJ has established corporate criminal culpability guidelines in a series of written memoranda drafted and revised by successive Deputy Attorneys General Thompson, Holder, and McNulty during the Bush administration which are used to determine whether or not to charge corporations with criminal violations of the law,⁷⁶ it is left to individual prosecutors and field supervisors to determine whether a corporation's conduct actually warrants criminal or civil treatment. Has the corporation cooperated meaningfully with the prosecuting office in its investigation and review? Has the corporation agreed to conduct its own investigation and waive any attorney-client privilege claims that

72. This consolidation of authority arguably is inconsistent with the underlying purpose of the Administrative Procedure Act, 5 U.S.C. §§ 551-559 (2006). The Act requires that those agencies that develop administrative rules establish independent procedures for determining if the rules have been violated. Here, DOJ interprets and applies the FDCA and FCA provisions, and enforces them through the settlement process with minimal judicial review, as discussed in the text below.

73. DEP'T OF JUSTICE, UNITED STATES ATTORNEYS' MANUAL (1997), available at http://www.usdoj.gov/usao/eousa/foia_reading_room/usam.

74. Letter from Daniel J. Popeo, Gen. Counsel, Wash. Legal Found., and Richard A. Samp, Chief Counsel, Wash. Legal Found., to James B. Comey, Deputy Attorney Gen., Dep't of Justice (Mar. 24, 2005) (on file with author).

75. Letter from Peter D. Keisler, Assistant Attorney Gen., Civil Div., U.S. Dep't of Justice, to David Price, Senior Vice President, Legal Affairs, Wash. Legal Found. (Oct. 5, 2004) (on file with author).

76. See, e.g., Memorandum from Paul J. McNulty, Deputy Att'y Gen., to Heads of Dep't Components, U.S. Attorneys (2006), available at http://www.usdoj.gov/dag/speeches/2006/mcnulty_memo.pdf.

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might otherwise apply in providing the prosecutors with the results of said investigation? Does the improper marketing and promotional activity suggest that it was the result of conscious corporate wrongdoing, or merely the result of a limited number of renegade sales representatives? And how should prosecutors make this determination? Prosecutors in the various U.S. Attorneys' Offices around the country may apply these standards in different ways and give different weight to the factors presented. Furthermore, given that meaningful review and oversight from senior officials in the Department present political sensitivities when reserved for the late stages of a delicate and complicated negotiated settlement, it is difficult to achieve transparency or consistency under the current process.⁷⁷

As an example, consider reconciling the criminal treatment accorded Eli Lilly in the 2003 case involving the alleged off-label promotion of Evista (raloxifene HCl) for a treatment subsequently approved by the FDA with the civil treatment of Bristol Myers-Squibb in 2007 for alleged promotional impropriety involving its drug Abilify (aripiprazole). As another example of disparate interpretation, some U.S. Attorneys' offices have begun to suggest in negotiations that drug company sales representatives are violating the law by "selling the side effects." The implication is that presenting possible adverse reactions seen by other physicians in their patients who have taken the drug for an off-label use, the company is effectively (if discreetly) promoting the product for that off-label use. This focus also suggests that prosecutors will take a dim view of companies whose sales representatives visit physicians who do not prescribe on-label.

In effect, the absence of clear guidelines in this area makes it exceedingly difficult to defend the company effectively.⁷⁸ This stems from a lack of clarity in

77. See Barry Meier, *Justice Dept. and Prosecutors Are Said To Have Disagreed on OxyContin Case*, N.Y. TIMES, July 31, 2007, at C4. In the absence of formal Department prosecutorial guidelines, some comfort might be taken from evidence that senior officials are providing policy oversight to the settlement of those cases prepared by U.S. Attorneys in this area. Published reports indicated that senior Department officials initially disagreed with local prosecutors over the noteworthy criminal plea agreement involving Purdue Pharma and three of its senior executives, though the recommendations of the U.S. Attorney for the Western District of Virginia eventually were accepted. This would seem to represent the kind of responsible policy oversight that we would expect of senior officials in any cabinet agency. However, the Department was criticized for what some regarded as an inappropriate attempt to politicize an investigation by an otherwise independent U.S. Attorney.

78. The involvement of various state Attorneys General offices presents added challenges and complexities, which makes it difficult for companies to develop global settlements with all relevant federal and state authorities. Some states have developed "anti-fraud" revenue objectives into their

the rules themselves and from a lack of transparency in the application and enforcement of the rules. It arises in the context of establishing—or refuting—a causal link between off-label prescribing and the company’s marketing of the product in question. In my experience, there is no evident willingness to engage on the question of whether the allegedly improper promotion has actually led physicians to prescribe off-label. Once counsel enters into settlement discussions, the government will emphasize the statutory bases of criminal and civil liability. For example, the FCA provides a civil penalty of up to three times the amount that was falsely claimed from the government.⁷⁹ On the criminal side, the government may apply a multiplier of up to two times the amount of the corporate gain or the government loss. However, these multipliers are only meaningful if the underlying base amount (which represents the alleged level of “inappropriate” off-label prescriptions) is derived in a fair and transparent manner.

Some advocates have encouraged DOJ officials to seek advice from the FDA prior to initiating investigations in order to determine whether the drug in question is being prescribed outside the approved labeling for medically appropriate reasons.⁸⁰ The FDA retains oversight responsibility for regulating the communication of scientific and medical information and, as such, holds institutional prerogative and memory. DOJ officials may well consult with the FDA in developing a sophisticated medical and clinical perspective on specific cases and in developing a broad policy approach to cases, but it is not evident that they are doing so. Indeed, the perspective of former FDA policymakers suggests that it does not occur other than at the investigatory level.⁸¹

annual budgets, creating an incentive to push for a particular outcome regardless of the underlying circumstances and federal policy imperatives. *See New York Will Exceed Medicaid Fraud Recovery Target for Fiscal Year 2008*, BNA’S HEALTH CARE DAILY REP., Sept. 19, 2008, http://news.bna.com/hdn/HDLNWB/split_display.adp?fedfid=108 (subscription access; on file with author) (describing how in exchange for federal monies granted in 2006, New York committed to recover hundreds of millions of dollars in Medicaid fraud and abuse in the state system).

79. 31 U.S.C. § 3729(a) (2006).

80. *See* Scott Gottlieb, Resident Fellow, American Enter. Inst. for Pub. Policy Research, *Off-Label Uses of Approved Drugs: Medicine, Law & Policy* (May 21, 2008) (video available at http://www.usdoj.gov/dag/speeches/2006/mcnulty_memo.pdf); *see also* Scott Gottlieb, *From FDA, a Good Framework for Distributing Information on Off-Label Uses*, HEALTH AFF. ONLINE, Apr. 23, 2008, <http://healthaffairs.org/blog/2008/04/23/from-fda-a-good-framework-for-distributing-information-on-off-label-uses>.

81. Perhaps not so much at the investigatory level either. A recent GAO report concluded that the FDA had failed to develop adequate performance measures and otherwise to properly manage its primary investigatory unit, the Office of Criminal Investigations (OCI). *See* U.S. GOV’T ACCOUNTABILITY OFFICE, *FOOD AND DRUG ADMINISTRATION: IMPROVED MONITORING AND*

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More extensive FDA involvement would not necessarily change the dynamic, approach, or outcome of these cases. Government officials, whether political appointees or career service, generally have strongly held policy perspectives and are inclined to use their authority to advance their personal ambitions, and to protect and strengthen the respective prerogatives and preferences of the institutions they serve. This is entirely natural, but it is troubling in light of the relatively limited bargaining power that companies possess when faced with the threat of prosecution, the sanction of exclusion, vicarious liability for executives, the costs of defense, and the prospect of public disclosure of inflammatory documents. The best way to limit the unintended impact of political motivations would be to establish a regulatory system based upon a clear understanding of the rules that provides notice to, and engagement with, the regulated parties, and then to apply the rules consistently and transparently.

C. The Paucity of Federal Judicial Review

Article III of the Constitution established judicial authority to interpret the law, and in so doing, provide a check on the power of the executive and legislative branches of government. The deficiencies outlined above, an absence of clarity in the regulations and an absence of transparency in rulemaking and enforcement, can be remedied by the courts. But there have been relatively few cases litigated by the drug companies accused of impropriety. This hesitancy to contest allegations occurs because firms are cognizant of a 1998 revision to a rule issued by the HHS Office of Inspector General (OIG). The revised rule significantly altered the legal landscape by expanding the authority of the OIG to exclude drug manufacturers from receiving federal health reimbursement monies if they are found to have engaged in significant financial or other impropriety.⁸²

DEVELOPMENT OF PERFORMANCE MEASURES NEEDED TO STRENGTHEN OVERSIGHT OF CRIMINAL AND MISCONDUCT INVESTIGATIONS (2010). However, this report will not necessarily result in senior FDA officials injecting additional medical and clinical perspective into the investigatory process. Instead, it seems likely to expand the potential criminal exposure of drug companies and their executives in cases of alleged off-label promotion. In response to the GAO Report, the FDA is developing criteria to increase the appropriate use of misdemeanor prosecutions, a valuable enforcement tool, to hold responsible corporate officials accountable. Letter from Margaret A. Hamburg, FDA Comm'r, to Senator Charles E. Grassley (Mar. 4, 2010), *available at* <http://grassley.senate.gov/about/upload/FDA-3-4-10-Hamburg-letter-to-Grassley-re-GAO-report-on-OCI.pdf>.

82. See Health Care Programs: Fraud and Abuse; Revised OIG Exclusion Authorities

Prior to this, only those institutions that provided services directly to patients (such as hospitals, hospices, day care providers, and diagnostic service providers) could be excluded or “debarred” from federal financing program eligibility.

In issuing this expanded rule, the OIG noted that they “would not expect that manufacturers would often be convicted and subject to mandatory exclusion.”⁸³ Drug companies receive a large portion of their total revenue and earnings from reimbursements under the federal Medicare and Medicaid programs, and to lose this would irrevocably cripple a company. Indeed, it is often said that no sane company would ever challenge in court allegations that, if proven, would result in a felony conviction and certain exclusion. In effect, companies that negotiate settlements with the government to resolve allegations of illegal off-label promotion can reasonably expect that the OIG will not exercise its discretion to exclude the company from continuing to receive federal reimbursement funds; companies that challenge the government’s allegations in court clearly put the company at risk of extinction as a felony conviction carries with it automatic exclusion.⁸⁴

It is difficult to overstate the immense impact that this seemingly technical clarification has had on the development of the legal and regulatory landscape. As a practical matter, companies accused of wrongdoing *must* cooperate and resolve the matter by settlement. They cannot realistically challenge the government in court either on the facts, the underlying theories of liability, or whether the charges alleged are compatible with the Constitution or even consistent with FDA regulations themselves. The risk/reward calculus is skewed dramatically in favor of settlement when a loss would jeopardize the firm’s viability by forfeiting government reimbursement for its products. As a result,

Resulting from Public Law 104-191, 63 Fed. Reg. 46,676 (Sept. 2, 1998).

83. See Health Care Programs: Fraud and Abuse; Revised OIG Exclusion Authorities Resulting from Public Law 104-191, 63 Fed. Reg. at 46,679.

84. See Dan Levine, *Marketing Tactics Put Johnson & Johnson Under DOJ Microscope*, NAT’L L.J., Dec. 3, 2009, available at http://www.law.com/jsp/article.jsp?id=1202436012057&Marketing_Tactics_Put_Johnson_Johnson_Under_DOJ_Microscope (reporting that federal prosecutors were considering indictment of Johnson & Johnson or its Scios unit, which could lead to exclusion of parent or subsidiary); Sue Reisinger, *In Their Long Battle with Big Pharma, The Feds Have Held Back Their Nuclear Option. Why?*, CORP. COUNS., Feb. 1, 2010, <http://www.law.com/jsp/cc/PubArticleCC.jsp?id=1202437870117> (Discretionary debarment is the OIG’s “nuclear bomb” that has never been applied to exclude a major company as it would limit patient access to drugs and “cost tens of thousands of jobs.”); see also Michael K. Loucks, *Drug Busts on the Cheap Lack Power To Deter*, BUS. WK., Mar. 8, 2010, <http://www.businessweek.com/news/2010-03-08/drug-busts-on-the-cheap-lack-power-to-deter-michael-k-loucks.html> (arguing that prosecutors need more resources to develop cases that will lead to exclusion from federal programs).

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there are few opportunities to advance the law in any fair and reasonable way. Some observers are skeptical generally of the ability of the courts to properly evaluate the administrative policymaker's judgment in areas, like this, which involve "social cost accounting."⁸⁵ But in an area that is replete with complexity and nuance, such that even drug industry critics acknowledge significant First Amendment considerations, fair-minded observers surely must ask why federal courts have not had more opportunities to opine on these critical issues of legal policy. The lawsuit brought last year by Allergan against the HHS Secretary and the FDA Commissioner, described below, demonstrates the extraordinary lengths to which companies will go in order to reduce enforcement risk and avoid debarment.

D. The Limits on Communicating Truthful Information

The current enforcement environment is focused on conducting investigations and threatening prosecution as a means of compelling settlements. There is very little meaningful engagement with private industry. DOJ officials fail to recognize the importance of communicating truthful, non-misleading information to physicians. One might expect that regulators would be motivated to satisfy policy objectives that protect the public health while facilitating informed prescribing decisions. From a public health perspective, regulators should consider whether or not the scientific and medical information is truthful and not misleading, and whether or not physicians are prescribing the product in a medically appropriate manner. However, the government is concerned solely with whether the FDA has approved the indication in question. If it has not, and the company conveys or in some way interacts with physicians on this unapproved indication, then there will be a lengthy investigation and, in all likelihood, a costly settlement under threat of prosecution.⁸⁶

DOJ officials have said that they do not believe the truthfulness of the information is relevant,⁸⁷ and that a manufacturer is liable under the FCA if it knowingly implements a marketing plan that foreseeably caused third parties to file claims for off-label uses that were not eligible for reimbursement.⁸⁸

85. Diver defines this term as the "sophisticated and sensitive application of common sense." Diver, *supra* note 49, at 109 (citing Jerry Mashaw, *Administrative Due Process as Social-Cost Accounting*, 9 HOFSTRA L. REV. 1423, 1441 (1981)). Courts are widely considered to lack the investigative resources, analytical tools, and technical competence to more than simply rely on the administrative record in upholding agency decisions.

86. See Loucks, *supra* note 21.

87. See *id.*

88. See *id.* A recent court decision suggests that the government may begin to see its theories

Consistent with this interpretation, the current DOJ policy perspective is evident in a court filing made in connection with a *qui tam* relator case against Pfizer.⁸⁹ In its filing, the DOJ rejects the view that a “false” statement under the False Claims Act need be an affirmative misrepresentation; rather, “a material omission will suffice.”⁹⁰ In the case of alleged off-label promotion, this omission may be established on the basis of the dissemination of information (even if truthful and non-misleading) if “the FDA has specifically concluded that the drug is not safe or effective for that use.”⁹¹ The DOJ also contends that medical compendia references to a drug’s off-label use in support of reimbursement coverage is insufficient to establish the veracity of a pharmaceutical company’s communication about that off-label use for purposes of the FCA.

Similarly, the OIG equates off-label promotion by a manufacturer with the submission of a false claim for reimbursement, regardless of the inherent truthfulness of the information.⁹² Its perspective may be gleaned from the

challenged, as some courts have criticized the *Franklin* result, and questioned whether off-label promotion violations of the FDCA can form the basis of FCA liability. *See United States ex rel. Polansky v. Pfizer, Inc.*, No. 04-cv-0704, 2009 WL 1456582, at *7 (E.D.N.Y. May 22, 2009). Here, the court rejected the government’s theory that drug companies effectively facilitate false claims by promoting illegally. “[T]he mere fact that Pfizer may have been violating FDA regulations does not translate into liability for causing a false claim to be filed . . . Pfizer did not file any claims for reimbursement and made no implied certifications to obtain payment.” *Id.* The case was dismissed under Federal Rule of Civil Procedure 9(b) for failing to assert with the requisite specificity facts that would establish that a physician prescribed the product and that a pharmacist filled a prescription based upon illegal off-label promotion. The court’s observations, if adopted more broadly, suggest that the reasoning of *Franklin* could be rejected or limited in subsequent rulings. This development illustrates again the problems inherent in our existing process, where a single federal district court ruling has exposed industry to billions of dollars in liability, as federal prosecutors leverage this ruling and companies’ inability to litigate to compel settlements.

89. United States’ Statement of Interest at 1, *United States ex rel. Rost v. Pfizer, Inc.*, No. 03-CV-11084 (D. Mass. 2008). The filing notes that the “United States has a keen interest in the development of the law in this area.” *Id.* The case involves the interpretation of the FCA, and the DOJ submission is focused on disputing various contentions and interpretations contained in an *amicus curiae* brief filed by the Washington Legal Foundation.

90. *Id.* at 9.

91. *Id.*

92. *See Allegations of Waste, Fraud and Abuse in Pharmaceutical Pricing: Financial Impacts on Federal Health Programs and the Federal Taxpayer: Hearing Before the H. Comm. on Oversight and Gov’t Reform*, 110th Cong. 6-7 (Feb. 9, 2007) (statement of Lewis Morris, Chief Counsel, Office of the Inspector General). Although drug manufacturers do not generally submit any claims for reimbursement, the government’s perspective is that prescription drug promotion outside the FDA-approved labeling effectively induces physicians to prescribe, which thereby causes pharmacists to fill prescriptions and (false) reimbursement claims eventually to be filed.

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evolving terms of its preferred model Corporate Integrity Agreement (CIA). As a condition of avoiding discretionary exclusion from federal reimbursement programs, the government demands that drug and medical device firms that are found to have violated the FDCA, the anti-kickback statute, or other provisions of federal law, enter into a CIA prior to settlement of the case. CIAs now address matters well beyond pricing and anti-kickback law compliance, and include provisions related to the promotion of products. The CIA with Bristol-Myers Squibb, for example, requires that the company direct all inquiries related to a potential off-label use to the company's internal medical information department.⁹³ The CIA also requires that the company evaluate its proposed call plan (for example, the plan specifying which physicians will be presented with product related information by company sales representatives), specifically for those products in its portfolio "having a high potential for off-label use that could be driven by detailing an inappropriate audience" of physicians.⁹⁴ There is no hint that the government is concerned about the truthfulness or falsity of the message. The OIG simply intends to limit the number and scope of physicians who receive product information from company representatives.

In concert, these policy perspectives establish that the government—specifically the FDA through its approval process—is the arbiter of what information may be shared with physicians.⁹⁵ Moreover, law enforcement

93. See CORPORATE INTEGRITY AGREEMENT BETWEEN THE OFFICE OF INSPECTOR GENERAL OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES AND BRISTOL-MYERS SQUIBB COMPANY 29-31 (Sept. 26, 2007). The use of monitors and other provisions of this Agreement have been criticized by legal scholars in that they interject law enforcement officials into the internal workings of a company, including decisions over personal and shareholder treatment. See Richard A. Epstein, *The Deferred Prosecution Racket*, WALL ST. J., Nov. 28, 2006, at A14.

94. See CORPORATE INTEGRITY AGREEMENT BETWEEN THE OFFICE OF INSPECTOR GENERAL OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES AND BRISTOL-MYERS SQUIBB COMPANY, *supra* note 93.

95. In contrast to the apparent views of the FDA, at least one federal court has seen fit to qualify its authority. "And, despite the FDA's occasional statements in its briefs to the contrary, physicians are a highly educated, professionally-trained and sophisticated audience. In making prescribing decisions, doctors want (and need) to know first and foremost if the drug is the most safe and effective means to treat the conditions suffered by the patients." Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 63 (D.D.C. 1998), *vacated on other grounds*, Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000). "[T]he court must again note that off-label prescriptions, presently legal, do constitute the most effective treatment available for some conditions. Through the government's well-intentioned efforts to prevent misleading information from being communicated, a great deal of truthful information will also be embargoed. In this case, the truthful information may be life saving information, or information that makes a life with a debilitating

officials will punish companies without regard to whether the promotional message is truthful,⁹⁶ and further may choose to limit the audience as to whom a company's promotional or scientific communication may be directed. This represents a disturbing level of intrusiveness on commercial speech and on the practice of medicine.

V. BRINGING IT DOWN TO EARTH: SOME PRODUCT-RELATED CASE STUDIES

In considering the regulation of truthful and non-misleading off-label communication, it is useful to consider the circumstances posed by several product-based case studies. Each of these cases may seem anachronistic, but together they illustrate the unworkable tension inherent in the current American regime as it limits the free exchange of medical and clinical information.

A. Gilead Sciences' Viread (tenovir disoproxil fumarate)

In 2001, the FDA approved Viread for the treatment of HIV infection in adults based upon its review of a study of previously treated adults infected with HIV.⁹⁷ Two years later, the FDA added clinical data to the labeling from a second study, which examined treatment-naïve patients and their experience with the drug. Gilead has run ongoing clinical trials in order to accumulate additional patient experience data from long-term observation.⁹⁸ Publication of these

condition more comfortable." *Id.* at 73.

96. For example, the 2005 settlement involving Eli Lilly and its drug Evista for osteoporosis was based exclusively on allegations of illegal, off-label promotion. In this case, the company was accused of improperly providing doctors with information about the efficacy of using Evista to treat breast cancer; this information turned out to be substantially truthful as evidenced by FDA approval in September 2007 for that very same indication. *See* Press Release, Dep't of Justice, Eli Lilly and Company To Pay U.S. \$36 Million Relating to Off-Label Promotion (Dec. 21, 2005), http://www.usdoj.gov/opa/pr/2005/December/05_civ_685.html (announcing the civil settlement and criminal plea agreement involving Eli Lilly and its product Evista). As another example, the government has investigated Genentech for several years concerning allegations that it improperly promoted off-label prescribing for its drug Rituxin in the treatment of certain kinds of lymphoma that subsequently were approved by the FDA. *See* Genentech, Inc., Annual Report (Form 10-K), at 24 (Feb. 25, 2008), *available at* <http://www.gene.com/gene/ir/downloadDoc.do?id=3841> (describing the ongoing investigation involving Genentech and its product Rituxan).

97. Prescribing and other background information on this product may be found at Gilead's website. *See* Gilead Sciences, Highlights of Prescribing Information (Mar. 2010), http://www.gilead.com/pdf/viread_pi.pdf.

98. *See, e.g., Gilead Sciences To Present Viread Phase III Clinical Trial Data*, MED. NEWS, Nov. 2, 2009, <http://www.news-medical.net/news/20091102/Gilead-Sciences-to-present-Viread-Phase-III-clinical-trial-data.aspx>.

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clinical results serves to advance the science and, more importantly, enable the medical community to better understand the safety and efficacy profile of the drug after years of patient exposure.

This is important clinical work, as those who suffer from HIV and associated health problems will likely remain on Viread for many years, at least as long as the drug continues to be effective and reasonably tolerable or until a superior treatment is developed and approved. As such, each public release of new long-term clinical data is eagerly anticipated and received at prominent medical conferences by physicians who treat patients with HIV. With each release of data, there is a pattern of information migration that runs from the company to conference attendees, to publication in peer-reviewed medical journals in the United States and abroad, to submission by the company to various regulatory authorities around the world. When the data finally is approved by the FDA and other agencies for inclusion in the product labeling, it has taken at least ten months, and usually far longer.

During the interim period, between the first presentation of the data to physicians at a medical conference and the eventual approval by regulatory authorities of modification of the product labeling, FDA regulations may not allow Gilead to have any role in disseminating this truthful, non-misleading, and extremely relevant clinical information.⁹⁹ At the very least, FDA regulations would not seem to permit Gilead field sales representatives or medical liaisons to discuss this data with physicians. As such, the only physicians who will become aware of the new clinical data on a timely basis would be those who were involved directly in the Gilead clinical study or those who obtain the information through their own independent efforts. Indeed, many physicians would not likely become aware of the new data, and would not take the data into consideration in their treatment of HIV patients. Although the data is at least arguably “consistent with” the existing labeling, since the clinical studies in question are of the same kinds of patients suffering from the same illness and being treated with the same drug, current FDA regulations do not make clear that these distinctions freely allow companies to disseminate information.¹⁰⁰

99. See *supra* text accompanying notes 26-32.

100. Viread also has been approved to treat patients with chronic hepatitis B infection (CHB). Gilead discovered this as the company reviewed data from its ongoing HIV clinical trials that included subsets of patients who were co-morbidly infected with HIV and CHB. While additional HIV patient data may be “consistent with” the existing labeling, it would not appear that data related to an entirely new prospective use, such as treating CHB, would have been covered by this broad standard prior to approval of the second indication. Press Release, Gilead Sciences, Phase III Study Evaluating Gilead’s Viread(R) for the Treatment of Chronic Hepatitis B Virus Meets

B. Cephalon's Provigil (modafinil)

Provigil was approved by the FDA in late 1998 for the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy.¹⁰¹ Although the precise mechanism of action is not fully understood, it appears to work by affecting an area of the brain that regulates wakefulness. The active ingredient, modafinil, is not an amphetamine but a mild stimulant, and as such most patients do not experience the jitteriness or other negative side effects associated with the use of amphetamines. Clinical data and anecdotal evidence has demonstrated that Provigil keeps patients awake and alert regardless of why they might be sleepy or tired.¹⁰²

Cephalon discussed its clinical development plans with the FDA early on, including the drug's potential utility in conditions other than narcolepsy. Following these discussions, the company initiated a series of placebo-controlled clinical studies with distinct groups of patients, each group representing a recognized model of underlying sleep disorder or other medical condition. The FDA suggested that if the company demonstrated efficacy and safety in each of these patient groups, it could seek a broad label for the treatment of EDS associated with any underlying medical condition.¹⁰³ The company studied patients who were sleepy due to one of three conditions: narcolepsy (the first approved indication), obstructive sleep apnea, or a disturbed circadian rhythm pattern due to extended periods of shift work known as "shift work-sleep disorder." These studies demonstrated efficacy across the board and showed a limited number of relatively minor adverse events. However, after the additional data was submitted to the agency in 2003, the FDA convened an advisory committee which recommended against approving the broad label in favor of a pseudo-specific label for use in EDS associated with each condition evaluated.¹⁰⁴

Primary Endpoint (June 6, 2007), http://www.gilead.com/pr_1012569 (announcing positive Phase III clinical results).

101. Prescribing and other background information on this product may be found at Cephalon's Provigil website. See Cephalon, Patient Information Provigil Tablets (Mar. 2008), http://www.provigil.com/media/PDFs/prescribing_info.pdf.

102. See Joel Garreau, *The Great Awakening*, WASH. POST, June 17, 2002, at C1. See also *All on the Mind*, ECONOMIST, May 22, 2008.

103. See CEPHALON, INC., PROVIGIL® (MODAFINIL) TABLETS (C-IV) SUPPLEMENTAL NDA: BRIEFING DOCUMENT FOR PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEETING 10 (Sept. 25, 2003), http://www.fda.gov/ohrms/dockets/ac/03/briefing/3979B2_01_Cephalon-Provigil.pdf.

104. Lois E. Krahn, Chair, Dep't Psychiatry and Psychology, Mayo Clinic, Remarks at the Meeting of the U.S. FDA Peripheral and Central Nervous System Drugs Advisory Committee 184 (Sept. 25, 2003) (transcript available at <http://www.fda.gov/ohrms/DOCKETS/ac/03/>

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This labeling decision virtually ensured a high level of off-label prescribing for the product.

Indeed, many physicians became aware of the product and its intriguing characteristics as the additional clinical studies were conducted, as data was presented at medical meetings, and as the mainstream news media began to write about the incredible “wonder drug”¹⁰⁵ that was being prescribed to pilots, college students, and others who simply were sleepy or tired during the day without any associated medical condition.¹⁰⁶ Unaffiliated physicians and other third parties conducted additional studies, which further increased awareness. For example, the U.S. military conducted a number of clinical studies of aviator performance and pilot sustained alertness while taking Provigil.¹⁰⁷ At the advisory committee meeting, the FDA’s Dr. Robert Temple suggested that he was not necessarily troubled by off-label use of Provigil in the case of truck drivers or others who might be driving while sleepy, noting that “[i]f they’re driving next to me, I think I’d prefer they be on it.”¹⁰⁸

transcripts/3979T2.pdf). Some committee members were concerned that a broader label would result in unwarranted prescribing for patients who did not suffer from any underlying medical disorder, but simply wished to have a “replacement for the normal amount of nighttime sleep.”

105. Wil S. Hylton, *The War. On Drugs.*, ESQUIRE, Feb. 1, 2003, at 116, 117.

106. Physicians have prescribed Provigil extensively for a number of off-label uses, but one often cited has been fatigue associated with multiple sclerosis (MS). In fact, the National Multiple Sclerosis Society characterizes the use of the drug as the standard of care (“medications commonly used in the management of MS”). See National Multiple Sclerosis Society, Medication Used in MS, <http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/medications/index.aspx>. The Society makes reference to two clinical studies with mixed results in its summary of the product, one study conducted over a nine-week period in 2000 by Cephalon that showed efficacy in a low dose of Provigil against placebo, and a second study conducted in 2005 by a physicians’ group in France that failed to show efficacy. However, the Society notes that the clinical experience of physicians treating patients with MS has shown “significant benefit for many patients with MS-related fatigue.” See National Multiple Sclerosis Society, *supra* note 9.

107. See, e.g., JOHN A. CALDWELL, JR. ET AL., U.S. ARMY AEROMEDICAL RESEARCH LABORATORY, THE EFFECTS OF MODAFINIL ON AVIATOR PERFORMANCE DURING 40 HOURS OF CONTINUOUS WAKEFULNESS: A UH-60 HELICOPTER SIMULATOR STUDY (1999); John A. Caldwell, Jr. et al., *A Double-Blind, Placebo-Controlled Investigation of the Efficacy of Modafinil for Sustaining the Alertness and Performance of Aviators: A Helicopter Simulator Study*, 150 PSYCHOPHARMACOLOGY 272 (2000); see also Memorandum from U.S. Dep’t of the Air Force, *supra* note 10.

108. Robert Temple, FDA, Remarks at the Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee 186 (Sept. 25, 2003) (transcript available at <http://www.fda.gov/ohrms/DOCKETS/ac/03/transcripts/3979T2.pdf>).

Two things are evident here. First, there is a host of factors outside the control and influence of the company, including government-sponsored activities that may well significantly affect the extent of off-label prescribing. Second, Provigil is a case of a company developing clinical data with studies in contemplation of a pending label expansion into related therapeutic areas in which the underlying medical cause may differ, but the condition being treated is the same or very similar. The initial, narrow indication approved by the FDA (EDS associated with narcolepsy) suggests that this additional clinical data, all related to efficacy in treating excessive daytime sleepiness, may not be “consistent with” the labeling and therefore may not lawfully be communicated by the company, and yet is truthful and relevant to physicians who might prescribe the drug.

C. Genentech’s Avastin (bevacizumab) and Lucentis (ranibizumab injection)

The saga of these two biological products, each a therapeutic monoclonal antibody designed to bind to and inhibit human vascular endothelial growth factor (VEGF), received substantial press coverage and generated controversy in the medical and patient community.¹⁰⁹ When VEGF is inhibited, the growth of new blood vessels, or angiogenesis, is subsequently halted. Avastin, produced by Genentech, was the first anti-angiogenesis therapy approved in the United States.¹¹⁰ In 2004, the FDA approved it as a first-line treatment for patients with metastatic carcinoma of the colon or rectum, and in 2006 it was approved as a second-line treatment of colon or rectal cancer and a first-line treatment of non-small cell lung cancer. Lucentis, a smaller molecule, or fragment version, of the same active agent in Avastin,¹¹¹ was approved in 2007 for the treatment of neovascular age-related macular degeneration (AMD), a severe disorder of the retina that is a major cause of vision loss in persons over age 60.¹¹²

Prior to the approval of Lucentis, a retinal specialist in Miami was reported to have been the first to experiment with off-label use of a modified form of Avastin to treat AMD. Subsequent to this reported experimentation with Avastin

109. See Andrew Pollack, *Drug Maker and Eye Doctors Settle Dispute Over Avastin*, N.Y. TIMES, Dec. 21, 2007, at C4; see also News Release, Am. Acad. Of Ophthalmology, Ophthalmologists Concerned About AMD Patients’ Access to Avastin (Oct. 12, 2007), <http://www.aaopt.org/newsroom/release/20071012.cfm>.

110. See Genentech, Medicines: Avastin, <http://www.gene.com/gene/products/information/oncology/avastin/> (last visited Mar. 29, 2010).

111. Morten la Cour, *Intravitreal VEGF-inhibitors: Is Avastin a Generic Substitute for Lucentis?* 85 ACTA OPHTHALMOLOGICA SCANDINAVICA 2, 3 (2007).

112. See Genentech, Medicines: Lucentis, <http://www.gene.com/gene/products/information/tgr/lucentis/> (last visited Mar. 29, 2010).

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and prior to the approval of Lucentis, Genentech struggled to address a number of difficult issues associated with the demand for off-label use of an approved but reformulated product, including drug access, distribution, pharmacy compounding, safety, and price. There also are interesting questions of off-label communication presented by this case.

Early on, Genentech acknowledged that the retinal physician community was acting “with noble intent, which is to help patients who are going blind as we speak . . . [but] there have been no safety and toxicity studies conducted on Avastin as an ophthalmic drug.”¹¹³ However, it also emphasized that off-label use was increasing “because of advice generated by the medical community.”¹¹⁴ What did Genentech do about communicating with physicians on the off-label use? “We make educational material available to the doctors but we don’t take a position,” said a Genentech executive.¹¹⁵

Although the two products were quite similar, and intravitreal use of Avastin was possible for those who purchased Avastin through a compounding pharmacy that would then dilute the potency of the formulation, it was not the preferred method of treatment. In fact, the company raised questions about the maintenance of sterility in the process of dividing the Avastin dose due to a lack of preservatives in that drug’s formulation; Genentech also cited a warning letter issued by the FDA to compounding pharmacies.¹¹⁶ Following the approval of Lucentis, the situation was further complicated by the company’s decision to charge far more for Lucentis on a volume basis, such that some retinal physicians continued to purchase and dilute Avastin and legislators sought to pressure the company into making Avastin readily available for the off-label use.¹¹⁷ The company responded that it continued to believe that Lucentis was “the most appropriate treatment for patients with . . . [AMD] because it was specifically

113. *Genentech: Avastin Not Intended for AMD; Company Cautions on Off-Label Use of Cancer Drug*, RETINAL PHYSICIAN, Jan. 2006, <http://www.retinalphysician.com/article.aspx?article=100181>.

114. *Id.*

115. *Id.*

116. Genentech, *Features: Open Letter* (Oct. 29, 2007), <http://www.gene.com/gene/features/avastin/open-letter.html>.

117. Genentech caused a firestorm by pricing Lucentis at approximately \$2,000 per one-time monthly dose and announcing that it would no longer allow compounding pharmacies to purchase Avastin from its wholesalers. Shortly thereafter, following the announcement by U.S. Senator Herbert Kohl (D-Wisconsin) that his Senate Committee on Aging would launch an investigation into Genentech’s decision to limit Avastin availability, the company announced that it had reached agreement to continue to allow retina specialists and ophthalmologists access to Avastin under certain circumstances. *See* Pollack, *supra* note 109.

designed, formally studied, approved by the [FDA] and manufactured for intraocular delivery . . . [but it] does not interfere with physicians' prescribing choices."¹¹⁸

Leaving aside the apparent contradictions inherent in government officials effectively encouraging off-label use of an untested product, Genentech was at the very least in a terribly awkward position during the period 2004 to 2007 as interest in off-label use of Avastin intensified. Although the company could freely reiterate and emphasize any statements made by the FDA, it is not clear that it could lawfully communicate directly to physicians any safety information that related to the off-label use. This alternate use, unrelated to the approved cancer indications and which, by the company's own admission, raised concerns of eye infections, could not possibly be said to be "consistent with" the FDA-approved labeling. From a public policy perspective, it would be preferable to permit companies to act in an ethically responsible manner and to share fully any concerns about prevailing physician practice, rather than to limit communication to a brief press statement and the dissemination of peer-reviewed journal articles. But the current regulatory environment does not allow companies to do this.

D. Allergan's Botox (botulinum toxin)

Botox, a purified form of botulinum toxic, is a popular injectable biologic product used cosmetically to combat wrinkles and facial lines as well as a prescription therapeutic approved by the FDA to treat abnormal tone in muscles known as dystonia.¹¹⁹ Physicians also prescribe Botox to treat spasticity, or involuntary muscle contractions. Botox has been approved in a number of countries outside the United States to treat spasticity, and Allergan recently obtained FDA approval to treat spasticity in the flexor muscles of the elbow, wrist, and fingers in adults.¹²⁰ However, physicians are likely to continue to use Botox for other off-label conditions, including lower limb spasticity and spasticity in juveniles suffering from cerebral palsy.

There is a risk of adverse "distant spread of toxin" associated with the injection of Botox. In connection with this risk, the FDA ordered Allergan and all other manufacturers of botulinum toxin to add a special "boxed warning" to the existing label and package insert, and to adopt a Risk Evaluation and Mitigation Strategy (REMS).¹²¹ In connection with its decision, the FDA noted that its

118. Press Statement, Genentech, Avastin Distribution Update (Dec. 20, 2007), <http://www.gene.com/gene/features/avastin/press-statement.html>.

119. See Allergan, Botox Portal, <http://www.botox.com> (last visited Mar. 29, 2010).

120. See FDA, FDA Approves Botox to Treat Spasticity in Flexor Muscles of the Elbow, Wrist and Fingers (Mar. 9, 2010), <http://www.fda.gov/newsevents/ucm203776.htm>.

121. See FDA, FDA Requires Boxed Warning for All Botulinum Toxin Products (Apr. 30,

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intention was not to discourage the use of botulinum toxins for spasticity, as they remain “very effective” and “commonly used.”¹²² The application of this order has placed Allergan and the other manufacturers of this product in an untenable position. While the FDA has approved the warning information included in the modified labeling and directed the companies to implement the terms of the REMS, the use of the product in spasticity has not yet been approved. As such, FDA regulations do not allow Allergan to speak freely with physicians about the fine points of product administration that might further reduce risk, such as dosing frequency, injection technique, and optimal patient selection.

In response to this conundrum, Allergan has brought an action against the FDA and the DOJ in federal district court in Washington.¹²³ The lawsuit asks the court to determine that a number of FDA regulations are unconstitutional, either on their face or as applied to truthful speech of drug manufacturers, and it asks for preliminary and permanent injunctions that would enjoin the government from taking any civil or criminal enforcement action against Allergan on the basis of its expression of truthful and non-misleading speech. This presents a unique opportunity for a federal court to consider the FDA framework for regulating off-label medical and scientific information. Unlike prior cases in which the First Amendment has been used as a defensive shield in circumstances where companies or their employees were accused of communicating false or misleading information, the company is asking the court to affirmatively permit it to discuss truthful information.

This case, and those others summarized above, might be seen as unusual, but they serve to illustrate the particularly anomalous results that can flow from a regulatory enforcement policy that deems all scientific and medical information not included in the FDA-approved labeling as unworthy of dissemination, and regards those who dare do so as criminals.

2009), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149574.htm>. A Risk Evaluation and Mitigation Strategy (REMS) is required for certain drugs and biological products determined by the FDA to present safety risks. *See* Food & Drug Admin., FDA Issues Draft Guidance on Risk Evaluation and Mitigation Strategies (Sep. 30, 2009), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm184399.htm>.

122. Ellis Unger, Office of New Drugs, Ctr. for Drug Evaluation and Research, Food & Drug Admin., Remarks at the FDA Media Briefing on Botulinum Toxin Products (Apr. 30, 2009) (transcript available at <http://www.fda.gov/downloads/NewsEvents/Newsroom/MediaTranscripts/ucm169170>).

123. *See* Johnathan D. Rockoff, *Allergan Suit Seeks to Lift Botox Curbs*, WALL ST. J., Oct. 2, 2009, at B4; Natasha Singer, *Botox Maker's Suit Cites Free Speech*, N.Y. TIMES, Oct. 3, 2009, at B3.

VI. AN ALTERNATIVE MODEL: THE BRITISH EXPERIENCE

Major drug companies operate on a global scale and are subject to oversight by authorities in various jurisdictions that act to enforce their respective laws and regulations. The broad policy objectives of regulators in Europe are identical to those in the United States: they want clear, hard rules that can be consistently enforced and which will lead to high levels of industry compliance.¹²⁴ However, the United Kingdom long has approached the regulation of advertising and promotion of medicines in a markedly different way. Consistent with a deep tradition of flexibility in its regulation, and more specifically of an evident fondness for private, self-regulation that began in the early twentieth century,¹²⁵ rulemaking and enforcement in this area are developed and led by a self-regulating body associated with the trade organization of British pharmaceutical manufacturers. Whereas the executive branch develops and enforces the rules in the United States, in Britain the responsible government agency has a more limited role, making the UK regulatory scheme even more unusual in that it is neither wholly private nor wholly public. Like the United States, the statutory language is necessarily written broadly. Unlike the United States, this statutory language is supplemented by a detailed code of practice that is adopted, interpreted, implemented, and largely enforced apart from the government. And unlike the United States, there have been virtually no prosecutions.¹²⁶

124. The observations set forth throughout this section are based, in part, on information obtained in interviews with Jeremy Mean, Group Manager, Information for Public Health, UK Medicines and Healthcare Products Regulatory Agency (MHRA), in London (Apr. 2008), and Heather Simmonds, Director, Prescription Medicines Code of Practice Authority (PMCPA), in London (Apr. & June 2008).

125. Britain “appears to be something of a haven for self-regulation.” Rob Baggott, *Regulatory Reform in Britain: The Changing Face of Self-Regulation*, 67 PUB. ADMIN. 435, 438 (1998). Another commentator observed that Britain generally is more “flexible and informal” in its regulation of society. DAVID VOGEL, NATIONAL STYLES OF REGULATION: ENVIRONMENTAL POLICY IN GREAT BRITAIN AND THE UNITED STATES 21 (1986). Consistent with these observations, there is a long history in Great Britain of private, self-regulation of advertising. See generally T.R. NEVETT, ADVERTISING IN BRITAIN (Heinemann on behalf of the History of Advertising Trust 1982). In 1919, the date often cited as the start of self-regulation of medicines advertising, an association of fifty manufacturers of patent medicines was established to control “inaccurate or misleading practices.” *Id.* at 104. Public criticism mounted, however. For example, a 1934 report by the Royal College of Surgeons found that advertising claims for medicines were “always exaggerated and are, in general, purely fraudulent,” and the medicines themselves often have “no substances of therapeutic value.” *Id.* at 164. In response to this criticism, and perhaps in a prescient effort to stave off government action, the association adopted a code of standards in 1936; in hindsight, many regard this first code as an important precedent supporting the concept of self-regulation. *Id.* at 164-65.

126. For a review of trends in effective corporate self-regulation, see CHRISTINE PARKER, THE

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By definition, the self-regulating model requires the full engagement of the regulated industry members,¹²⁷ who must agree on the conceptual framework as well as the specific rules that delineate, refine, and clarify the language of the code over time; drug manufacturers developed and adopted the code in Great Britain and thus, have a substantial stake in its success. They also fear reprisals, which carry the stigma of peer condemnation.¹²⁸ Moreover, the self-regulating system is accompanied by government oversight and an implicit threat of enhanced government enforcement or statutory enactment. Ultimately, if the system is seen as ineffective by public officials and their constituents, industry risks losing a relatively sophisticated and benevolent taskmaster that, while it may threaten to withhold the carrot of association membership, does not wield a

OPEN CORPORATION: EFFECTIVE SELF-REGULATION AND DEMOCRACY (2002). As Parker suggests, the United States has a degree of self-regulation in the form of the U.S. Sentencing Commission Guidelines that were established in the late 1980s, reflecting the common use of criminal sanctions for corporate malfeasance. These guidelines encourage private firms to adopt extensive internal compliance programs, including education and self-reporting mechanisms, and provide reduced sentences for those companies that do so and yet are later found to have committed violations of the law. *Id.* at 259-60.

127. See A. Ogus, *Rethinking Self-Regulation*, 15 OXFORD J. LEGAL STUD. 97 (1995), reprinted in A READER ON REGULATION 375 (Robert Baldwin, Colin Scott & Christopher Hood eds., 1998). Noted regulatory scholar John Braithwaite also has written favorably of self-regulation, noting that it may well be more efficient, more flexible, and less costly than traditional command and control methods. See John Braithwaite, *Enforced Self-Regulation*, 80 MICH. L. REV. 1466 (1982). See also JOHN BRAITHWAITE, *CORPORATE CRIME IN THE PHARMACEUTICAL INDUSTRY* (1984), in which he concludes that large drug firms effectively allocate responsibility for corporate misdeeds to subordinates and external contractors.

128. All breaches of the Association of the British Pharmaceutical Industry (ABPI) Code of Practice are posted on the website of the Prescription Medicines Code of Practice Authority (PMCPA), a quasi-autonomous unit of the ABPI, with the following characterization: “[Company] has breached the ABPI Code of Practice for the Pharmaceutical Industry and brought discredit upon, and reduced confidence in, the pharmaceutical industry.” Prescription Medicines Code of Practice Authority, Advertisements, <http://www.pmcpa.org.uk/?q=advertisements> (last visited Mar. 29, 2010). As one executive based in the United Kingdom told me in a confidential interview, “we all have a huge incentive to avoid coming before the panel.” In the United States, the Pharmaceutical Research and Manufacturers of America (PhRMA) in 2002 first adopted a Code of Interactions with Healthcare Professionals, which was useful in developing an industry consensus as to appropriate marketing and promotional practices. But its public policy impact is limited in that there is no functional equivalent to the quasi-private enforcement mechanism of the British PMCPA, as discussed below. See PHARMACEUTICAL RESEARCH & MANUFACTURERS OF AM., *CODE ON INTERACTIONS WITH HEALTHCARE PROFESSIONALS* (Jan. 2009), available at <http://www.phrma.org/files/attachments/PhRMA%20Marketing%20Code%202008.pdf>.

heavy club in the manner of the state.

This section will summarize the European and British statutory frameworks for the regulation of advertising and promotion of medicines. It will review a 2005 House of Commons Health Committee report on the undue influence of the pharmaceutical industry and consider the responses to the report from the responsible government agency, the trade group, and the industry. Next, the section will review some recent panel cases and other anecdotal and qualitative outcome data in an effort to gauge the effectiveness of the system. Finally, it will compare the British to the American system according to the normative criteria set forth above. There are significant differences in the respective reimbursement environments for off-label use of drugs, and the concomitant financial incentives to promote or otherwise encourage off-label prescribing are lower in Britain. Still, in keeping with its tradition of self-regulation, Britain has reasonably clear rules that allow for cases to be brought and resolved expeditiously in a transparent process with opportunity for appeal and with an unusually high level of engagement with industry.

A. Statutory Framework

Within the European Union there are multiple layers of law, regulation, and industry standards that govern the advertising and promotion of prescription drugs. At the highest level, the current EU directive¹²⁹ requires that member states adopt local legislation that broadly prohibits the unauthorized advertising and promotion of prescription medicine and requires that all advertising comply with the approved labeling. Significantly, this directive permits “voluntary control of advertising of medicinal products by self-regulating bodies.”¹³⁰ The European Federation of Pharmaceutical Industries and Associations (EFPIA) Code of Practice on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals establishes a more detailed framework that all member state private associations may reference and further expand.¹³¹

129. Council Directive 2004/27, art. 88, 2004 O.J. (L.136) 34, 51 (EC).

130. *Id.*

131. See EUROPEAN FED’N OF PHARM. INDUS. & ASS’NS, EFPIA CODE ON THE PROMOTION OF PRESCRIPTION-ONLY MEDICINES TO, AND INTERACTIONS WITH, HEALTHCARE PROFESSIONALS (2007), available at <http://www.efpia.eu/content/default.asp?PageID=559&DocID=3483>. The EFPIA Code provides clear, useful guidance in certain areas. For example, Article 12 proscribes service agreements that would induce the recommending, prescribing, or selling of medicine. *Id.* at 12. Article 14 goes into detail regarding consulting agreements with health care professionals, noting that “token consultancy arrangements should not be used to justify compensating healthcare professionals.” *Id.* at 13. Article 18 mandates that each national member include local enforcement

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The Medicines Act of 1968 provides the basic statutory framework for the promotion and sale of prescription drugs in the United Kingdom. The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for protecting public health by ensuring the safe use of pharmaceuticals. In contrast with the FDA, the MHRA does not assume primary responsibility for routine oversight of pharmaceutical company advertising and promotion. Instead, it reserves for itself the prerogative to focus on those matters and products that present the potential for serious risk to public health. Simultaneously, it works to ensure that a quasi-autonomous unit of the Association of the British Pharmaceutical Industry (ABPI), known as the Prescription Medicines Code of Practice Authority (PMCPA), effectively controls advertising and promotion through the interpretation and enforcement of its code of practice on a day-to-day basis.¹³²

One of the most readily apparent differences between the environment in the United States and that in the United Kingdom is the level of clarity provided to industry about the rules of engagement. The MHRA “Blue Guide”¹³³ offers reasonably clear and understandable guidance on promotion and advertising.¹³⁴

provisions that are “proportionate to the nature of the infringement, have a deterrent effect and take account of repeated offences of a similar nature or patterns of different offences.” *Id.* at 18.

132. The relationship between the MHRA, the ABPI, and the PMCPA was established formally in a memorandum of understanding in 2005. *See* MEMORANDUM OF UNDERSTANDING BETWEEN THE ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY, THE PRESCRIPTION MEDICINES CODE OF PRACTICE AUTHORITY AND THE MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (2005), *available at* http://www.abpi.org.uk/links/assoc/PMCPA/Memo_understanding_nov3.pdf. The memorandum characterizes the British regulatory framework as “robust” and comprised of “two complementary systems of control, self regulation by the pharmaceutical industry by means of the ABPI Code of Practice . . . administered by the PMCPA, and UK law, administered by the MHRA.” *Id.* at 1. The underlying philosophy is that “[e]fficient, stringent and transparent self regulation via the ABPI Code enables the Government to ensure that regulatory requirements are met . . . with intervention by the MHRA when there is a clear case for protection.” *Id.*

133. MEDS. AND HEALTHCARE PRODS. REGULATORY AGENCY, THE BLUE GUIDE: ADVERTISING AND PROMOTION OF MEDICINES IN THE UK (2005), *available at* http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007552&RevisionSelectionMethod=Lates tReleased.

134. For example, Section 5.14 provides that company press releases “should be genuinely newsworthy rather than having the intention of promoting a product . . . [and] should provide the context in which the medicine will be used and the population for which it has been licensed.” *Id.* at 23. Section 5.15 makes clear that companies may respond to questions from health care professionals, though the answers must be balanced and fairly responsive to the question asked. *Id.*

This is not to suggest that the European and British codes are so clear that all queries are

resolved, or that there is no room left for interpretation. A critical question in the European Union, as it is in America, lies in defining where scientific exchange ends and advertising or promotion begins. This question is at issue in the European Commission's proposal on the dissemination directly to the general public of non-promotional information on prescription medicines. As the Commission noted, the "current legal framework (Directive 2001/83/EC, as amended by Directive 2004/27/EC) does not provide for sufficient harmonised rules on the provision of information about medicines to patients." European Commission, Information to Patients, Legislative Approach, http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/information-to-patient/legislative_en.htm (last visited Apr. 21, 2010). The Public Consultation provides that information to be provided to patients "should be compatible with approved summaries of product characteristics . . . and it should not go beyond the key elements specified in them." EUROPEAN COMMISSION, PUBLIC CONSULTATION: LEGAL PROPOSAL ON INFORMATION TO PATIENTS 6 (Feb. 5, 2008), available at http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/pharmacos/docs/doc2008/2008_02/info_to_patients_consult_200802_en.pdf. Interestingly, the United Kingdom's response to the Public Consultation on this very point notes that, in the view of the MHRA, "it is not possible to develop a clear definition, based solely on the content of the information, of what is non-promotional information about medicines in order to distinguish clearly between advertising and information." Letter from Pub. Health Meds. & Healthcare Prods. Regulatory Agency, to European Comm'n Enter. & Indus. Directorate-Gen. (Apr. 25, 2008), available at http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014932&RevisionSelectionMethod=LatestReleased. Following Public Consultation, the Commission adopted two proposals that, subject to affirmation by the Council of Europe and the European Parliament, would amend existing EC Directives governing the provision of information to the general public on prescription drugs. See *Commission Proposal for a Directive of the European Parliament and of the Council Amending, as Regards Information to the General Public on Medicinal Products Subject to Medical Prescription, Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use*, COM (2008) 663 final (Oct. 12, 2008), available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0663:FIN:en:PDF>; *Commission Proposal for a Regulation of the European Parliament and of the Council Amending, as Regards Information to the General Public on Medicinal Products for Human Use Subject to Medical Prescription, Regulation (EC) No 726/2004 Laying Down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency*, COM (2008) 662 final (Oct. 12, 2008), available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0662:FIN:en:PDF>.

Commentators are generally skeptical that the proposals will be adopted, as many are concerned that it will be difficult in practice to distinguish between the provision of medical and scientific information, and advertising itself, which will continue to be prohibited. See, e.g., Ian Schofield, *EU Pharmaceutical Package Struggles with Information Overload*, INFORMA UK (Nov. 6, 2009) ("The pharmaceutical industry and many members of the European Parliament are in favour of the patient information proposal, but most EU member state governments are not. They agree on the need to improve the provision of reliable, unbiased information on prescription drugs throughout Europe, but not by giving pharmaceutical companies a role.").

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There is a refreshing level of candor and engagement with industry by British government officials that extends well beyond the issuance of mere rules, to encompass meaningful, ongoing discussion about the kinds of practical challenges faced on a routine basis.¹³⁵ The ABPI Code of Practice for the Pharmaceutical Industry¹³⁶ attempts to define the line between promotion and scientific exchange by making clear that promotion does not include responding to physician inquiries, providing factual information without making a claim, or providing information related to human health or disease while omitting reference to a specific medicine. It also provides guidance concerning gifts from pharmaceutical companies to health care professionals by limiting them to inexpensive items of modest value that are relevant to their work. In recent years, the MHRA has also undertaken multiple publication initiatives that are designed to convey more clearly its policy views on industry advertising material, and in so doing, significantly improve transparency, and has undertaken significant additional pre-launch review of promotional materials, as well as certain other advertising.¹³⁷

The essence of the British system is that competitors, former employees, physicians, patients, and the MHRA itself can bring complaints against ABPI members for violating the advertising and promotional rules and regulations. The complaints are frequent (more than one hundred per annum), they are decided promptly (within months if not weeks generally), they may be appealed (generally only about 20% of the initial rulings are overturned), and they allow

135. For example, Jeremy Mean of the MHRA presented on the topic of web-based pharmaceutical company communication in Manchester in September of 2007. In his presentation, Mr. Mean acknowledged the fundamental definitional problem up front—namely, that there are clear rules covering labeling language and formal business announcements, and clear rules covering the content and use of promotional material, but, in his words, “what about everything in between?” Mr. Mean then went on to attempt to answer the question he himself raised, spelling out the conditions under which companies may communicate via the web, but noting as well that there is likely to be new legislation in this area forthcoming. Jeremy Mean, Group Manager, Info. for Pub. Health, Meds. & Healthcare Prods. Regulatory Agency, Address at British Pharmaceutical Conference: From Manchester to Malta—Communicating to Patients across Europe (Sept. 7, 2007) (on file with author).

136. ASS’N OF THE BRIT. PHARM. INDUS., CODE OF PRACTICE FOR THE PHARMACEUTICAL INDUSTRY (2008), available at http://www.pmcpa.org.uk/files/sitecontent/ABPI_Code_of_Practice_2008.pdf. The ABPI Code of Practice was first established in 1958, and the most recent version came into force on July 1, 2008. It is developed by the ABPI in consultation with the MHRA, the British Medical Association, the Royal Pharmaceutical Society of Great Britain, and the Royal College of Nursing, adopted by the ABPI, and administered by the PMCPA.

137. Mean, *supra* note 135.

full participation of the parties.¹³⁸ Perhaps the most significant aspect of this process, especially as it relates to the question of improper off-label promotion, is that panel decisions convey heightened levels of clarity and transparency to industry.

B. The Politics of Self-Regulation

The British system has not been without its critics, but when faced with a scathing report issued by a Parliamentary Committee, government and industry responded expeditiously to address the perceived deficiencies. In 2004 and 2005, a select Committee on Health of the British House of Commons undertook a sweeping review of the influence of the pharmaceutical industry in the country,¹³⁹ encompassing among many subjects advertising, promotion, and medical education. In its review of existing circumstances related to the advertising and promotion of prescription drugs, the Committee levied criticism at each of the involved parties. It criticized the industry for inappropriate activities such as employing ghostwriters for medical journal articles and soliciting physicians excessively.¹⁴⁰ It criticized physicians themselves for lacking independence.¹⁴¹ It

138. See Prescription Medicines Code of Practice Authority, Constitution and Procedure, in ABPI, CODE OF PRACTICE, *supra* note 136, at 39-53. The statistics provided were compiled by the author based on the case information available at Prescription Medicines Code of Practice Authority, Completed Cases, <http://www.pmcpa.org.uk/?q=completedcases> (last visited Mar. 29, 2010).

139. HEALTH COMM., HOUSE OF COMMONS, THE INFLUENCE OF THE PHARMACEUTICAL INDUSTRY (Mar. 22, 2005), available at <http://www.parliament.the-stationery-office.co.uk/pa/cm200405/cmselect/cmhealth/42/42.pdf> (U.K.). The Committee's perspective was fair and reasonable on its face, as it acknowledged that companies have every right to market their products and to attempt to influence the market environment, but at the same time should not rely on misleading communications or fail to disclose new safety data or potential risks associated with the product. The Committee further identified the government's role as one of using impartial judgment to detect excess and limit actions that might be adverse to the public interest, a task it acknowledged as difficult and that required productive collaboration between the private and public sectors.

140. *Id.* at 53-55. The Committee criticized the aggregate number of company promotional details and repeat visits of individual sales representatives ("drug company representatives' contact with doctors 'can almost be on a daily basis'"), the extent of free meals and other "promotional hospitality masquerading as education," and what it called the "scale of medicines advertising." *Id.* at 57-59, 64. On the latter point, the Committee expressed concern with product launch commercialization activities where "explosive marketing occurs at precisely the period in which we know least about the effects of a drug in the community." *Id.* at 58. "The intensive marketing which encourages inappropriate prescribing of drugs must be curbed." *Id.* at 105. The Committee cited, for example, benzodiazepines as a group of products that well illustrated the problems associated

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criticized the MHRA for inadequate pre-vetting of advertising and marketing materials and for the length of time taken to resolve complaints presenting serious risks to public health.¹⁴² It criticized the PMCPA for the duration of time taken to complete self-initiated investigations and for its failure to sufficiently coordinate its work with the MHRA.¹⁴³ In general, the Committee was not convinced that the private, self-regulatory system was working effectively, noting delays in investigations and in the issuance of corrective statements, and that sanctions for violations often were not serious.

With the system of private, self-regulation of medicines advertising at risk, the MHRA, the PMCPA, and the industry initiated a series of changes in direct response to the House of Commons report. The MHRA, as the responsible government agency acting under the direction of the British Parliament, faced substantial political pressure to respond to the report and reform the system. Rather than resorting to broadside attacks on drug companies, the agency reiterated the significance of the industry to Great Britain by endorsing its many contributions to public health.¹⁴⁴ The MHRA expanded its pre-vetting of all promotional material for newly approved drugs, encouraged the PMCPA to consider changes to its code of practice, and sought to better coordinate its work with the PMCPA. In addition, the MHRA completed an internal review that

with what it characterized as “over-promotion and over-prescription.” *Id.* at 65.

141. “[T]he blame for inadequate or misinformed prescribing decisions [also lies] with . . . doctors and other prescribers who do not keep abreast of medicines information and are sometimes too willing to accept hospitality from the industry and act uncritically on the information supplied by the drug companies.” *Id.* at 64.

142. “We recommend that all the promotional material for a new product be pre-vetted by the MHRA prior to publication . . .” *Id.* at 105. In addition, the Committee “recommend[ed] that there be an independent review of the MHRA.” *Id.* Such a review could “determine whether the processes now used for decision-making are adequate and reflect a patients’ health needs and society’s expectations.” *Id.* at 106.

143. “When the PMCPA has evidence that a company has breached the regulations it should inform the MHRA. . . . [C]orrective statements [should] always be required.” These statements should be “given as much prominence as the original promotional piece.” *Id.* at 106.

144. “The pharmaceutical industry is an important sector for the UK. It has an outstanding record of innovation for the benefit of patients, and of investment in the economy. It has to be recognised that to carry out its business Government and its agencies will have dealings with the industry. It has long been the Government’s policy that these dealings must be balanced and appropriate with an aim of securing beneficial outcomes for patients and the economy.” SEC’Y OF STATE FOR HEALTH, GOVERNMENT RESPONSE TO THE HEALTH COMMITTEE’S REPORT ON THE INFLUENCE OF THE PHARMACEUTICAL INDUSTRY 1 (Sept. 2005), *available at* http://www.dh.gov.uk/dr_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4118608.pdf.

resulted in changes to the complaint investigation process with enhanced transparency from publications of decisions and guidance, shorter duration in the investigation and decision making process, and increased use of corrective statements and consideration of prosecution in extreme cases.¹⁴⁵ The MHRA publicly expressed its intolerance with any future failure to comply with the law.¹⁴⁶ In 2006, the PMCPA adopted a stricter code of practice.¹⁴⁷ Companies themselves examined their business practices, limited the extent of their hospitality, and excised the influence of commercial organizations in meetings with outside scientific and medical advisers.

C. UK Code of Practice Panel Decisions

In reviewing a range of PMCPA cases from the last few years that raised questions of improper advertising and promotion outside the approved labeling, some important principles are apparent. In general, the panel decisions present a fairly high level of sophistication and judgment. Moreover, the decisions serve to enhance significantly the level of clarity of guidance and transparency of thought process, which are publicly available to firms operating in the United Kingdom.

First, the PMCPA panels appear more inclined than U.S. prosecutors to give the benefit of the doubt to the company if preliminary documentation is not damning and will not launch a multi-year investigation on the basis of a single complaint.¹⁴⁸ In a case brought by an anonymous employee, the panel noted that

145. For a summary of the MHRA internal review, see Jeremy Mean & Beryl Keeley, *Review of Advertising Procedures*, 17 INT'L J. PHARM. MED. 185 (2003).

146. As an example, the MHRA upheld complaints against two drug distribution and retail firms in the United Kingdom for excessive promotion and discounting, and went on the BBC to publicize its enforcement actions. *2-for-1 Painkiller Deals Attacked*, BBC NEWS, June 14, 2005, <http://news.bbc.co.uk/1/hi/health/4091184.stm>.

147. The 2006 code of practice enhanced its provisions related to patient safety warning requirements, better defined and restricted promotional gifts and hospitality, better defined permissible relationships with patient groups, banned promotional competitions and placed a cap on advertising pages, accelerated the pace of complaint resolutions, and strengthened various penalties for code violations. See ASS'N OF THE BRIT. PHARM. INDUS., CODE OF PRACTICE FOR THE PHARMACEUTICAL INDUSTRY (2006), available at <http://www.pmcpa.org.uk/files/sitecontent/code06use.pdf>. Sanctions meted out by the PMCPA have become more severe. Although there has still only been one prosecution for promotional impropriety in British history, there have been suspensions from ABPI membership of several leading multinational drug companies, including Abbott Laboratories, Roche, and Merck's affiliate, MS&D.

148. See, e.g., Prescription Medicines Code of Practice Auth., *CASE AUTH/2043/9/07, Anonymous Employee v Sanofi-Aventis*, CODE PRAC. REV., Nov. 2007, at 139, available at <http://www.pmcpa.org.uk/files/2007%20November%20Review.pdf>. This case stands in contrast to the American practice, where "whistleblower" complaints are kept confidential under the *qui tam*

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although it had some concerns about the company using its cardiovascular scientific advisors to initiate promotional discussions using unlicensed data with “difficult to access customers,” there was no direct evidence of impropriety and no way to obtain additional information since the complainant was anonymous.¹⁴⁹ Second, there is an ongoing effort to clarify ambiguous areas of the law. In a case brought by a physician, the panel’s decision focused on website linkage questions in finding that the company breached the code by referring health professionals from a patient group website to another website that itself contained references on the use of its product for a then-unapproved condition.¹⁵⁰ Third, the panels are willing to consider the most difficult definitional and contextual issues in the area, including subtle distinctions between scientific exchange and promotion. In a case brought by a competing company, the panel engaged in a detailed analysis of the specific circumstances related to sponsorship of an independent abstract with an unrestricted medical grant.¹⁵¹ Here, although the company expected that the published abstract would contain some favorable reference to its then unapproved protease inhibitor, the panel found that this did not constitute illegal off-label promotion since there was no direct contact with the editor and no substantive influence on the publication.¹⁵² Fourth, in reaching judgments, the panels are sensitive to prevailing clinical and medical practice issues. For example, a panel found that a company’s promotion of combination therapy in the treatment of breast cancer was permissible in that the approved labeling did not specifically limit the product’s use to monotherapy, and that combination therapy was an integral part of accepted medical practice.¹⁵³

statute, and the DOJ is required to investigate the allegations.

149. *See id.* at 140.

150. *See* Prescription Medicines Code of Practice Auth., *CASE AUTH/1801/2/06, General Practitioner v GlaxoSmithKline*, CODE PRAC. REV., Aug. 2006, at 20, 24, available at http://www.pmcpa.org.uk/files/August_2006.pdf. Although GSK strongly refuted the allegation since the advertisement containing the referral was published by a patient support group and did not disclose proprietary product names or make product claims, this ruling was upheld on appeal. The panel regarded the website linkage as inappropriate, noting that otherwise “companies would be able to refer to independent websites as a means of avoiding the restrictions in the Code.” *Id.*

151. *See* Prescription Medicines Code of Practice Auth., *CASE AUTH/1696/3/05, Bristol Myers-Squibb v Boehringer Ingelheim*, CODE PRAC. REV., Aug. 2005, at 125, 127, available at http://www.pmcpa.org.uk/files/2005_August_Review.pdf. Boehringer subsequently distributed the abstract on an unsolicited basis to physicians, though other HIV treatment products also were referenced in the publication. This was found to constitute scientific exchange, and not promotion.

152. *See id.* at 127.

153. *See* Prescription Medicines Code of Practice Auth., *CASE AUTH/1674/1/05, Sanofi-Aventis v Pierre Fabre*, CODE PRAC. REV., Aug. 2005, at 58, 60-61, available at

These cases illustrate several important features of the self-regulatory system in the United Kingdom. The MHRA process is expeditious, as it does not involve extensive discovery and investigatory burden. It also is transparent, as it moves from broad EU guidelines to slightly refined UK law, to more detailed ABPI codification, to yet more detail in the interpretation of rules in the context of actual business practice. The opinions themselves are clear in expressing both results and reasoning. The panel process is equitable and adheres to widely accepted due process principles, as it addresses complaints from all interested parties, including competitor companies, and allows for appeals. Although the UK system is focused on ensuring compliance with the law and applicable regulation, it appears to be congruous with the prevailing realities of medical practice and the consideration of relevant clinical data.

VII. EQUITY, EFFICIENCY, AND EFFECTIVENESS: TOWARD AN ETHICALLY RESPONSIBLE MODEL?

The House of Commons Health Committee Report and the associated reforms and policy changes adopted by the MHRA, together with the ongoing enhancement by the PMCPA to its code of practice, have had a reformative impact on the behavior of drug companies operating in Britain, though it is difficult to assess precisely the aggregate impact on industry promotion and marketing practices. The British regulatory environment appears less confrontational than the prevailing system in the United States. This may reflect differences in the underlying political dynamic, in which government officials in Britain are more readily willing to engage with industry and more apt to recognize the contributions that the pharmaceutical industry has made to the economic prosperity and public health of the citizenry.¹⁵⁴

A number of UK industry executives conveyed in informal discussions that their companies have significantly restricted policies related to sales, marketing, and medical education policies since 2005 in response to the changed

http://www.pmcpa.org.uk/files/2005_August_Review.pdf. The applicable regulatory submission included clinical data from a range of combination treatments, though the panel expressed concerns about Pierre Fabre's effective promotion of an oncology treatment developed by Roche since the approved labeling of the Roche product specified combination use only with two other named products. *Id.* at 59, 61.

154. At one point, British Prime Minister Tony Blair described the pharmaceutical industry as "a prime example of what is needed in a successful knowledge economy" along with praising the industry for its "very substantial contribution to our economy and welfare of our citizens." Corporate Watch, The Association of the British Pharmaceutical Industry (ABPI), <http://www.corporatewatch.org/?lid=332> (last visited Apr. 21, 2010). It is difficult to conceive of a senior American official or member of Congress uttering similar sentiments.

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environment.¹⁵⁵ More specifically, companies recently have modified policies and practices in response to PMCPA panel decisions in areas such as the provision of bonus payments, the awarding of unconditional medical grants, and the need to distinctly separate promotional activities from the provision of medical and educational goods and services.¹⁵⁶

Not surprisingly, American drug and device firms also have changed their practices in the face of an *ad hoc* hostile enforcement environment. For example, companies have limited the range of physicians to whom they detail their products, they have curtailed or limited strictly the discretion held by individual sales representatives to engage physicians in broader discussions about their patients and treatment options, and they have changed compensation schemes to reduce or eliminate incentive pay stemming from off-label prescribing.

In the short run, this environment does not seem likely to change. There will continue to be regular announcements of civil settlements with staggering financial penalties and criminal plea agreements with individual charges for

155. Interviews conducted with pharmaceutical company executives from various firms in the United Kingdom between April and June, 2008, including those at GlaxoSmithKline, AstraZeneca, and Merck Serono. More than one executive working in Great Britain for a multi-national pharmaceutical company emphasized that self-regulation is effective largely because the APBI has been willing to suspend company membership in the case of flagrant abuse. *See supra* note 128. APBI membership is important for firms since the Association negotiates with the government of the United Kingdom to obtain price approvals for new products and modifications for existing ones.

156. *See, e.g.*, Prescription Medicines Code of Practice Auth., *CASE AUTH/1186/5/01, Anonymous v Pfizer*, CODE PRAC. REV., Feb. 2002, at 10, 29, available at http://www.pmcpa.org.uk/files/2002_February_review.pdf#page=10 (holding that so-called medical liaison executives were too closely linked to the sales force, and should not be communicating with physicians during pre-license approval time period); Prescription Medicines Code of Practice Auth., *CASES AUTH/1807/3/06 and AUTH/1810/3/06, The Sunday Times/Director and a General Practitioner v Pfizer*, CODE PRAC. REV., Nov. 2006, at 3, available at http://www.pmcpa.org.uk/files/1807_and_1810_November.pdf#page=1 (describing allegations that payment to sponsored service providers cannot be linked to specific level of product sales or receive bonuses based on product sales); Prescription Medicines Code of Practice Auth., *Case AUTH/1859/6/06, Anonymous Employees v Merck Sharp & Dohme*, CODE PRAC. REV., Feb. 2007, at 15, 16, available at http://www.pmcpa.org.uk/files/1859_Feb_2007.pdf#page=1 (company return on investment calculations were alleged inconsistent with the concept of unrestricted grants, need to have procedures to ensure funds spent for valid purposes); Prescription Medicines Code of Practice Auth., *CASES AUTH/1902/10/06 and AUTH/1903/10/06, Employee v Sanofi-Aventis and Procter & Gamble*, CODE PRAC. REV., Nov. 2007, at 3, 34, available at <http://www.pmcpa.org.uk/files/2007%20November%20Review.pdf> (challenging company-funded nurse audit program as too closely linked to promotion of the underlying product to treat osteoporosis).

executives likely. However, perpetuating this trend is untenable over the long term, particularly when the rules are not clear, there are significant individual and institutional political biases at work, and the outcomes are inconsistent. While the promotional and financial excesses of pharmaceutical companies in recent years cannot be excused, it is especially troubling that companies seeking to act in an ethically responsible manner cannot find substantial clarity in existing law and regulations. In turn, this lack of clarity raises an important constitutional dimension when measuring the law's requirements for specificity against the potential for criminal judgments under the strict liability framework of the FDCA.¹⁵⁷

The critical question is how best to motivate companies to behave ethically in adopting sound policies, exercising self-restraint in their business practices, and engaging in self-policing under an effective compliance program. Based upon field research interviews with government and private sector officials, as well as a review of the pattern of panel cases brought in the past few years, the British system appears to be working effectively to allow for the dissemination of truthful, non-misleading information under appropriate circumstances while significantly enhancing clarity and transparency.¹⁵⁸ Admittedly, empirical analysis would be useful in refining our understanding of the British model and its role in encouraging compliant policies and practices in the United Kingdom.

157. See George Terwilliger, former U.S. Deputy Att'y Gen., Address at the American Enterprise Institute for Public Policy Research: Off-Label Uses of Approved Drugs: Medicine, Law, and Policy (May 21, 2008) (criticizing the application of the exclusionary rule and current DOJ policy and practice). An illustrative case involves three former executives of Purdue Pharma, under which they were compelled to plead guilty to personal misdemeanors under a strict vicarious liability theory in which their service as "responsible corporate officers" made them individually liable for the alleged misdeeds of the corporation in making false claims related to its OxyContin opioid painkiller medicine. See Barry Meier, *3 Officials Are Sentenced In Case Involving OxyContin*, N.Y. TIMES, July 21, 2007, at C4; Barry Meier, *Narcotic Maker Guilty of Deceit over Marketing*, N.Y. TIMES, May 11, 2007, at A1.

158. As suggested above, these cases typically arise in the context of whether or not the conveyance of truthful scientific and medical information constitutes promotion. See, e.g., Prescription Medicines Code of Practice Auth., *CASE AUTH/1100/11/00, Abbott v Roche*, CODE PRAC. REV., May 2001, at 22, available at http://72.47.199.56/files/2001_May_review.pdf; Prescription Medicines Code of Practice Auth., Completed Cases, *CASE AUTH/2234/5/09–Lilly v Novo Nordisk*, Interim Case Report, <http://www.pmcpc.org.uk/?q=node/750> (last visited Apr. 21, 2010) (company may provide truthful scientific information about an unapproved drug to current and potential clinical investigators, especially if grant of marketing authorization is not imminent).

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VIII. POLICY RECOMMENDATIONS

There is much to absorb from the regulatory approach of our colleagues in Britain. Beginning with the development and adoption of reforms in 2005, there has been evident substantial collaboration between the government and the private sector. The embrace of regulatory strictures by British executives has precipitated changes in company policies and business practices and a concomitant rise in reputation, thereby further reinforcing industry's commitment to the process. This is not a panacea; PMCPA proceedings make clear that some companies in Britain continue to break the rules, and their employees and those of rivals continue to complain about improper promotional practices. However, in such cases these complaints are presented, confronted, investigated, and resolved efficiently, transparently, and effectively without criminal exposure and excessive cost.

It is unrealistic politically to imagine the wholesale importation of the British approach to regulating off-label promotion. Among other things, America lacks the tradition and experience of decades of private, self-regulation of advertising and promotion. However, the United States would do well to consider modifying its approach such that it better achieves the efficiency and transparency now prevailing in the United Kingdom. Our public policy should support the sound practice of medicine without restricting the prerogative of physicians to make decisions. Granted, government oversight is necessary on some level to ensure that firms provide consistently accurate and balanced information about their products when profits and sales commissions are at issue. But our current system, which is based on the precept that a paternalistic FDA is uniquely situated to shield consumers and doctors from the vulgar commercial motivations of industry, is grossly unbalanced. We must trust academic physicians and practicing doctors to digest and evaluate medical and scientific information as it becomes available.

What should be done to address this imbalance? First and foremost, the FDA should adopt new regulations that eliminate ambiguity and provide clear guidance as to company behavior in each of the areas in which pharmaceutical companies interact with physicians and payers: consulting agreements, continuing medical education, internet and electronic media postings, reimbursement information, sales representative promotional messages, and the permissible activities of medical liaison and medical affairs. These areas can and should be addressed just as the FDA did early in 2009 when it adopted its final rule on the dissemination of peer-reviewed journal articles.¹⁵⁹ Moreover, the

159. See Good Reprint Practices for the Distribution of Medical Journal Articles and Medical

pharmaceutical industry could work with the agency to develop jointly a code of conduct that embraces these principles.¹⁶⁰ While there likely will be disagreement as to the restrictions on speech associated with these commercial activities, many companies are so anxious for clarity that they would be willing to accept a Faustian bargain that embraces certainty in lieu of autonomy. Second, HHS should reassert its prerogative and wrest control from the DOJ of off-label enforcement actions. As described in this article, the DOJ has the authority and responsibility to prosecute and threaten the prosecution for criminal matters, and the FDCA includes criminal sanctions for violating its statutory provisions. I am suggesting a subtle shift in the government's perspective, such that HHS and the FDA have the authority to address cases as they develop, and referral to the DOJ for criminal investigation is reserved for those egregious cases that, based upon the FDA's understanding of the drug and company in question, present significant malfeasance. Regulatory enforcement must minimize the likelihood of disseminating untruthful and misleading information, but unless companies are found to have intentionally misled physicians or the public and caused injury or damage to health, violations should be treated as civil regulatory infractions and not criminal offenses. Accordingly, one alternative to the present criminal enforcement approach would be to establish significant, statutory civil penalties for the dissemination of false or misleading information. This scheme could establish a legal presumption in favor of liability based upon some showing by the government or private plaintiffs that could then be rebutted by the accused company. One might consider as well an enforcement panel operated by the OIG, with medical, legal, and policy input from the FDA, that metes out civil liability penalties in a streamlined process reminiscent of that used by Britain's PMCPA. Third, as others have suggested,¹⁶¹ the FDA could provide incentives or mandates to compel companies to conduct clinical studies and submit data to the agency for review prior to speaking about it. Fourth, Congress should increase its appropriations for the FDA to allow the agency to more effectively and efficiently review supplemental New Drug Applications for expanded indications. In turn, the FDA should consider developing an expedited process that would allow new indications to be approved without the same extent of clinical testing currently required for NDAs. Fifth, while I recognize that many support using the federal False Claims Act to provide an incentive for

or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices; Availability, 74 Fed. Reg. 1,694.

160. See PHARMACEUTICAL RESEARCH & MANUFACTURERS OF AM., CODE ON INTERACTIONS WITH HEALTHCARE PROFESSIONALS, *supra* note 128.

161. See Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476 (2009).

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whistleblowers in the health care arena, my experience leads me to believe that Congress should evaluate the wisdom of applying this statute to off-label promotion cases, as it has created a vehicle for current and former employees to ignore the in-house compliance process and go directly to the government in pursuit of extraordinary wealth.

IX. CONCLUSION

In the end, public policy should create incentives for self-reform and ethical corporate behavior. Rather than destroying our research-based drug companies by applying the “death penalty”¹⁶² of debarment, a far better outcome for society would follow if the companies that are responsible for much of the innovation that drives our future health and well-being are allowed to “reform themselves.”¹⁶³ Companies must adopt and enforce rigorous compliance policies and programs, and more than that, must act in a meticulous, ethical manner when speaking about products for human health. Pharmaceutical company executives must be brutally honest with themselves, their various stakeholders, and other third parties as they evaluate clinical and medical data. In many cases, this may require extensive consultation with medical experts in the field, and the timely publication of comprehensive summaries of all relevant product information. Above all, they must act with the highest levels of integrity in their relationships with physicians and patients so as to avoid even the appearance of impropriety. This kind of responsible behavior will be reinforced by the fair application of clear rules.

Each of the stakeholders in this area should reflect on their respective interests and values. Industry leaders must develop a greater degree of genuine respect for government regulators and policymakers and must operate their firms with integrity. At the same time, government policy makers should recognize that if we transform the research-based pharmaceutical and biomedical device industries into the functional equivalent of public utilities, we will have cheaper medicine and technology in the short run but not much in the way of new medicine or technology in the long run. Physicians need to consider whether they value the products, medical education, and information provided by drug companies, and if they do, break their lengthy silence on this issue. Patients, whether suffering from rare diseases or otherwise, should serve as advocates for the products that they believe are vital to their health, even if the use happens to

162. *See supra* note 84.

163. John Simons, *Why Do Drug Companies Fear This Man?*, FORTUNE, Oct. 27, 2003, at 167 (quoting Michael Sullivan, then-United States Attorney for the District of Massachusetts).

be off-label.

These developments will not transform the present environment in the near term. There are substantial political forces at work and there is substantial momentum in favor of continued regulation by threat of prosecution as companies scramble to reform their practices in light of evolving government policy. Perhaps the Supreme Court ultimately will hear the *Allergan* case and will rule that those FDA regulations prohibiting companies from speaking about truthful scientific and medical information are unconstitutional. Absent this, policy makers and regulators might regard favorably the British model of private, self-regulation combined with meaningful, effective government regulatory oversight. While empirical work undertaken over a longer time frame would be useful to validate this conclusion, substantial anecdotal evidence suggests that the UK approach has succeeded in curtailing many of the very same troubling promotional and marketing practices by many of the very same companies in a fair and expeditious manner. It is time for America to learn something from the old country.