to haunt practice, from thalidomide to Vioxx, from DES to Avandia.

Extending this renaissance of skepticism, some questioned the overall role of medicine itself in improving public health. In 1962, the physician-demographer Thomas McKeown published an analysis of the decline of tuberculosis in England and Wales.[5] Noting that the decline had begun before the bacillus was discovered and had nearly concluded before streptomycin was developed, McKeown argued that modern therapeutics had been falsely credited with public health improvements that could be better explained by secular changes in nutrition and standards of living. Similarly, those attempting to bring the benefits of modern tuberculosis drugs to impoverished populations in the 1960s realized that drugs were necessary but not sufficient for transforming health — a lesson that would be relearned through global efforts to treat malaria, tuberculosis, and HIV infection in the 21st century (2006).[6]

RECONTEXTUALIZING THERAPEUTICS

From the leeches, lancets, and purgatives of the early 1800s to today's targeted molecular medicines, doctors have constantly sought new and better therapies. Yet the evolution of the field of therapeutics has not been linear, and none of the therapeutic revolutions of the past two centuries have been immediate or complete. Rather, our field's progress owes as much to changing forms of therapeutic skepticism as to changing forms of therapeutic enthusiasm.

As the locus of disease has narrowed from the afflicted person to the molecular mechanism, and the target of magic bullets has followed suit, physicians have faced regular reminders of the limits of the reductionist approach. The history of therapeutics offers a space to reflect on these more subtle logics of medical knowledge and practice, restoring our appreciation for the breadth of the physician's task and the complexity of our mission.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Punishing Health Care Fraud — Is the GSK Settlement Sufficient?

Kevin Outterson, J.D., LL.M.

On July 2, 2012, the Department of Justice announced the largest settlement ever in a case of health care fraud in the United States. GlaxoSmithKline (GSK) agreed to plead guilty to three criminal counts and settle civil charges brought under various federal statutes; the company will pay a total of $3 billion to the federal government and participating states. Since 2009, the federal government has collected more than $11 billion in such settlements under the False Claims Act.

In the Federal District Court in Boston a few days later, GSK pleaded guilty to two criminal counts for sales of misbranded Paxil (paroxetine) and Wellbutrin (bupropion). These drugs are considered misbranded when they are promoted for indications for which they have not been approved by the Food and Drug Administration — the practice commonly known as off-label promotion. Providers cannot be reimbursed for misbranded drugs under federal and state rules. GSK also pleaded guilty to a third crime, failing to report safety data related to Avandia (rosiglitazone). Failing to report safety data violates the Food, Drug, and Cosmetic Act and leads to serious questions about wheth-

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Table 1. Largest Pharmaceutical-Company Settlements with the U.S. Government, 2009–Present.*

Company and Year of Settlement	Settlement Amount (billions of $)	Drugs	Alleged Misconduct
Amgen, pending	0.76	Aranesp (darbepoetin alfa)	Kickbacks, off-label promotion
Johnson & Johnson, pending	1.50–2.20	Risperdal (risperidone), Natrecor (nesiritide), Invega (paliperidone)	Deceptive marketing practices, kickbacks
GlaxoSmithKline, 2012	3.00	Paxil (paroxetine), Wellbutrin (bupropion), Avandia (rosiglitazone), Advair (fluticasone/salmeterol), Lamictal (lamotrigine), Zofran (ondansetron), Imitrex (sumatriptan), Lotronex (alosetron), Flovent (fluticasone), Valtrex (valacyclovir)	Off-label promotion, failure to report safety data, false and misleading promotion
Abbott Laboratories, 2012	1.50	Depakote (valproic acid)	Off-label promotion and marketing despite inadequate evidence of effectiveness
Merck, 2011	0.95	Vioxx (rofecoxib)	Off-label promotion, false and misleading statements about safety
Novartis, 2010	0.42	Trileptal (oxcarbazepine), Diovan (valsartan), Zelnorm (tegaserod), Sandostatin (octreotide), Exforge (amlodipine and valsartan), Tekturna (aliskiren)	Off-label promotion, kickbacks
AstraZeneca, 2010	0.50	Seroquel (quetiapine)	Off-label promotion, kickbacks
Pfizer, 2009	2.30	Bextra (valdecoxib), Geodon (ziprasidone), Zyvox (linezolid), Lyrica (pregabalin), Aricept (donepezil), Celebrex (celecoxib), Lipitor (atorvastatin), Norvasc (amlodipine), Relpax (eletriptan), Viagra (sildenafil), Zithromax (azithromycin), Zoloft (sertraline), Zyrtec (cetirizine)	Off-label promotion, promotion with the intent to defraud or mislead, kickbacks
Eli Lilly, 2009	1.40	Zyprexa (olanzapine) and others	Off-label promotion, failure to provide information on side effects

* Information is from the Department of Justice and from Securities and Exchange Commission filings.

er clinicians are basing their decisions on the best evidence. GSK also settled related civil liabilities for these and other drugs.

Despite the size of the fine and civil settlements, it would be a mistake to assume that GSK was an outlier in the global pharmaceutical and medical-device industries. Indeed, many of the major companies have settled with the Department of Justice in recent years (see Table 1). When the GSK settlement was announced, 25 major companies and 8 of the top 10 global pharmaceutical companies were under "corporate integrity agreements" (see Table 2). Corporate integrity agreements, now a routine part of settlements for health care fraud, typically require enhanced compliance activities within the company for 5 years, including reports to the government from an independent monitor.

But questions remain about the efficacy of fines and corporate integrity agreements in deterring corporate misbehavior. The 2012 fines against Abbott Laboratories and GSK represent a modest percentage of those companies' revenue.[1] Companies might well view such fines as merely a cost of doing business — a quite small percentage of their global revenue and often a manageable percentage of the revenue received from the particular product under scrutiny. If so, little has been done to change the system; the government merely recoups a portion of the financial fruit of firms' past misdeeds.

One partial solution would be to impose penalties on corporate executives rather than just the company as a whole. Boston whistleblower attorney Robert M. Thomas, Jr., embraces this approach: "GSK is a recidivist. How can a company commit a $1 billion crime and no individual is held responsible?"

The GSK corporate integrity agreement does include some provisions that attempt to change corporate culture. First, GSK must revise its compensation systems to "ensure that financial incentives do not inappropriately motivate" sales representatives; these

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Table 2. Corporate Integrity Agreements in Force with Pharmaceutical and Medical-Device Companies, as of July 2, 2012.*

Company	Years Covered
Abbott Laboratories	2012–2017
Allergan	2010–2015
AstraZeneca	2010–2015
Aventis Pharmaceuticals, Sanofi-Aventis U.S.	2007–2012
Bayer HealthCare	2008–2013
Biovail, Valeant Pharmaceuticals International	2009–2014
Boston Scientific	2009–2014
Bristol-Myers Squibb	2007–2012
Cell Therapeutics	2007–2012
Cephalon	2008–2013
CVS Caremark	2008–2013
Eli Lilly	2009–2014
Forest Laboratories	2010–2015
GlaxoSmithKline	2012–2017
Ivax Pharmaceuticals	2009–2014
Jazz Pharmaceuticals	2007–2012
Medtronic, Medtronic Sofamor Danek USA	2009–2014
Medtronic Spine	2008–2013
Merck	2011–2016
Novartis Pharmaceuticals	2010–2015
Novo Nordisk	2011–2016
Omnicare	2009–2014
Otsuka America Pharmaceutical	2008–2013
Pfizer	2009–2014
Purdue Pharma	2007–2012
Walgreen	2008–2013

* Information is from the Office of Inspector General of the Department of Health and Human Services and from public sales data.

changes include new restrictions on compensation for off-label promotion. GSK has now implemented a program to eliminate incentive-based compensation for sales representatives based on "territory/individual level sales goals," which will alter the financial incentives for sales representatives who meet with physicians. Second, GSK senior executives and other employees who are paid bonuses and other compensation may in the future be asked to repay those amounts if certain types of fraudulent behavior occur that violate the corporate integrity agreement. As has been noted in the financial press, this requirement does nothing to recoup several substantial recent bonuses given to senior management at such firms,[2] but it does make it more difficult to repeat the practice, at least at GSK. Third, in view of the serious questions about failure to report negative data related to Avandia's safety, GSK must commit itself to "research and publication practices" designed to make more clinical trial information available to clinicians and regulators. These commitments have several disturbing exceptions: GSK will "generally" seek publication for research results, and summaries of clinical trial data will be posted on a clinical study register "with rare exception." These are but partial steps toward transparency.

These measures can certainly be improved. For one thing, though all these provisions seem advisable, they are imposed only under a corporate integrity agreement, as opposed to official regulations, and expire in 5 years. Legislative reformers should consider whether the entire industry should be regulated on a level playing field, as opposed to through piecemeal agreements. In addition, individuals must be held responsible in appropriate circumstances. Models might include federal tax law, under which directors and officers of nonprofit corporations cannot be indemnified against fines imposed on them as individuals for particularly egregious violations.[3] Key leaders can also be excluded from participation in federal health programs. The academic researchers involved in the controversy regarding the safety data for Avandia has thus far escaped sanctions as well.[4]

If the corporate fines are too small, the False Claims Act will need to be amended so that a higher percentage of the revenues derived from fraudulent activities is recouped. At the same time, federal law must insist on greater transparency for clinical trial re-

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sults, so that negative safety data are not hidden from clinicians and regulators.

Finally, these types of fraud are hard to detect from the outside. Internal documents are often critical to these cases. Most of the time, these documents are provided by internal whistleblowers. In a recent survey, researchers identified several ways in which the whistleblower provisions of the False Claims Act could be strengthened to encourage whistleblowers to come forward and to protect them from retaliation.[5] Whistleblowers should be encouraged, not punished for their testimony.

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