

Environments and Scientific Misconduct

**SCIENTIFIC MISCONDUCT, THE PHARMACEUTICAL
INDUSTRY, AND THE TRAGEDY OF INSTITUTIONS**

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Abstract: This paper examines how current legislative and regulatory models do not adequately govern the pharmaceutical industry towards ethical scientific conduct. In the context of a highly profit-driven industry, governments need to ensure ethical and legal standards are not only in place for companies but that they are enforceable. We demonstrate with examples from both industrialized and developing countries how without sufficient controls, there is a risk that corporate behaviour will transgress ethical boundaries. We submit that there is a critical need for urgent drug regulatory reform. There must be robust regulatory structures in place which enforce corporate governance mechanisms to ensure that pharmaceutical companies maintain ethical standards in drug research and development and the marketing of pharmaceuticals. What is also needed is for the pharmaceutical industry to adopt authentic “corporate social responsibility” policies as current policies and practices are insufficient.

Keywords: Pharmaceuticals; ethics; drug industry; pharmaceutical ethics; business ethics; scientific misconduct.

INTRODUCTION

The research-based pharmaceutical industry likes to emphasize it is in the business of health. This is desirable insofar as companies produce drug therapies that can help treat or prevent illness. But what is inherently problematic with the pharmaceutical industry is precisely the point that it *is* a business and by

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definition, a business seeks to maximize profits. This is what all for-profit industries do and it is not problematic if actions related to this are within the boundaries of ethical, legal, and responsible practice. But oftentimes, the drive for profit, particularly in an intensely competitive market, may foster unethical practices and even scientific misconduct unless tightly monitored.¹

We argue that existing legislative and regulatory frameworks (both governmental and self-regulation) are not strong enough. We demonstrate this by illuminating examples where the pharmaceutical industry has exhibited blatant scientific misconduct in the following areas: the drug approval process, selective reporting of research results, protection of human research subjects, and marketing practices. We define scientific misconduct broadly as “.. an intentional or unintentional departure from the methodology or procedure of scientific enquiry, self-criticism, or data recording, verification, storage, interpretation, or presentation without an explanation consistent with such methodology or procedure.”^a More narrowly, scientific misconduct is that which can be considered inconsistent with accepted scientific standards, which can range from undeclared conflicts of interest to falsification and fabrication of results.² Under this definition, we include the unethical treatment of research subjects and we consider scientific misconduct as applied in the drug approval process and marketing practices. Based on our examples, we propose that governments need to critically examine whether regulations and legislation are robust enough to ensure pharmaceutical industry practices do not slip into the area of unethical behaviour. We also advocate for the pharmaceutical industry to earnestly apply the principles of corporate social responsibility. The combination of tighter governmental controls and a meaningful industry ethos of doing “good” are necessary for meaningful change to happen.

The Drug Approval Process

All governments rely on drug regulatory institutions to control products that are available in the market through the process of drug registration. Drug registration

a. This is a definition provided to the authors by Professor Bernard Dickens, Faculty of Law, University of Toronto. We are grateful for his assistance here.

1. Cohen JC, Illingworth P, Schuklenk U. *The Power of Pills: Social, Ethical, and Legal Issues in Drug Development, Marketing, and Pricing*. London: Pluto Press; 2006.

2. Nylenna M, Simonsen S. 2006. Vol 367. *The Lancet*. “Scientific misconduct: a new approach to prevention.”

involves several processes, which are dependent upon and linked to the scientific integrity of research. This includes the evaluation of a product's efficacy, safety, indications for use, and subsequently, ensuring appropriate labeling, warnings, and restrictions on marketing and prescribing. But globally, as the WHO notes, one-third of drug regulatory authorities have either limited or no capacity to regulate medicines.^{3]} And even when drug regulatory agencies have the requisite institutional structures and human resources in place, institutions are tragically imperfect—if an oversight happens, public health can be compromised. Part of this is a result of the fact that regulatory agencies have imperfect information about the products, which they are regulating. This is discussed below. What is of equal concern is that drug regulatory agencies are not always impartial and can be captured by the pharmaceutical industry, which they are charged with regulating. While regulation itself may commence with the public's interest in mind, it can evolve to become a mechanism through which industry promotes its private interests to the extent that the industry through seemingly benign interface effectively “capture” the regulator.

One well-known contemporary example of information asymmetry between the manufacturer and the regulator is the Vioxx (rofecoxib) case. This drug was withdrawn from the market in September 2004 after Merck reported that it doubled the risk of heart attack or stroke.⁴ Internal company communications reveal that Merck was well aware of rofecoxib's cardiovascular risks yet encouraged representatives to downplay physicians' concerns.^{5, 6} Merck's “obstacle handling guide” instructed company representatives to respond in an indirect manner to physicians' concerns by stating that the drug “would not be expected to demonstrate reductions” in cardiovascular events and that it was “not a substitute for aspirin.”⁵

However, the Vioxx debacle does not simply reveal internal problems within a corporation. The U.S. Food and Drug Administration (FDA) was also

3. World Health Organization. WHO Medicines Strategy Countries at the Core 2004-2007. Geneva: World Health Organization; 2004: 5.

4. Avorn J. Evaluating drug effects in the post-Vioxx world: there must be a better way. *Circulation* 2006;113:2173-6.

5. Wilde-Mathews A, Martinez B. E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage. *The Wall Street Journal*. 2004 Nov 1;Sect. A:1.

6. Horton R. Vioxx, the implosion of Merck, and aftershocks at the FDA. *Lancet* 2004; 364:1995-6.

implicated in the widespread use and marketing of Vioxx. An FDA internal review showed a “clear cut excess” in the number of heart attacks associated with rofecoxib. The FDA failed to mandate that Merck conduct further clinical tests.⁶ The FDA finally ordered Merck to include warnings on package inserts in 2002.⁷ By the time that Merck “voluntarily” pulled the drug off the market, approximately 20 million people had used the medication for about 5 years.⁴ Whether this case was a clear-cut example of regulatory capture is still up for debate. Some claim that it is a question of political interference from Congress, pressuring the FDA regulators to speed up the drug review and approval process.⁸ Others point towards a combination of consistent under-funding and lack of resources. A report released by the Institute of Medicine in September 2006, criticized the FDA on a number of grounds among which included the lack of the FDA’s “clear authority” to ensure compliance with the regulations.⁹ All of these criticisms emphasize the importance of having institutions in place that can manage the pharmaceutical industry effectively. The dangerous mixture of profit incentives, an increasingly competitive industry, and the inherent uncertainty in medical science and practice demand more careful regulation and attendant procedures. The pharmaceutical industry is a high-risk research industry and is largely opaque. Much of its conduct falls outside of the public domain due to restrictions on access to data and transparency of business practices. The level of disclosure required for adequate regulation can threaten the market price of their stocks, which is a disincentive for shareholders but it is in the public’s interest. There is a growing recognition that inappropriate scientific misconduct can affect share prices. This ideally may lead to more ethical corporate behavior – a phenomenon that we are now observing in our post-Vioxx world.

Selective Reporting of Research Results

The Merck-Vioxx case highlighted the problem of the suppression of research results and put the onus on medical journals for tougher standards and practices.

7. Topol EJ. Failing the public health: rofecoxib, merck, and the FDA. *N Engl J Med*. 2004;35:1707-9.

8. Hawthorne F. *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*. New Jersey: John Wiley & Sons Inc; 2005.

9. Institute of Medicine. The Future of Drug Safety: Action Steps for Congress. Sept 2006. Available from: <http://www.iom.edu/CMS/3733.aspx> [Accessed Mar 21, 2007].

In December 2005, the editors of the *New England Journal of Medicine* stated that at least two of the authors of the VIGOR trial were aware of three deaths due to myocardial infarction in the rofecoxib group. Investigators argued that they did not include this information in the study analysis because they occurred after the trial's cardiovascular event cut-off date.¹⁰ Recent reports implicate *The New England Journal of Medicine* as well. Emerging evidence suggests that the editors failed to respond to concerns about the validity of the study results and the safety profile of rofecoxib.¹¹ This reservation was raised as early as 2001. The suppression of data on three serious adverse events is an example of the inherent risks of business incentives in the proper conduct of scientific research.

While the Vioxx case is a glaring example of scientific misconduct on the part of the pharmaceutical industry, it is not atypical. In June 2004, then New York State Attorney General Eliot Spitzer filed a lawsuit against GlaxoSmithKline (GSK). The lawsuit alleged that they withheld research results on their antidepressant drug, Paxil. He accused the company of "having engaged in repeated and persistent fraud by misrepresenting, concealing and otherwise failing to disclose to physicians information in its control concerning the safety and effectiveness of its antidepressant medication paroxetine HCL ("paroxetine") in treating children and adolescents with Major Depressive Disorder ("MDD").¹² According to the allegations, GSK reported to the FDA the results of only one of the five studies conducted. The Attorney General's office reports that the remaining four unreported studies suggest "a possible increased risk of suicidal thinking and acts."¹³ An internal company memo advised sales representatives to avoid discussion of the clinical trial data that

10. Curfman GD, Morrissey S, Drazen JM. Expression of concern: Bombardier *et al.*, "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," *N Engl J Med* 2000;343:1520-8. *N Engl J Med* 2005;353:2813-4.

11. Armstrong D. Bitter Pill: How the New England Journal Missed Warning Signs on Vioxx. *The Wall Street Journal*. 2006 May 15;Sect. A:1.

12. The People of the State of New York, by Eliot Spitzer, Attorney General of the State of New York against Glaxosmithkline, plc., Smithkline Beecham Corporation. (June 2, 2004). Available from: http://www.oag.state.ny.us/press/2004/jun/jun2b_04_attach1.pdf [Accessed Mar 27, 2005].

13. Office of New York State Attorney General Eliot Spitzer. Major Pharmaceutical Firm Concealed Drug Information [press release on the Internet]. 2004 June 2. Available from: http://www.oag.state.ny.us/press/2004/jun/jun2b_04.html [Accessed Mar 27, 2005].

suggested the increased suicide-related risk of Paxil/Seroxat with physicians.¹⁴ The FDA has since recommended against the use of Paxil in those under the age of 18.¹⁵ Shortly after, GSK settled the lawsuit for 2.5 million dollars and committed to the establishment of a clinical trials register to provide public online access to their clinical study summaries.¹⁶ Their full disclosure has led to increased scrutiny of their products, which recently led to claims questioning the safety of their popular anti-diabetic drug Avandia (rosiglitazone maleate).¹⁷

Perhaps the primary reason for the prevalence of scientific misconduct is the growing commercialization of medical research. Commercialization has led to an industry “intertwined” with academe, regulatory bodies, government policies, and the protection of research subjects.¹⁸ While regulatory regimes have adjusted to accommodate pharmaceutical innovation and development, mechanisms aimed to protect patient safety and research subjects have not adequately recognized these changing relationships. As a result, existing regulatory standards are failing to serve their purpose.¹⁸ These new relationships need to be recognized, understood, and addressed with proper checks and balances. This should include implementing the Institute of Medicine’s recommendation to make the registration of all Phase 2-4 clinical trials mandatory if they are to be considered valid for drug approval.⁹ Accordingly, mechanisms to ensure the timely and comprehensive reporting of research

14. Silverman E. Sales reps told not to divulge Paxil data. *The NJ Star Ledger*. 2004 Sep 29. Available from: <http://www.ahrp.org/infomail/04/09/30.php> [Accessed Mar 27, 2005].

15. US Food and Drug Administration, Center for Drug Evaluation and Research [homepage on the Internet]. Questions and Answers on Paxil (paroxetine hydrochloride); [created 2003 Jun 19]. Available from: <http://www.fda.gov/cder/drug/infopage/paroxetine/paxilQ&A.htm> [Accessed May 27, 2006].

16. United States District Court, Southern District of New York. The People of the State of New York by Eliot Spitzer, Attorney General of the State of New York (Plaintiff), against, GlaxoSmithKline PLC, d/b/a GlaxoSmithKline, Smithkline Beecham Corporation, c/b/a GlaxoSmithKline (Defendant). Civil Action No. 04-CV-5304 MGC. Consent Order and Judgment. Available from: http://www.oag.state.ny.us/press/2004/aug/aug26a_04_attach1.pdf [Accessed June 2, 2007].

17. Meier B. For drug makers, a downside to full disclosure. *The New York Times*. 2007 May 23. Available from: <http://www.nytimes.com/2007/05/23/business/23drug.html?ex=1180929600&en=64c1829b668cf799&ei=5070> [Accessed June 2, 2007].

18. Lemmens T. Leopards in the Temple: Restoring Scientific Integrity to the Commercialized Research Scene. *J Law Med Ethics*. 2004;Winter:2-18.

results must be applied vigilantly

Pharmaceutical industry critics have pointed out that questionable research practices such as improper study design result in the wastage of hundreds of millions of dollars (US) for healthcare expenditures and also have a negative impact on public health outcomes.¹⁹

Protection of Human Research Subjects

The protection of human research subjects is another area where the pharmaceutical industry goal of obtaining fast marketing approval can foster scientific misconduct, which obviously has an impact on patient safety. This problem is particularly acute in settings where governmental institutions are weak and where the outsourced clinical research industry is booming. In a 2004 survey of researchers in developing countries, Hyder and colleagues found 46 of 203 (25%) respondents reported that “their studies did not undergo an ethics review by an IRB, ethics board, or Ministry of Health in the country.”²⁰ In countries lacking adequate regulatory and monitoring structures, the weakness in research ethics regulation has the potential to cause widespread and serious harm.

For-profit contract research organizations (CROs), which coordinate and run clinical research trials for pharmaceutical companies around the world, play an important role within the outsourced clinical research industry. Angell estimates that in 2001, approximately 1,000 CROs globally, accounted for revenues upwards of \$7 billion.²¹ One example is Igate Clinical Research International (based in Pittsburgh and Mumbai). This company’s website describes the “India Advantage” as including a “huge patient base...drug naïve population...high enrollment rates...[and an] increasingly accommodating regulatory environment”.²² However, patients who do not have access to

19. Steneck NH. Fostering Integrity in Research: Definitions, Current Knowledge, and Future Directions. *Sci Eng Ethics*. 2006;12:53-74..

20. Hyder AA *et al*. Ethical review of health research: a perspective from developing country researchers. *J Med Ethics*. 2004;30:68-72.

21. Angell M. *The Truth About the Drug Companies: How They Deceive Us and What To Do About It*. New York: Random House; 2004.

22. IGATE Clinical Research International [homepage on the Internet]. About Us. Available from: <http://www.igatecorp.com/icri/html/aboutus/tia.htm> [Accessed Mar 30, 2005].

health care may be more willing to join these clinical trials for the promise of free medical care. Because clinical trials provide a means of obtaining access to better health care, they can be easily recruited and quickly enrolled. Medical literacy and cultural and economic barriers can make informed consent a problem. Furthermore, these CROs pay local doctors and nurses well for recruitment. In developing countries, these payments can raise a physician's salary considerably.²¹ Financial incentives could increase the likelihood of stretching eligibility criteria or deceiving patients and obtaining poorly informed consent. With the pressure that pharmaceutical companies face in achieving fast approval of a drug — industry claims that a one-day delay in getting a drug to market can cost them \$1.3 million²³ — the incentive exists for unethical practices.

In 2001, over 24 families from Nigeria filed a lawsuit in a US court against Pfizer (*Abdullahi v. Pfizer*, No. 01 Civ. 8118, 2002 WL 31082956). Their lawsuit concerned a clinical trial conducted in 1996 on Trovan (trovafloxacin). This drug is an antibiotic to treat bacterial meningitis.²⁴ According to *The Lancet*, the families claimed that Pfizer gave their children a “new, untested and unproven drug without first obtaining their informed consent” or without explaining that Trovan was an experimental drug which they could refuse and instead receive the proven effective treatment for meningitis at no cost. Pfizer claims that they had received ethics approval from Nigerian authorities and that informed consent was obtained from the families.²⁴ A US federal judge dismissed the case in 2002 on the basis that the trial was not appropriate for the US courts.²⁵ In May 2006, *The Washington Post* described the contents of a leaked report by a panel of Nigerian medical experts. They concluded that Pfizer violated Nigerian law, the Declaration of Helsinki, and the UN Convention on the Rights of the Child.²⁶ Among the allegations, the report states that Nigerian ethics approval was only obtained after the study was

23. Bodenheimer T. Uneasy alliance: clinical investigators and the pharmaceutical industry. *N Engl J Med*. 2000;342:1539-44.

24. Ahmad K. Drug company sued over research trial in Nigeria. *Lancet*. 2001;358:815.

25. Hensley S. Court revives suit against Pfizer on Nigeria Study. *The Wall Street Journal*. 2003 Oct 13. Available from: http://www.drugawareness.org/Archives/4thOtr_2003/record0041.html [Accessed Mar 30, 2005].

26. Stephens J. Panel faults Pfizer in '96 clinical trial in Nigeria: unapproved drug tested on children. *The Washington Post*. 2006 May 7; Sect. A:01.

completed and that the approval was then backdated. Most recently, the Nigerian government filed another lawsuit against Pfizer demanding \$7 billion in damages.²⁷

In 1997, Lurie and Wolfe alerted the international community of unethical placebo-controlled antiretroviral therapy trials in developing countries.²⁸ Almost three years after the 1994 AIDS Clinical Trials Group Study 076 proved that zidovudine reduced vertical mother-to-child HIV transmission by two-thirds, Lurie and Wolfe identified 15 randomized controlled trials — either already underway or about to enroll patients — taking place in developing countries, where some or all of the patients were not provided with antiretroviral therapy. Some of these trials were sponsored by the National Institutes of Health and the Centers for Disease Control. Critics argued that the failure to provide the established standard of care violated the international Declaration of Helsinki, US Department of Health and Human Services regulations on foreign research, and WHO ethical guidelines.²⁹ The NIH, CDC and UNAIDS, which oversaw the PETRA studies in Africa, defended their use of placebo-controlled trials primarily on scientific grounds.^{30, 31} No action was taken against the agencies or the researchers, however the controversy spurred a surge of debate over what constitutes ethical conduct in the design and implementation of clinical trials in developing countries.²⁹⁻³³ Since then, the Declaration of Helsinki has

27. McGreal C. Nigeria sues Pfizer for \$7bn over 'illegal' tests on children. *The Guardian*. 2007 June 5. Available from: <http://www.guardian.co.uk/medicine/story/0,2095955,00.html> [Accessed 6 June 2007].

28. Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the Human Immunodeficiency Virus in developing countries. *N Engl J Med*. 1997;337:853-6.

29. Angell M. The ethics of clinical research in the third world. *N Engl J Med*. 1997;337:847-9.

30. John F. Kennedy School of Government Case Program, Harvard University. The debate over clinical trials of AZT to prevent mother-to-infant transmission of HIV in developing nations. C14-99-1535.9. Available from: <http://www.ksg.harvard.edu/case/azt/ethics/home.html> [Accessed June 2, 2007].

31. Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *N Engl J Med* 1997;337:1003-5.

32. Benatar SR, Singer PA. A new look at international research ethics. *BMJ* 2000;321:824-6.

33. Macklin R. After Helsinki: unresolved issues in international research. *Kennedy Institute of Ethics Journal*, 2001;11:17-36.

been amended three times³⁴ and the Council for International Organizations of Medical Sciences (CIOMS) revised their ethical guidelines for biomedical research in 2002³⁵, in the attempt to be more responsive to the social, economic and political context of the host country, especially for multinational and transnational research. The interpretation and precise application of these principles continues to be ongoing issue, including how to define what the standard of care should be in developing countries.³⁶

Of great concern is the dearth of information on the behavior of local companies in developing countries.³⁷ In the context of little regulation or enforcement, we cannot be sure that human research subjects are being treated ethically and according to internationally set standards. This can be compensated to some extent by strong regulatory structures in developed countries where the drugs are to be registered for approval. For example, the FDA requires disclosure of clinical trials that are conducted abroad but the resources dedicated to monitoring these trials is low.³⁸ More resources must be dedicated to meet these ends. Participation of civil society becomes important in countries with little institutional capacity, as they can play a watchdog role. However, active scrutiny by human rights agencies and nongovernmental organizations, while important, is not sufficient in itself. Ultimately, developing country governments, with the assistance of extra-budgetary funding from the WHO, must commit the funds and resources to strengthen their IRB capacity and improve transparency.

34. The World Medical Association. Policy: World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects. Available from: <http://www.wma.net/e/policy/b3.htm> [Accessed June 2, 2007].

35. Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva 2002. Available from: http://www.cioms.ch/frame_guidelines_nov_2002.htm [Accessed June 2, 2007].

36. Benatar SR. Towards progress in resolving dilemmas in international research ethics. *Journal of Law, Medicines and Ethics*. 2004;Winter:574-82.

37. Nair VM, Martin DK. Concerns about ethical review of health research in India. *Indian J Med Ethics*. 2004;1:119-20.

38. Committee on Oversight and Government Reform. Chairman Henry A. Waxman, 110th Congress. Prescription for Harm: The Decline in FDA Enforcement Activity. (June 26, 2006). Available from: <http://oversight.house.gov/story.asp?ID=1074&Issue=Prescription+Drugs> [Accessed Mar 22, 2007]

Scientific Misconduct through Marketing Practices

The interface between the pharmaceutical industry and physicians is an area that is particularly laden with the potential for scientific misconduct partly due to the lack of regulation in this area. The information asymmetry between manufacturer and physician makes physicians vulnerable to the inaccurate presentation of research on manufacturers' products. The industry may argue that physician-industry interaction is necessary to educate doctors about the therapeutic qualities of new drugs and advances made in disease treatment. However, there is compelling evidence suggesting that a powerful motivation of corporate-sponsored events is not health education but profit maximization. For example, a study by Wazana in 2000 found that physician interaction with the pharmaceutical industry was associated with increased requests for additional drugs on hospital formularies and changes in prescribing practice.³⁹ As Carl Elliot wrote in a thoughtful essay in the *Atlantic Monthly* "Doctors' belief in their own incorruptibility appears to be honestly held. It is rare to hear a doctor-even in private, off-the-record conversation- admit that industry gifts have made a difference in his or her prescribing."⁴⁰ But, drug companies possess sophisticated marketing techniques. Estimates from 2001 suggest that "marketing and administration" accounted for as much as 35% of industry revenues.²¹ While this figure is contested, industry's heavy reliance on marketing for the promotion of its drug products is widely recognized.

Elliott describes pharmaceutical marketing practices in the following way. "Many reps can tell stories about occasions when, in order to move their product, they pushed the envelope of what is ethically permissible. I have heard reps talk about scoring sports tickets for their favorite doctors, buying televisions for waiting rooms, and arranging junkets to tropical resorts."⁴⁰

A high profile case of unethical marketing involved Warner-Lambert. In 2004, Warner-Lambert (now a subsidiary of Pfizer) agreed to a settlement and paid \$430 million after flagrant off-label promotion of its anti-epileptic drug

39. Wazana A. Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift? *JAMA* 2000;283:373-80.

40. Elliot C. The Drug Pushers. *The Atlantic Monthly*. 2006; 297:5.

Neurontin.⁴¹ Evidence demonstrated that Warner-Lambert “aggressively marketed” Neurontin to treat conditions ranging from bipolar mental disorder, Lou Gehrig’s disease, attention deficit disorder, migraine, and other off-label indications. Neurontin was even promoted as “monotherapy for epileptic seizures” despite the fact that the FDA specifically rejected the approval for this use.⁴¹ The company was charged with a “widespread, coordinated, national effort” which involved tactics including one-on-one sales pitches, payments for expensive events, dinners and trips to conferences, and allowing sales representatives to shadow physicians while seeing patients and at times, advising treatment.⁴¹

Physician-industry interaction may be even more problematic in developing and transition countries where doctors make paltry salaries and sometimes rely heavily on gifts from the pharmaceutical industry to supplement their livelihood. Aggressive marketing is frequently cited, with the use of expensive gifts.⁴² Unethical promotion practices range from expanding indications for use, exaggerating therapeutic efficacy and underplaying risks and side effects.^{43, 44} An analysis of pharmaceutical industry drug information materials in India, published in the WHO Essential Drugs Monitor, showed “many discrepancies between claims made and independent scientific data.”⁴⁵ The WHO issued *Ethical Criteria for Medical Drug Promotion* in 1988. However, almost a decade later, WHO acknowledged that inappropriate drug promotion remained a problem in developing and industrialized countries.⁴⁶ More helpfully,

41. US Department of Justice [homepage on the Internet]. Warner-Lambert to pay \$430 million to resolve criminal and civil health care liability relating to off-label promotion [press release]. The Office of Public Affairs Press Room [2004 May 13]. Available from: http://www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm [Accessed Mar 27, 2005].

42. Bal A. Can the medical profession and the pharmaceutical industry work ethically for better health care? *Indian Journal of Medical Ethics*. 2004;1:17.

43. Gulhati C. Marketing of medicines in India. *BMJ*. 2004;328:778-9.

44. Menkes DB. Hazardous drugs in developing countries: the market may be healthier than the people. *BMJ*. 1997;315:1557-8.

45. Gopalakrishnana S, Murali R. India: campaign to tackle unethical promotion. *WHO Essential Drugs Monitor*. 2002;31:22.

46. Drug Promotion Database [homepage on the Internet]. Geneva: World Health Organization Department of Essential Drugs & Medicines Policy; c2002. Why was the Database Developed? Available from: <http://www.drugpromo.info/about.asp> [Accessed May 27, 2006].

the IOM has put forward recommendations to result in stronger regulations. Fines, injunctions and withdrawals of drug approval need to be implemented forcefully. However, fines must be severe enough to discourage these practices and not simply a trivial amount for the industry.

Codes of Conduct and International Standards

In view of the potential for undue influence on prescribing behaviour, a number of professional bodies have developed codes of conduct. The *American Medical Association* states that “Any gifts accepted by physicians individually should primarily entail a benefit to patients and should not be of substantial value...*cash payments should not be accepted*”. However, all gifts, no matter their size, have expectations for reciprocal behavior. The acceptance of gifts risks undermining the professional objectivity of physicians. Changes in the standards of professional conduct are required. To be succinct, physicians simply should not accept gifts from pharmaceutical representatives.⁴⁷

The International Federation of Pharmaceutical Manufacturers (IFPMA) has its own Code of Pharmaceutical Marketing Practices. This Code requires its terms to apply to any company belonging to at least one member association. Unfortunately, self-regulatory codes of conduct may do no more than delay meaningful reform in the pharmaceutical industry, as imposed by external enforceable regulations. Current voluntary codes are not audited, enforced with meaningful penalties, or overseen by independent and objective observers.⁴⁸

In recent years, there have been advances made at the international policy level to place social responsibilities on business enterprises as a way to encourage ethical behavior. The United Nations Sub-commission on the Promotion and Protection of Human Rights in 2003 issued “Norms on the responsibilities of transnational corporations and other business enterprises with regard to human

47. Katz D, Caplan AL, Merz JF. All Gifts Large and Small: Towards an Understanding of the Ethics of Pharmaceutical Industry Gift-Giving. *American Journal of Bioethics*. 2003;3:39-46.

48. Canada's Research-based Pharmaceutical Companies [homepage on the Internet]. Code of Marketing Practices [updated 2005 Jan]. Available from: http://www.canadapharma.org/Industry_Publications/Code/code_e05Jan.html [Accessed Mar 15, 2005].

rights.”⁴⁹ Another United Nations initiative is the Global Compact of 2000, a voluntary international corporate network, which seeks to advance responsible corporate citizenship. The principles proposed were worthy but vague. The United Nations called to “embrace, support and enact a set of values” defining a new era of corporate responsibility, without giving a clear view of how this proposal should be implemented.⁵⁰ However, the Compact was updated in 2004 with Principle 10: “(t)he promotion and adoption of initiatives to counter all forms of corruption, including extortion and bribery.”⁵¹ While these international declarations have good intentions, they, like other guidelines lack the requisite “teeth” to ensure that corporations abide by the standards. In the context of increasing recognition of corporate misconduct, it is unlikely that voluntary self-regulation will do much more than distract governments for implementing the bold solutions that are needed.

Moving Forward: Mitigating the Risk for Scientific Misconduct in the Pharmaceutical Industry

Corporate ethics and scientifically responsible conduct can be left alone as a desirable and even wistful goal. More helpfully, it ought to be governed by a combination of meaningful self-regulation and government regulation, with sanctions that would matter. While international statements and professional guidelines on best practices of corporate behaviour and marketing practices have good intentions, the reality is that they have limited positive impact unless they are enforced with legislation and regulation with teeth. Governments need to do some critical evaluations of their regulatory policies and procedures and how effective they are in terms of managing the risk of scientific misconduct. If assessments suggest that institutions are weak, then reform needs to happen on an urgent basis to avoid unnecessary tragedies as a result of institutional

49. UN Subcommission on the Promotion and Protection of Human Rights, E/CN.4/Sub.2/2003/12/Rev.2. Minnesota: University of Minnesota Human Rights Library; c1995-2004 [updated 2005 Oct 30]. Available from: <http://www1.umn.edu/humanrts/links/norms-Aug2003.html> [Accessed Mar 28, 2005].

50. Paine E. The Road to the Global Compact: Corporate Power and the Battle Over Global Public Policy at the United Nations. Global Policy Forum, October 2000. Available from: <http://www.globalpolicy.org/reform/papers/2000/road.htm#1> [Accessed May 27, 2006].

51. The Global Compact [homepage on the Internet]. New York: United Nations; [updated 2005 May 17]. The Ten Principles. Available from: <http://www.unglobalcompact.org/AboutTheGC/TheTenPrinciples/index.html> [Accessed May 27, 2006].

failure. The problems of regulatory capture or political inference may require the establishment of an independent, arms-length institution to actively register and monitor the conduct of clinical trials. To be sure forceful regulations and other policies, while arguably necessary in this area, can often be messy to implement.

While this idea is in its earliest stage, we suggest that potentially, an international agency could be established that is set up to act as an over-arching monitor of individual country governance related to scientific conduct in the pharmaceutical area. Like other international bodies, countries would apply for membership. Funding ideally could be derived from regulatory fees which pharmaceutical companies pay to an individual country. For this institution to have meaning, it would need to ensure that countries would be sanctioned heavily if standards were not enforced sufficiently. It should ensure public notice of pending or past actions (likely through an institutional website) and assume an active role in communicating its actions to its member countries to demonstrate its value and ideally act as a deterrent by demonstrating that scientific misconduct is costly for governments that do not act against it and for companies that engage in it.

But the onus should not be lodged solely on the government or an international agency. The pharmaceutical industry that is so often the subject of public scorn and mistrust, partially as a result of its scientific misconduct practices, needs to examine its corporate culture and rethink how it does business. Corporate commitment to the concept of corporate social responsibility, which would severely limit scientific misconduct, should not be a meaningless tool to appease detractors but an integral part of company culture and practice. This is surely no easy task but change never is.

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Competing Interests

The authors declare no conflict of interest.

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