
Leopards in the Temple: Restoring Scientific Integrity to the Commercialized Research Scene

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Leopards break into the temple and drink to the dregs what is in the sacrificial pitchers; this is repeated over and over again; finally it can be calculated in advance, and it becomes part of the ceremony.—Franz Kafka

Recent Controversies in Medical Research

For more than two decades, significant controversies have been brewing over the efficacy and safety of Selective Serotonin Reuptake Inhibitors (or SSRIs) and other treatments for depression, and also over the expansion of their use for the treatment of a variety of other conditions. These controversies culminated, in June 2004, with a lawsuit intended by Eliot Spitzer, Attorney General of the State of New York. The lawsuit accused pharmaceutical giant GlaxoSmithKline of “repeated and persistent fraud by misrepresentation, concealing and otherwise failing to disclose to physicians information in its control concerning the safety and effectiveness of its antidepressant medication paroxetine” (better known as “Paxil”) in treating children and adolescents suffering from depression.¹ The statement of claims discusses how GlaxoSmithKline (GSK) manipulated the results of five different clinical trials of this SSRI drug, conducted throughout the 1990s. These studies failed to demonstrate the drug’s efficacy and indicated a possible increased risk of akathisia, suicidal ideation and suicidality in children and adolescents. Even so, GSK had embarked on a well-planned advertising campaign, using data from only one of these trials. They published carefully selected data in a peer-reviewed scientific journal, the *Journal of the American Academy of Child and Adolescent Psychiatry*, and distributed the article to sales representatives, with a memo emphasizing Paxil’s “REMARKABLE Efficacy and Safety in the treatment of adolescent depression.”² Their Medical Information Letters for physicians confirmed this message, and referred to the journal article. The company continued to distribute such letters, even after it had admitted to several regulatory agencies that there were concerns about safety and a lack of evidence of efficacy for the use of this drug in children and adolescents.

The selective release of data was part of the company’s marketing strategy, as is clear from a confidential internal memo drafted in 2002, by a research team within GSK. It explicitly states that “the efficacy data are insufficiently robust to support a regulatory submission” and that reporting such a statement to the regulatory authorities would be “commercially unacceptable” since it would undermine the overall status of the

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Healy was offered the position of the director of the Mood and Anxiety Program at the Centre for Addiction and Mental Health (CAMH), a leading psychiatric research institution affiliated with the University of Toronto. This offer was rescinded shortly after he gave a public lecture at CAMH reiterating his view that pharmaceutical companies had failed to fully investigate the link between SSRIs and an increased risk of suicide.

drug.³ Admitting that clinical trials involving children and adolescents had produced negative results could perhaps also have harmed the profile of the drug for the treatment of adults.

The New York lawsuit came in the wake of U.S. Food and Drug Administration (FDA) hearings on the safety and efficacy of SSRIs for children and adolescents suffering from depression. The hearings arose from public warnings of a potential link between increased risk for suicide and the use of SSRIs among children and adolescents. Unlike the British regulatory agency⁴ and Health Canada,⁵ the FDA had decided to set up a task force and to hold public hearings on this issue. How high the stakes were became apparent by the attempts to influence the process. Ten days before the hearings began, the American College of Neuropsychopharmacology (ACNP) launched an “executive summary” of a “preliminary report” of its “Task Force on SSRIs and Suicidal Behavior in Youth” which declared that SSRIs were effective and safe for use in children and adolescents.⁶ Nine out of ten members of this Task Force had consultancy and other financial relations with major pharmaceutical companies.⁷ Three had co-authored the journal article used to promote paroxetine (Paxil) though, alarmingly, they admitted not having seen the full data.⁸

The FDA’s Psychopharmacologic Drugs Advisory Committee and Pediatric Drugs Advisory Committee, which organized the hearings, ultimately recommended that SSRIs should contain a “black box” warning informing physicians and the public of the increased risk of suicidal thoughts and behavior; and the FDA followed this recommendation.⁹ However, the review process was beset with other controversies, for example when it became known that an FDA drug safety analyst had concluded one year earlier that some patients became suicidal as a result of taking SSRIs, and that in children and adolescents, the drugs’ risks outweighed the benefits. Moreover, when some pharmaceutical companies wanted to add warning labels on their drugs, the FDA had asked them to scale down these warnings because they might discourage physicians from prescribing the drug, thus leaving many children and adolescents untreated.¹⁰

Authorship concerns recur in another controversy surrounding SSRIs. In the *British Journal of Psychiatry*, David Healy and Dinah Cattell show how Pfizer’s SSRI drug sertraline (distributed under the name “Zoloft” in North America”) was promoted through the publication of ghost-written articles that appeared in the most influential medical journals, including the *Journal of the American Medical Association*, the *American Journal of Psychiatry* and the *Archives of General Psychiatry*.¹¹ The article by Healy and Cattell exposes the growing involvement of specialized medical communication agencies in the preparation, publication and distribution of the results of medical research. Marcia Angell adds that these communication companies are increasingly an integrated part of medical research conglomerates created by the world’s largest advertising agencies.¹²

David Healy has been a central figure in controversies concerned with the impact of commercial interests on academia. In addition to his academic critique on the continuing expansion of the SSRI use, Healy has appeared since 1999 in American lawsuits as an expert witness for claimants who argued that SSRIs had been responsible for their family member’s suicide and/or violent behaviour.¹³ Such activities have brought him on a collision course with the producers of SSRIs and with some members of the academic community. When the *Hastings Center Report* included an article by Healy in a special issue on Prozac¹⁴ Eli Lilly, producer of the drug, withdrew its funding. Around the same time, Healy was offered the position of the director of the Mood and Anxiety Program at the Centre for Addiction and Mental Health (CAMH), a leading psychiatric research institution affiliated with the University of Toronto. This offer was rescinded shortly after he gave a public lecture at CAMH reiterating his view that pharmaceutical companies had failed to fully investigate the link between SSRIs and an increased risk of suicide. The official explanation was that his lecture had “created an extraordinary stir among his future colleagues” who felt that his views were “scientifically irresponsible, incompatible with published scientific evidence and hence incompatible with the mantle of responsibility of leadership of a clinical and academic program.”¹⁵ The

news media immediately linked Healy's dismissal with the high percentage (about 40%) of pharmaceutical funding for the Mood and Anxiety Program, as well as close institutional research collaboration between the CAMH and Eli Lilly. Healy suggests that the interference was indirect,¹⁶ and connects Dr. Charles Nemeroff to his dismissal. Nemeroff is a leading American psychiatrist with close ties to the pharmaceutical industry, who had attended the same conference and had previously had an altercation with Healy about his public positions on SSRIs.¹⁷

Healy's lawsuit against CAMH and the University was settled out of court, and Healy became as part of the settlement a visiting professor at the University of Toronto. But the case has become a seminal example of how commercial interests can impact or appear to impact hiring decisions within academically-affiliated research institutes. It creates the perception that commercial interests can harm the careers of academics whose work threatens industry interests.¹⁸

The nature of the conditions for which SSRIs are prescribed, the characteristics of the drug itself, and the nature of the alleged side-effects may explain why so many controversies surround SSRIs. SSRIs were originally developed for the treatment of depression, which is alleged to touch millions of people worldwide and is the leading cause of disability in the world.¹⁹ But as David Healy pointed out in *The Anti-Depressant Era*, pharmaceutical sponsors have been able to mould the definitions of diseases for which SSRIs are claimed to work.²⁰ This was possible largely because SSRIs seemed to affect a variety of mental conditions and states connected to depression. While recognizing the potential human suffering behind depression and related conditions, Carl Elliott states that many of these disorders are surrounded by "a wide zone of ambiguity that can be chiseled out and expanded."²¹ As a result, the conceptual boundaries of depression "have been expanded relentlessly outward."²² SSRIs are now prescribed for anxiety, post-traumatic stress disorder, premenstrual dysphoric disorder, obsessive compulsive behaviour and other disorders, the expression of which is sometimes severe, but sometimes akin to more modest human ailments.

The scientific and political difficulties associated with investigating the side-effects also explain part of the controversies. Clinical case-reports of individuals developing suicidal thoughts, becoming agitated, or attempting or committing suicide while on anti-depressants have long been dismissed as inconclusive, because anti-depressants are prescribed to treat depression, which is already associated with a significant risk of suicide. Clinical trials need to be designed quite carefully to be able to detect *increased* risk of suicide in this population.

In the absence of solid data, several researchers and the regulatory agencies may be genuinely worried about the impact of "fear-mongering" on public health efforts to control depression. They fear that issuing warnings based on preliminary findings of the side effects of these drugs could increase the incidence of suicide due to patients' hesitation to seek treatment.²³ The serious nature of the alleged risk, i.e., death by suicide, makes it very cumbersome to weigh the risks and potential benefits of disclosure of this still speculative information.

The controversies over SSRIs are, however, not isolated cases. For instance, in the 1990s, the drug combination Fen-Phen was prescribed to millions of people until research associated it with an increased risk for pulmonary hypertension and heart valve disease.²⁴ In 1997, the drug's producer Wyeth-Ayerst agreed to pay \$3.75 billion to settle one class action lawsuit, among other on-going lawsuits.²⁵ The same company had also promoted estrogen therapy for decades, first as a remedy to rejuvenate post-menopausal women, and subsequently to reduce the risk of heart attacks, strokes and osteoporosis. It is only in 2002 that a large independent study provided strong evidence that estrogen caused small increases in breast cancer, heart attacks, strokes and blood clots.²⁶

In May 2004, the pharmaceutical giant Pfizer agreed to pay \$430 million to settle a lawsuit by a former employee turned whistle-blower, who was joined in the lawsuit by the U.S. federal government and 11 state governments. The lawsuit exposes various marketing practices by the company Warner-Lambert – later bought by Pfizer. Leading academic researchers were paid to deliver promotional lectures at educational events and to publish favourable reports on the off-label use of its epilepsy drug, Neurontin.²⁷

Most recently, Merck Frosst announced it was withdrawing its top selling arthritis drug Vioxx from the market after research showed increased risk of heart attack and stroke. Already in 1991, experts urged for appropriate clinical trial to assess cardiovascular risks and many epidemiological studies confirmed the existence of such risks.²⁸ According to *The Washington Post*, the FDA even ignored safety reports by one of its reviewers.²⁹ For the *Lancet*, "[t]he Vioxx story is one of blindly aggressive marketing by Merck mixed with repeated episodes of complacency by drug regulators."³⁰

The Controversies in Context: The Commercialization of Medical Research

The SSRI and other controversies can be situated in the context of the commercialization of medical research.³¹ The enactment of the Bayh-Dole Act of 1980³² is generally heralded as the primary cause of the increasingly commercial orientation of medical research in the

United States. The Act allowed American universities and researchers to obtain privately-owned patents on the results of federally-funded research. The goal of this legislation was to spur the development and commercialization of technology by providing universities and researchers with incentives to focus their research on marketable products. Before 1980, scientists, particularly basic scientists, often frowned upon privatization of research findings as heresy.³³ Science was

The pharmaceutical industry also started to boom in the 1980s. Various blockbuster drugs have flooded the markets since then. The U.S. dollar sales figures associated with certain drugs reveal what is at stake. Pfizer's cholesterol-lowering drug Lipitor had sales of \$9.2 billion in 2003;³⁶ one tenth of the estimated total market for that drug category.³⁷ The new market for the penile erection dysfunction drugs is estimated at \$6 billion by 2010.³⁸ Global sales of Glaxo-SmithKline's successful

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largely considered a public calling in which research findings should be shared and made publicly accessible. After 1980, however, researchers enthusiastically joined the patent race, and several funding agencies started encouraging commercial partnerships, sometimes imposing private matching funding and patentable outcomes as preconditions for funding. The number of patents obtained and the creation of start-up companies became measures of success for academically-funded programs. Although one of the ultimate goals of patenting is to promote the introduction of innovative technologies on the market and thereby to make innovations publicly accessible quickly, patenting affected the culture of sharing of data.

Governments of other industrialized countries have also promoted the commercialization of research. The Canadian Institutes of Health Research, for example, emphasize that they want to stimulate the fast application of research, and the contribution of this research to the "knowledge-based economy."³⁴ Other Canadian granting agencies more explicitly focus on promotion of high quality health research as a means toward development of a vibrant biotechnology commercial sector.³⁵

As a result of these developments, researchers and academic institutions are increasingly involved in the development of start-up companies with industry and often hold significant stock in companies that are bringing their research to the market. Researchers have become part-time entrepreneurs. Since they themselves are increasingly being asked to be involved in patentable research endeavours within academia, requiring delays in offering access to data, it may have become harder for them to see problems with pharmaceutical sponsors doing the same.

SSRI paroxetine (Paxil) amounted to \$4.97 billion last year.³⁹

With profits have come power, and the incentive to influence the market. The pharmaceutical industry has extended its tentacles particularly to those involved in the process of creating and regulating scientific knowledge and of transforming that knowledge into commercial products. It has attracted scientists to their ranks and created strong financial ties at all levels. Academic researchers now top up their salaries with fees or stock options that often surpass in value their academic income, for activities such as consultation, membership on advisory boards, and functioning as a member of pharmaceutical companies' speaker bureaus. Even scientists of the National Institutes of Health (NIH) have developed paid relations with industry, receiving thousands of dollars and stock options for consulting services.⁴⁰ Many members of very influential Food and Drug Administration (FDA) advisory panels and other governmental panels also have financial relations with industry.⁴¹

Industry tactics increasingly seem to involve more long-term strategies to influence change. Pharmaceutical companies financially support those who can influence indirectly drug consumption and/or create political pressure on the drug approval and government funding processes. Consumer and advocacy groups receive generous funding from pharmaceutical companies. While benevolence and good corporate citizenship is often the official explanation for such funding, teaming up with advocacy groups is clearly a business strategy.⁴² A market report sold through various public relations agencies states bluntly that working with patient advocacy groups should be a "prime target for sus-

tained competitive advantage for drug companies.⁴³ While such strategic alliances are primarily useful to increase sales and create new markets by promoting disease ‘awareness,’ they are also used to exercise pressure to permit new forms of research (e.g. involving stem cells), to speed up drug approval, or to prioritize research.⁴⁴

Another aspect of the corporate strategy is the blurring of the line between the research stage and post-approval marketing of drugs. Companies can strategically use special access programs and large phase 3 and phase 4 trials to boost doctors’ and patients’ awareness of a drug and to jump-start prescription patterns before or just after a drug hits the market.⁴⁵ Including more subjects in such trials than are strictly needed also “occupies the field” so that competitors who want to access the same patient population for drug testing will have difficulty finding sufficient subjects.

Sheldon Krinsky shows how commercialization has affected academic research, which is increasingly funded by industry.⁴⁶ Overall, corporate contributions to research and development in academic institutions in the United States have risen by 875% between 1980 and 2000. The increase in industry funding has been phenomenal in many leading academic institutions. Krinsky reports, for example, that Duke University’s industry funding, which rose by 280% in the 1990s, now constitutes 31% of its overall budget. In the same period, the University of Texas saw a 735% increase in its private funding, compared to a 491% increase at the University of California at San Francisco. And 20% of the budget of the prestigious Massachusetts Institute of Technology now comes from industry.⁴⁷

In addition, much more research is now taking place outside academia, particularly within Contract Research Organizations (hereinafter CROs). CROs conduct large numbers of clinical trials within specialized research centers, or coordinate such research undertaken in the community by primary care physicians. The Office of Inspector General in the United States reports that the number of physicians in private practice participating in research has risen by 300%.⁴⁸ More than 60 percent of all clinical trials funded by industry are now undertaken outside of academia, in contrast to only 20% in 1990.⁴⁹ As a result of the growing competition, the costs, and the problems of access to research subjects, clinical trials are also increasingly conducted in Africa, India, and Eastern Europe, raising concerns about exploitation and future availability of these drugs in developing countries, representativeness of research results, and a host of other issues.

Governmental policies, consequent shifts in institutional approaches to commercialization, and developments in industry has created a cozy space for interac-

tion between industry and other “stakeholders,” fulfilling a governmental desire to promote economic development through industry-academia collaboration. While it is hard to oppose the increased creation of health care products, it is clear that these developments come at a price. The increased emphasis that governments place on the commercial outcomes and the creation of patentable products orients health research in a very specific direction. Health research inevitably focuses more on technological interventions and the use of new drugs and devices, and less on public health measures which may be more cost-effective and offer more public benefit. There are, however, more direct and immediate concerns.

Traditional Research Ethics Concerns

The commercialization of medical research raises a number of typical research ethics concerns related to the recruitment of research subjects, exploitation of impoverished research subjects, and violations of informed consent. The growing use of financial recruitment incentives, targeting both research subjects and the health care workers who recruit them, has been discussed in the literature.⁵⁰ Commentators have also pointed out that financial interests may negatively impact researchers’ dealings with research subjects during a trial. When huge profits lure, and pressure mounts to bring novel drugs or therapies quickly to the market, potential risks may be perceived somewhat more lightly, and inclusion or exclusion criteria may become more flexible. This seems to have happened in the well-known case of Jesse Gelsinger. Jesse Gelsinger died in a gene transfer study for the treatment of OTC, a rare and potentially lethal liver disease.⁵¹ The researchers and their institute at the University of Pennsylvania had significant financial interests that may have influenced their appreciation of the risks involved, and their decision to include Gelsinger in the fatal study.

The paradigmatic nature of the Gelsinger case has been recognized by the research and medical community. In the wake of the Gelsinger case, various influential reports have emphasized that the growing financial interests in research may create risks to research participants. A special Committee of the Institute of Medicine states in a 2003 report that the failure to protect Jesse Gelsinger was “paradigmatic of failures in the system of protections itself.” Included among these failures are the insufficient control over “conflicts of interest of the investigators and the institutions” and the inadequacy of the review process.⁵² The report emphasizes further how “[a] process for scrutinizing potential financial conflicts of interest...is vital to the subsequent evaluation of participant risks and benefits.”⁵³ A Task Force of the Association of American Medical Colleges

states in its 2001 report on individual financial conflicts of interest that “opportunities to profit from research may affect – or appear to affect – a researcher’s judgments about which subjects to enroll, the clinical care provided to the subjects, even the proper use of subjects’ confidential health information.”⁵⁴ Similarly, a 2004 Guidance document issued by the Department of Health and Human Services recommends that those involved in research should “consider whether specific financial relationships create financial interests in research studies that may adversely affect the rights and welfare of subjects.”⁵⁵ Other reports have analyzed how research subjects may be affected by specific practices developed in the context of the commercialization of research.⁵⁶

Systemic Concerns: Threats to the Integrity of Medical Research

Commercialization of research raises also other fundamental concerns. “Financial interests threaten scientific integrity,” the Task Force of the Association of American Medical Colleges writes, “when they foster real or apparent biases in study design, data collection and analysis, adverse event reporting, or the presentation and publication of research findings.”⁵⁷

Several empirical studies demonstrates a statistically significant association between source of funding and research outcome. Industry-sponsored research is much more likely than non-commercially-sponsored research to lead to a conclusion that a new therapy is better than the standard therapy.⁵⁸ Although these studies do not establish a causal relationship between industry funding and an outcome that benefits the sponsors, they raise a red flag. For Sheldon Krinsky, “the appearance of a conflict of interest provides circumstantial evidence of an influencing motivation.”⁵⁹ But while the results of these studies can still be explained by the subtle, unconscious impact of investigators’ financial interests on the outcome of their research, several of the controversies mentioned earlier suggest the outright manipulation of science for marketing purposes. Medical research in these cases becomes a fundamental link in a sophisticated marketing scheme.

In the new research environment, control of the research design, the selection of subjects, the interpretation of results and the release of data have become easier. Research is organized by sponsors directly or within specialized Contract Research Organization, and involves a large number of community physicians and academic researchers in different locations. Physicians

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and academic researchers get involved in many of these industry-sponsored clinical trials as a side-activity, without strong intellectual investment. While academic researchers may seem to offer greater legitimacy to a study, they are not necessarily involved in the design of the study, often do not have access to the complete data and may do nothing more than collect and forward information about a small number of research subjects in exchange for authorship credit. Even if they want to challenge the research design, they may not be in a position to obtain fundamental changes to the protocol.

Commercial interests have also affected the integrity of the scientific literature, a crucial component of independent science. For years, advertising revenues by pharmaceutical sponsors have been a core source of funding for various medical organizations, such as the American Medical Association, impinging upon their independence.⁶⁰ Academic journals have also struggled with the question of how financial relations may influence the independence of the authors and manuscript reviewers. While disclosure of financial interests has now become standard in all but a few of the major academic journals, some journals have recently become more lenient, for example towards conflicts of interests of authors of editorials and review articles. The gold standard was always that those comparing various treatment options and making recommendations for clinical practice should have no financial relations with either the producers or competitors of the products discussed. Nevertheless, the *New England Journal of Medicine* recently announced that it would not always require this because, according to the editors, it has become increasingly hard to find medical researchers who have no financial links with producers or competitors.⁶¹

The potential bias of financially interested authors of review articles is clear from a widely publicized controversy around *Nature Neuroscience*. Until recently, that journal had stubbornly maintained that even disclosure of financial interests is not warranted, since science is transparent and independent. The journal published a review article discussing new experimental treatments without disclosing that the first of two authors held a patent for a recommended product and was

a member of the scientific advisory board of two other companies whose products were praised.⁶² Under the public pressure created after the *New York Times* publicized this story, the journal finally revised its disclosure policy.⁶³

Relying entirely on the integrity of all the researchers involved seems naïve when so much money is at stake. Warner-Lambert's promotional tactics for Neurontin, mentioned above, included payments of more than \$300,000 to a professor of the University of Minnesota for the publication of a book on the treatment of epilepsy, and a similar amount to a colleague of the University of Florida for promoting the drug on the lecture circuit.⁶⁴ The *Los Angeles Times* mentions even higher amounts that prominent scientists within the NIH have received for consulting with industry.⁶⁵ Marcia Angell invokes these and other reports to illustrate the significance of the financial conflicts of interest. Is it reasonable to trust the independence of researchers with such significant financial interests and let them play an important role in determining evidence-based medical practice?

The growing phenomenon of ghost writing is clearly the most extreme challenge to the integrity of the medical literature. Healy and Cattell's article, discussed above, is not the first to raise such concerns.⁶⁶ A 1998 article in the *Journal of the American Medical Association* discusses an analysis of 809 articles in three leading medical journals. It concludes that up to 11% of the articles used ghost authors, and 19% of them used honorary authors, even though both practices violated existing authorship guidelines.⁶⁷ Marcia Angell also details the unscrupulous search of Warner-Lambert for academic authors willing to sign their name to "scientific publications" promoting a drug's efficacy in exchange for money.⁶⁸

The concerns raised here traverse the traditional boundaries that have been drawn between research ethics, drug regulation, and the regulation of medical practice. It is widely accepted that an Institutional Review Board (IRB) must ensure that a trial has validity; that the sample is representative; and that results of a study are publicly accessible. But already overburdened IRBs rely on the existing framework in which medical evidence is established and in which the safety and efficacy of therapeutic products has been vetted by regulatory agencies. When they evaluate the validity of a comparative trial, for example, they will readily accept claims about the efficacy of an existing drug based on the peer-reviewed literature and on the fact that the drug has been approved. The recent controversies tell us that that this reliance is inappropriate.

Drug regulatory agencies also seem to rely on a well-functioning research ethics review system. Various

guidance documents on conflicts of interest⁶⁹ and research ethics guidelines⁷⁰ indicate that it is within the mandate of research ethics boards to review conflicts of interest. Health Canada's Therapeutic Products Directorate even explicitly relies on research ethics boards (REBs) as a crucial link within the regulatory process to prevent conflicts of interest from affecting research.⁷¹

In an era of evidence-based medicine, evidence gathered in clinical trials and published in the scientific literature forms the basis for the development of clinical practice guidelines. Furthermore, the FDA approval system determines the therapeutic claims pharmaceutical companies can make about particular drugs. If this approval system does not work adequately or if pharmaceutical companies are allowed to circumvent the rules, for example through the promotion of off-label use of drugs, clinical practice can no longer claim to be evidence-based. An editorial in the *Lancet*, accompanying a meta-analysis of SSRI studies in children, rightly describes the SSRI saga as a "disaster" for evidence-based medical practice.⁷²

The controversies discussed here suggest that while the integrity of research is a crucial requirement at any of these levels, the existing regulatory mechanisms that exist at each level are not sufficient. But what are the mechanisms that have failed us?

Countervailing Forces

The Market as a Corrective Force?

It seems clear that market mechanisms do not curb the negative impact of conflicts of interest in the context of medical research. There is a fundamental asymmetry when large pharmaceutical companies control the development of scientific knowledge about their products and then influence how these products are used by doctors and patients. Competing interests of other producers do not compensate in this market structure, because pharmaceutical companies often share core interests that remove incentives to challenge a competitor's research. For example, as mentioned above, commercial interests have led to an expansion of categories of disease for which drug treatments are available.⁷³ Pharmaceutical companies share a common interest in promoting such treatments even in cases where public health measures and preventive medicine may be more effective and safer. This is certainly a concern in the context of SSRIs, which are used to treat a wide range of conditions, where the line between disorder and variable mood is often porous. Market-driven research will not dispel any myths about the need for aggressive drug treatment for even the mildest expressions of these disorders.

Despite industry-sponsored commercials emphasizing a corporate commitment to improving health, a

pharmaceutical company's first commitment is to realize profits by promoting sales. The specific nature of pharmaceutical products makes the clash between the public interest and industry interests particularly problematic. Expanding markets for soaps and perfumes can occur without significant harm, but expanding consumption of drugs beyond those who really need them creates serious risks to health.⁷⁴ Philip J. Hilts, in his history of the FDA, agrees that "oversupply and over-promotion in medicine is a serious matter. It does not conform to the nature of the illness, or the practice of medicine, or the desire of the consumers, but purely to the needs of the industrial marketing department."⁷⁵

Independent Scrutiny

In light of the growing commercialization of academia, we cannot rely on the continuing commitment of dedicated researchers who remain oblivious to the lure of lucrative relations with industry. Ultimately, it will require a strong commitment, both by governmental agencies and by academic institutions, to reverse the trend and to ensure a vibrant critical research scene. Reports that many researchers within the NIH, including directors of specialized institutes, have supplemented their regular income with industry contracts are not encouraging.⁷⁶ We will need to strengthen the independence of research institutes and increase support for organizations such as the Cochrane Group, an independent not-for-profit organization dedicated to providing independent information on health care, to promote independent research.⁷⁷

One of the problems that those committed to independent scrutiny and meta-analysis will face is access to research data, as is clearly highlighted by the SSRI controversies. It is this widely expressed concern⁷⁸ that the editors of the major medical journals have tried to address recently. In the wake of Eliot Spitzer's lawsuit against GlaxoSmithKline, the International Committee of Medical Journal Editors issued a joint statement that its journals will require, "as a condition of consideration for publication," registration of clinical trials prior to patient enrollment.⁷⁹

Such a clinical trials database will surely help. Access to data is a precondition for a critical review. If all trials are registered, researchers can put pressure on sponsors and researchers to release data whenever a registered clinical trial is finished and its results have not been publicized. The registry requirement would have made it much harder for GlaxoSmithKline to publish selective results in the most influential peer-reviewed journals. The journal editors acknowledge, however, that a registry is "only part of the means to an end: that end is full transparency with respect to performing and reporting clinical trials."⁸⁰

The registry initiative does not bind all medical journals. Industry can still publish selective results using less rigorous journals or other promotional tools. Moreover, this registry does not necessarily promote appropriate comparative trials which could challenge studies controlled by pharmaceutical sponsors. Even if clinical trials are registered and later published in leading medical journals, will there be independent scrutiny of the methodology, data analysis and interpretations? The problems of potential bias in industry-sponsored studies and the declining number of truly independent researchers remain a major challenge that requires structural reform. A registry can only function appropriately if it is part of a well-functioning regulatory system.

Unfortunately, the regulatory system currently in place seems insufficient. Two areas of regulatory oversight are worth mentioning here. The first is the research review system, built around local review of research protocols, prior to commencing a study, by Research Ethics Committees (RECs). The second is the review structure of governmental drug regulators such as the U.S. Food and Drug Administration.

Review by Research Ethics Committees

The requirement that research involving human subjects be reviewed by a committee independent from the investigator and the sponsor is firmly entrenched in medical research all over the world. Research Ethics Committees (RECs) – called Research Ethics Boards (REBs) in Canada and Institutional Review Boards (IRBs) in the U.S.A. – are widely expected to deal with the inherent conflict of interest between the duties of physicians towards their patients and the duties of clinician-researchers towards the advancement of science. The imposition of review by RECs constitutes recognition of the danger that physician-investigators can be tempted to relinquish their duty to the patient by giving priority to their scientific endeavours. It provides an extra safeguard to ensure that in research involving humans, the interests and welfare of research participants remains the paramount concern.

But even in the U.S.A., where IRBs have been particularly integrated into the regulatory system, various reports and commentators have questioned the efficacy and appropriateness of the existing system in the changed research environment.⁸¹ It exceeds the scope of this paper to discuss all of the problems identified in these reports. But one problem in particular should be highlighted here: the conflict of interest embedded in the REC system itself.

In most countries, RECs are part of established academic institutions and its members are connected to the research interests within these institutions. Membership of RECs is dominated by medical professionals

The FDA and drug regulatory agencies in other countries were established to enable an independent assessment of the safety and efficacy of drugs before they are allowed onto the market. But the controversies raise questions about how well they function and reveal some of their limitations.

and/or people with research interests within the institution. Although community representation has gradually been added as a core requirement, it seems fair to argue that REC review in most countries currently remains a largely peer-dominated, internal review system, tightly integrated in the local culture.⁸² A recent survey of U.S. medical school faculty members serving on IRBs raises also concerns about financial conflicts of interests of IRB members. Of the more than 2900 IRB members who responded to the survey, 47% had done consultancy work for industry, which is a higher percentage than among medical faculty members who do not serve on IRBs.⁸³ It is fair to assume that these IRB members will less likely be concerned about the potential impact of such consultancy relations on research. One could argue that they are themselves in a situation of conflict of interest when evaluating the potential impact of financial relations in industry sponsored research.

As RECs have assumed a more significant administrative role, with a mandate to evaluate the potential impact of individual and institutional conflicts of interest, this model seems much less appropriate. Institutionally-based RECs are generally composed of people who, in their capacity as researchers or clinicians, report directly to institutional officials with vested interests in the conduct of research. As such, they may be reluctant to make decisions detrimental to the financial interests of superiors and of the institution, since this may bring them on a collision course with their superiors and ultimately even threaten their employment.⁸⁴

In addition, the commercialization of medical research has also led to a boom in the development of commercial RECs, which are fully integrated in the industrialized research scene.⁸⁵ Some Contract Research Organizations have set up their own internal RECs, and several private RECs have also found a niche in the commercialized research environment. The latter are for-profit organizations that have as their sole commercial activity the review of research protocols for a fee. These RECs play an increasingly important role, as more and more research has moved out of the academic setting and into the community. From a regulatory perspective, it is problematic that they are in a client-

provider relationship and that they have a direct financial interest in offering a service that satisfies their client. Refusal to approve a study may have significant financial consequences for the contract research organization or sponsor who contracts with the private REC; nothing in the system prohibits these sponsors from taking

their study to another REC for approval, undermining the RECs ability to make fully independent administrative decisions.

Many of these RECs, institutional and commercial, may be doing a decent job. But the question is whether these committees can be relied upon as independent administrative bodies entrusted with an important public policy task.

The Department of Health and Human Services⁸⁶ and the Association of American Medical Colleges⁸⁷ recommend that specialized Conflict of Interest Committees be set up within institutions. These would have an explicit mandate to review financial relations between individual researchers, the institution and the research sponsors and would serve as an important resource for the review by RECs. Delegation of conflict of interest review to such specialized committees would help to prevent RECs from becoming even more overburdened and could provide more effective control of financial interests. It is not clear, however, why they would not face similar problems as RECs with respect to the lack of independence. Unless Conflict of Interest Committees are established as independent administrative entities, it is not clear that they will offer much additional protection. It is also interesting to point out that RECs and Conflict of Interest Committees have been active in several institutions for some time, but their efforts did not prevent some of the most serious research controversies of recent years. As the father of the late Jesse Gelsinger points out, the University of Pennsylvania had a Conflict of Interest Committee and it had its research protocols reviewed by an appropriately-constituted IRB. Even so, major conflicts of interests were not dealt with.⁸⁸ Moreover, the problem of the integrity of research clearly extends beyond academic institutions. It would be unrealistic, for example, to establish Conflict of Interest Committees within Contract Research Organizations.

Other initiatives must be mentioned in this context. Over the years, various institutions have developed their own institutional policies and guidelines to deal with conflicts of interest.⁸⁹ A variety of issues can be covered by institutional policies. Several institutions have developed policies related to finder's fees, prohibiting pay-

ment for the mere referral of patients to research studies.⁹⁰ Many institutions impose a careful review of research contracts, in hope of ensuring that researchers have access to the full data of a study, and that they are not bound by confidentiality clauses that could prevent them from disclosing the research results. These institutional policies are important and useful. They raise the ethical standards in those institutions that implemented them.

However, they cannot be seen as sufficient to safeguard the integrity of the entire system of medical research. First of all, they only cover academic institutions. Secondly, the institutional policies vary, with many institutions retaining a very flexible approach. A 2002 survey of provisions in clinical trials-agreements between American medical schools and sponsors suggests that much work remains to be done within academic institutions. The authors state that “academic institutions routinely participate in clinical research that does not adhere to ICMJE standards of accountability, access to data, and control of publication” and that institutions “rarely ensure that their investigators have full participation in the design of the trials, unimpeded access to trial data, and the right to publish their findings.”⁹¹

Review by Drug Regulatory Agencies

The most significant power to counterbalance the power of pharmaceutical companies lies with the drug regulatory agencies. The FDA and drug regulatory agencies in other countries were established to enable an independent assessment of the safety and efficacy of drugs before they are allowed onto the market. But the controversies raise questions about how well they function and reveal some of their limitations.

Before commencing clinical trials, sponsors have to file an Investigational New Drug Application, with data from laboratory and animal studies to support the claim that research subjects will not be put at unreasonable risk. They have to keep the agency informed of any serious and unexpected adverse events associated with the experimental treatment and any other data that suggests risks to human subjects. After having tested the drug through three stages of clinical trials, they have to submit data supporting the efficacy and safety of the product to obtain approval for a specified use of the drug. The FDA also exercises control over marketing and post-approval safety of drugs and medical devices.

Concerns have been expressed that the FDA’s mandate to protect public health has gradually expanded to include protecting the interests of the pharmaceutical industry. Several developments suggest that the FDA has also become the promoter of “industry wealth.”⁹²

First, drug regulatory agencies have yielded to significant pressure by industry, and originally also patient advocacy groups, to decrease the administrative burden and speed up drug approval. While legitimate concerns about regulatory delays in access to potentially life-saving drugs were part of the motivation, industry interests seem to be the primary reason for continued pressure on regulatory agencies to keep shortening the review. In 2000, an investigative report analyzed the FDA’s withdrawal from the market of “seven deadly drugs,” associated with 1,002 deaths.⁹³ FDA reviewers interviewed for the article indicated that they were overwhelmed by the workload and felt pressured to approve drugs. The article raised concerns that faster review may lead to hasty approvals and mistakes. Marcia Angell points out that the FDA has also been slow in pulling drugs off the market when there were clear indications of harm.⁹⁴ Writing about the Vioxx controversy, Topol argues that the FDA’s inaction is partially responsible for “an enormous public health issue,” affecting millions of people.⁹⁵

While more drugs are developed than ever before, the budget of the regulatory agencies has not increased in ways that promote best public protection. Since the adoption of the Prescription Drug User Fee Act in 1992,⁹⁶ the FDA receives a significant part of its budget from user fees paid by drug companies.⁹⁷ The fees paid by industry are explicitly designated to speed up the review process of new drugs. Philip J. Hilts points out that industry has obtained significant leverage because of its contributions to the drug approval system.⁹⁸ This explains why monitoring of drug safety and control of marketing practices have not received the same attention. In an article in the *Washington Monthly*, Stephen Pomper captures it nicely: “[T]he FDA is in approval overdrive, while its safety side is stuck in low gear.”⁹⁹

Rebecca Eisenberg notes that arising out of its regulatory role, the FDA has gained an important function when it comes to the promotion of innovation.¹⁰⁰ The regulatory regime for drugs and medical devices has *de facto* become an important regulatory means to obtain market exclusivity for new products and to guarantee financial returns for investors.¹⁰¹ This is a result of various legislative changes that aimed at influencing specific areas of drug development. The Orphan Drug Act of 1983,¹⁰² for example, provides seven-year market exclusivity for drugs that are designated by the FDA to treat “orphan diseases.” The Drug Price Competition and Patent Term Restoration Act of 1984,¹⁰³ widely known as the “Hatch-Waxman Act,” aims at giving generic drug companies faster access to the market by lifting the requirement that generic drugs be submitted to the same clinical testing requirements as new innovative drugs. At the same time, it tries to balance the in-

terests of the generic drug industry with those of patent-holding companies. One of its most controversial provisions obliges the FDA to automatically halt the regulatory review and approval of a generic drug for a period of 30 months when a patent-holder claims that the generic drug company is infringing a patent listed with the FDA. This provision, which works even when

tremely flexible, and “riddled with legalistic exceptions and deference to investigator judgment on critical matters.”¹⁰⁷ At the end of the process, the FDA determines whether the evidence provided shows the drug’s efficacy and safety. On the basis of the clinical trials evidence, it determines how the drug ought to be labeled.¹⁰⁸ The agency relies, however, very much on the sponsors, the

The FDA is obliged to keep the reports about the safety and efficacy of these trials and any other communication about these trials confidential, since they are defined as trade secrets. When approving a product, the FDA releases a “Summary Basis of Approval,” which includes the reviews of pharmacological, toxicological data and the comments of the FDA reviewers but not all the detailed reports submitted to the agency.

a claim is clearly unfounded, allows patent-holders to delay generic competitors from entering the market, thus providing *de facto* a patent extension. Finally, in 1997, the FDA Modernization Act¹⁰⁴ contained provisions to promote pediatric clinical trials which also gave the FDA additional power to provide market exclusivity to pharmaceutical companies. Companies which agree to test their drug in pediatric clinical trials receive an additional 6 months of exclusivity for their product, during which time the FDA would not approve generic competitors.

These statutory provisions create direct connections between the FDA review process and the review by the Patent and Trademark Office, blurring the distinction between drug regulation and patent protection.¹⁰⁵ As a result, the FDA has grown into a crucial pillar of the regulatory promotion of innovation, a function that may cause tension with its mandate to protect the public. For example, the role of the FDA in the patent regime, with its inherent respect for the proprietary nature of information, may undermine its accountability to the public with respect to its evaluation of drug safety and efficacy.

There are also significant limits to how drug safety and efficacy are reviewed. Before a new drug can be tested, the FDA reviews the toxicity profile and other relevant information provided in the Investigational New Drug Application. Since 1998, applications have to include information on the financial interests of the researchers involved in the supporting studies,¹⁰⁶ although it is not clear how the agency uses this information. It approves the proposed trial methodology and is involved in subsequent approval of the various trial stages. Strict reporting obligations exist also during the trials. But as Michael Baram observes in the American context, the reporting obligations are ex-

researchers, and the IRBs to conduct and manage the trials.¹⁰⁹ It has little control over how research subjects are recruited, where they are recruited, where the research is taking place, who is involved in the conduct of the trials, and so on. This gives contract research organizations and pharmaceutical sponsors considerable leeway. For example, they may try to select a patient population that is more likely to respond to drug treatment; or choose one that is more “drug naïve.” Moreover, nothing prevents sponsors from repeating or modifying clinical trials after the first fail to show favourable results.

There are limits on public scrutiny of the FDA’s decisions. The FDA is obliged to keep the reports about the safety and efficacy of these trials and any other communication about these trials confidential, since they are defined as trade secrets.¹¹⁰ When approving a product, the FDA releases a “Summary Basis of Approval,” which includes the reviews of pharmacological, toxicological data and the comments of the FDA reviewers but not all the detailed reports submitted to the agency.¹¹¹

Drug regulatory agencies primarily analyze whether the drugs tested seem safe and have a positive effect. They do not evaluate *how effective* the drugs are and whether they are better than products that are already on the market. Marcia Angell points out that for drug approval purposes it generally suffices to submit a few positive trials showing that this is the case.¹¹² Considering the liberties that sponsors have in selecting the patient population and conducting the trial, this requirement is not too much of a hurdle. In the context of the SSRI trials, David Healy states that since the late 1980s, “it has not ... been uncommon for new drugs to be presented to the FDA which can only be shown to be superior to placebo in perhaps two out of six trials.”¹¹³ Once a drug is approved, publication of selected clini-

cal trial results and other marketing strategies do the rest.

The SSRI controversy is revealing in this respect. As discussed earlier, the FDA hearings and the recent revelations in the scientific literature show us that publications in the scientific literature give a different story about the efficacy and safety of those drugs for children and adolescents than the data collected and analyzed internally by pharmaceutical sponsors.¹¹⁴ The clinical trials evidence supporting claims of efficacy and safety of these anti-depressants in adults also seems quite weak.¹¹⁵ Contrary to popular belief about the efficacy of these drugs, the data suggested that these drugs may not be much better than a placebo. For all these years, the regulatory agencies sat on information about negative trial results that a reasonable consumer and the research community would have deemed relevant to public health. Yet, the agencies seemed to lack the mandate and the legislative basis to reveal information that was not used to support the approval.

The SSRI controversy also shows that the FDA does not currently focus its attention on post-marketing monitoring for long-term effects. The biggest hurdle for drug companies remains the approval stage. It seems remarkable, for example, as Healy reports, that after the 1991 hearings into the safety of SSRIs, FDA officials already discussed with Eli Lilly the need to undertake further research on the safety of Prozac and to develop a more sensitive clinical scale to measure potential increased suicidal ideation. According to Healy, the research was designed but never undertaken and the scale was developed but never used.¹¹⁶

Another significant concern that arises from the SSRI controversies is the potential lack of independence of the specialized standing advisory committees on which the FDA relies to review drug applications.¹¹⁷ These committees can also be called upon to review new data about safety of approved drugs, as was done in the context of the debate about the safety of SSRIs for children and adolescents. The members on these advisory boards are established medical researchers, many of whom have financial connections to the pharmaceutical industry. News media investigations reveal that in more than 90% of the FDA committee meetings, members with financial conflicts of interest participate in the discussions.¹¹⁸

The SSRI controversy also brings to light how in the current research environment, the regulatory requirement to conduct large clinical trials may be counter-productive if imposed blindly. The manufacturers of SSRIs have always rejected clinical case-reports linking their products to increased suicidal ideation by referring to the absence of statistical evidence. Critics argue that clinically significant results can be obtained

through small studies and clinical case-reports, and that the company-sponsored trials used to support the efficacy and safety of SSRIs were not designed to detect the occurrence of suicidal ideation. The regulatory requirement of data gathering through clinical trials offers large pharmaceutical companies much power over the gathering of information. Although these requirements are clearly intended to promote the establishment of safety and efficacy before allowing a potentially harmful product on the market, they may in the current context be manipulated for commercial purposes. Large pharmaceutical companies have the financial means to conduct wide-ranging trials, but may be selective in the type of questions they want answered. Once a drug is approved, there is considerable commercial pressure not to inquire further into potential side-effects, and this absence of statistical evidence is then used as a shield against criticism. Few independent organizations have the financial means to conduct these trials in lieu of the companies. And until an organization such as the NIH commits the time, personnel and finances to launch a large independent study, the drug can continue to be promoted on the market.

Conclusion: Controlling the Leopards

This discussion demonstrates how drug regulations, governmental patent policies, protection of human subjects, and the integrity of medical research are fundamentally intertwined. The corporatization of medical research stimulated through changes in the patent regime has clearly affected all levels of the production, review and use of medical knowledge. Medical research has become integrated into a highly lucrative, competitive market environment. The drug regulatory system has been adapted to accommodate innovation and drug development. Academic research has been significantly commercialized, and the proportion and influence of commercial research outside of academia have systematically increased. But the regulatory regimes aimed at protecting research subjects and the public have not been significantly adapted to this changing environment. Medical research continues to be regulated as if it were a charitable practice with a pure humanitarian mission.

A solution must be based on an understanding of the interactions between the various regulatory regimes and of their respective strengths and weaknesses. In all of these regulatory regimes, the integrity of scientific research is crucial. Drug and device regulatory agencies rely on the data gained through clinical trials to assess product safety and efficacy. Health care agencies, whether they are private or public, decide whether to fund therapies on the basis of the results of scientific re-

search. RECs have to evaluate risks and benefits to human subjects, relying on data provided by sponsors and on the scientific literature and otherwise publicly accessible data. As mentioned, their work is affected by conflict of interests.

But while all these regulatory regimes pay lip service to the concern that conflicts of interest may affect the conduct and outcome of research, none of them deal sufficiently with the underlying structural causes of the demise of scientific integrity. In fact, as mentioned earlier, each seems to rely on the appropriate functioning of the other regulatory regimes.¹¹⁹

Fundamental change in the regulatory review of clinical trials is needed to separate those who design, conduct and review the research from those who have financial interests in the outcome. Krinsky recommends the establishment of a new National Institute for Drug Testing (NIDT).¹²⁰ A company wishing to apply for approval of a new drug would negotiate an appropriate protocol with the NIDT. The NIDT would itself organize the clinical trial, using qualified drug assessment centers. In Canada, a report of Royal Commissioner Roy Romanow also supports the establishment of an independent National Drug Agency.¹²¹ Angell recommends that a similar institute be established within the National Institutes of Health.¹²² Such an institute or agency would be able to root out many of the most troubling practices highlighted earlier. Industry would no longer be able to hide negative trial data or selectively publish favourable results. Manipulation of research design and patient selection would also be rooted out. Ghost-authorship would no longer be a concern for physicians or for organizations involved in the development of clinical trials guidelines which rely on the medical literature.

The centralization of clinical trials would also make it possible to prioritize drug trials and to avoid the use of research as a marketing tool. Currently, which drug trial goes ahead is determined more by commercial ingenuity and the use of financial recruitment incentives than by promising science. Questionable practices related to competitive research subject enrolment would become much harder in a centralized system. The Romanow report further recommends in the Canadian context that the drug testing agency evaluate the efficiency of drugs in comparison with other drugs and therapies, to determine their role in evidence-based medical practice; and that it should also be involved in negotiating and monitoring drug prices. The implementation of these recommendations would constitute a major support for trustworthy evidence-based medicine and accessible health care.

An independent drug-testing agency or institute will unlikely be established overnight. But other less radi-

cal measures are quickly needed to tackle at least partially conflict of interest, which one commentator described as “the foremost medical research issue of our age.”¹²³ As mentioned earlier, there is an urgent need for a mandatory clinical trials registry, the strengthening of REC review and a further development of institutional policies within academia.

Existing professional regulations and traditional legal rules can also be used in the context of research. In 1995, Bernard Dickens already noted that rules of professional conduct and the law of fiduciary duties can be used to target inappropriate behaviour of individual health care professionals resulting from conflict of interests.¹²⁴ More recently, Paul E. Kalb and Kristin Graham Koehler have shown how regulatory and law enforcement agencies in the U.S. are increasingly using provisions in the False Claims Act and regulations dealing with kickbacks and referral fees to combat inappropriate research practices.¹²⁵ Professional organizations and law enforcement agencies could also use other regulatory and legal means to curb detrimental research practices.¹²⁶ The initiative by the Attorney General of New York shows what legal remedies may be available when pharmaceutical sponsors hide relevant risk information. An interesting more recent development is that the Securities and Exchange Commission is starting to scrutinize whether pharmaceutical companies have misled investors by hiding negative data of clinical trials.¹²⁷ When people are harmed by inappropriate drug promotion practices, the tort system remains a possible remedy.

However, focusing the blame on certain health care workers, researchers, companies, institutions and government agencies, and only after something goes wrong in research or after an approved drug causes harm is unlikely to heal the medical research enterprise as a whole. An overemphasis on remedies after harm has occurred ignores the rationale behind drug regulation and research ethics review. These regulatory regimes are both based on the premise that when it comes to the health and well-being of people who participate in research or who are in need of treatment, prevention of harm should be our goal.

Krinsky and the Association of American Medical Colleges appropriately call for a new “culture of conscience” and a revitalization of the values of academic science. A strong independent academic sector in medical research is indeed crucial. While most medical researchers and academics will appreciate this as an independent value, it may help to invoke a more utilitarian argument. In an interview with the *Atlantic Monthly*, Nobel Prize Winner Paul Berg claims that the ability to conduct research without concern for immediate commercial applications is what lies behind

many of the most innovative discoveries, including Berg's own theoretical academic research, which underlies much of the biotechnology revolution, so much heralded by industry.¹²⁸

The necessary change within academia cannot be achieved without some incentives. The development of tighter regulatory control and the threat of legal and regulatory sanctions as well as changes to the internal professional reward structures of academia and increased public funding should provide the necessary incentives.

Not unlike the leopards in Kafka's parable, the pharmaceutical industry has clearly become a fundamental part of the ceremony of science. But while Kafka's leopards are unaware of their role in the ceremony, industry has deliberately taken control. The recent controversies constitute a wake-up call for regulatory and funding agencies, academic institutions, the political community and the public. Industry can no longer be removed from the temple of which it has become a constitutive part. New rules will not evict them, but may still prevent them from interfering where it matters most: the inner sanctum of research, where research integrity is held sacrosanct, research data are shared and scrutinized, and uncontrolled self-interested behavior should be banned. While the leopards will still roam around in some parts of the temple, they should no longer be allowed to dominate our most important rituals.

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 51. J.A. Goldner, "Dealing with Conflicts of Interest in Biomedical Research: IRB Oversight as the Next Best Solution to the Abolition Approach," *Journal of Law, Medicine & Ethics* 28 (2000): 379-404. See also J. Silberner, "A Gene Therapy Death," *Hastings Center Report* 30, no. 2 (2000): 6.
 52. Committee on Assessing the System for Protecting Human Research Participants, Institute of Medicine, *Responsible Research: A Systems Approach to Protecting Research Participants* (Washington D.C.: National Academies Press, 2001), at 38.
 53. *Id.* at 10-11.
 54. Association of American Medical Colleges, Task Force on Financial Conflicts of Interest in Clinical Research, *Protecting Subjects, Preserving Trust, Promoting Progress: Policy and Guidelines for the Oversight of Individual Financial Conflict of Interest in Human Subjects Research* (2001): at 3, available at <<http://www.aamc.org/members/coitf/start.htm>>.
 55. Department of Health and Human Services, *Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection*, (2004) 69 Federal Register 26393 at 26394 [DHHS, *Guidance Document*]. See also E.J. Emanuel *et al.*, "Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals," *Annals of Internal Medicine* 141 (2004): 282-291.
 56. For the impact of commercial recruitment practices, see e.g. Department of Health and Human Services, Office of Inspector General, *Recruiting Human Subjects: Pressures in Industry-sponsored Research* (2000). For further references, see the articles *supra* note 50.
 57. Association of American Medical Colleges, *supra* note 54.
 58. See J. Lexchin *et al.* "Pharmaceutical Sponsorship and Research Outcome and Quality: Systemic Review," *British Medical Journal* 326 (2003): 1167-1177; and J.E. Bekelman, Y. Li and C.P. Gross, "Scope and Impact of Financial Conflicts of Interest in Biomedical Research," *JAMA* 289 (2003): 454-465 at 463.
 59. Krinsky, *supra* note 31, at 148-149.
 60. Hilts reports how concerns about advertising revenues led the

- American Medical Association to stop publishing lists of fraudulent and useless drugs in the early 1950s. The association was losing the revenue of drug advertisements in its publications. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (New York: Alfred Knopf, 2003): at 127.
61. See J.M. Drazen and G.D. Curfman, "Financial Associations of Authors," *New Engl. J. of Med.* 346 (2002): 1901-1902.
 62. C.B. Nemeroff and M.J. Owens, "Treatment of Mood Disorders," *Nature Neuroscience* 5, suppl. (2002): 1068. See the discussion of the controversy in S. Brownlee, "Doctors Without Borders," *Washington Monthly* 36, no. 4 (2004): 38-43.
 63. Editorial, *Nature Neuroscience* 6 (2003): 997.
 64. See Petersen, *supra* note 26.
 65. See Willman (2003), *supra* note 40.
 66. See D. Rennie and A. Flanagan, "Authorship! Authorship! Guests, Ghosts, Grafters, and the Two-Sided Coin," *JAMA* 274 (1994): 469-471; Bodenheimer, *supra* note 31; W.T. Carpenter, "From Clinical Trial to Prescription," *Archives of General Psychiatry* 59 (2002): 282-285.
 67. A. Flanagan *et al.* "Prevalence of Articles with Honorary Authors and Ghost Authors in Peer-Reviewed Medical Journals," *JAMA* 280 (1998): 222-224.
 68. *Supra* note 12 at 157-161.
 69. See *e.g.* *supra* note 55.
 70. See *e.g.* Medical Research Council of Canada (MRC), Natural Sciences and Engineering Research Council of Canada (NSERC), Social Sciences and Humanities Research Council of Canada (SSHRC), *Tri-Council Policy Statement* (Ottawa: Minister of Supply and Services, 1998), at Art. 4.1. In the section dealing with clinical trials, the *Policy Statement* also explicitly requires REBs to examine the budgets of clinical trials (see Art. 7.3).
 71. *Regulations Amending the Food and Drug Regulations* (1024 - Clinical Trials), P.C. 2001-1042, C. Gaz. 2001.II.1116, at 1131. See the discussion in Lemmens and Miller, *supra* note 50.
 72. Editorial, *supra* note 39.
 73. See Healy *supra* note 20.
 74. H. Dowling, cited in Hilts, *supra* note 60, at 125.
 75. *Id.* at 126.
 76. See text *supra* at note 41 and 65.
 77. The Cochrane Group keeps, for example, a detailed evidence-based database of various therapeutic products. Available at <<http://www.cochrane.org/index0.htm>>.
 78. See R. Drummond, "Fair Conduct and Fair Reporting of Clinical Trials," *JAMA* 282 (1999): 1766; and A.D. Sniderman, "The Need for Greater Involvement of Regulatory Agencies in Assessing Adverse Drug Reactions," *Canadian Medical Association Journal* 162 (2000): 209.
 79. C. De Angelis *et al.* "Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors," *New Engl. J. Med.* 351 (2004): 1250-51. The committee includes the editors of the *Journal of the American Medical Association*, the *New England Journal of Medicine*, the *Lancet* and the *Canadian Medical Association Journal*.
 80. *Id.*, at 1251.
 81. Office of Inspector General, Department of Health and Human Services, *Institutional Review Boards: A Time for Reform* (Boston, MA: Office of Inspector General, 1998); U.S. National Bioethics Advisory Commission, *Ethical and Policy Issues in Research Involving Human Participants* (Bethesda, MD: National Bioethics Advisory Commission, 2001); Committee on Assessing The System for Protecting Human Research Participants, Institute of Medicine, *Responsible Research: A Systems Approach to Protecting Research Participants* (Washington DC: National Academies Press, 2001). Similar criticism can be found in the Canadian context. See: Law Commission of Canada, *The Governance of Health Research Involving Human Subjects*, Michael M. McDonald, ed. (Ottawa: Law Reform Commission of Canada, 2000).
 82. See the discussion in D.R. Waring and T. Lemmens, "Integrating Values in Risk Analysis of Biomedical Research: The Case for Regulatory and Law Reform," *University of Toronto Law Journal* 54 (2004): 249-290 at pp. 277-282.
 83. E.G. Cambell *et al.*, "Characteristics of Medical School Faculty Members Serving on Institutional Review Boards: Results of a National Survey," *Academic Medicine* 78 (2003): 831-836, at 833-834.
 84. See L. Francis, "IRBs and Conflicts of Interest," in R.G. Spece, D.S. Shimm and A.E. Buchanan, eds, *Conflicts of Interest in Clinical Practice and Research* (New York: Oxford University Press, 1996): 418-436; M.K. Cho and P. Billings, "Conflict of Interest and Institutional Review Boards," *Journal of Investigative Medicine*, 45 (1997): 154-159; T. Lemmens and B. Freedman, "Ethics Review for Sale? Conflict of Interest and Commercial Research Review Boards," *Milbank Quarterly* 78 (2000): 547-584.
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 86. DHHS, *Guidance Document*, *supra* note 55, at 26396.
 87. Association of American Medical Colleges, *supra* note 54; and Association of American Medical Colleges, Task Force on Financial Conflicts of Interest in Clinical Research, *Protecting Subjects, Preserving Trust, Promoting Progress II - Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research* (2002), available at <<http://www.aamc.org/members/coitf/2002coireport.pdf>> (last visited October 24, 2004).
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 91. K.A. Schulman *et al.*, "A National Survey of Provisions in Clinical-Trial Agreements between Medical Schools and Sponsors," *New Engl. J. Med.* 347 (2002): 1335-1341, at 1339.
 92. A.R. McCabe, "Note: A Precarious Balancing Act - The Role of the FDA as Protector of Public Health and Industry Wealth," *Suffolk University Law Review* 36 (2003): 787-819.
 93. D. Willman, "How A New Policy Led to Seven Deadly Drugs," *Los Angeles Times*, December 20, 2000, at A-1, available at <<http://www.drugawareness.org/Archives/Miscellaneous/122002Howa new.html>>.
 94. See Angell, *supra* note 12, at 209.
 95. See Topol, *supra* note 28, at 1708.
 96. Pub. L. No. 102-571, Title I, 102-105 Stat. 4491 (codified at 21 U.S.C. 379g, 379h). The permission to use user fees was renewed in the *Food and Drug Administration Modernization Act of 1997*, 21 U.S.C. 301 (1997). For a discussion of this Act, see J. Kulynych, "Will FDA Relinquish the 'Gold Standard' for New Drug Approval? Redefining 'Substantial Evidence' in the FDA Modernization Act of 1997," *Food Drug Law Journal* 54 (1999): 127-149, at 127.
 97. See the discussion in Angell, *supra* note 12, at 210. See also Hilts, *supra* note 60, at 276-290; and McCabe, *supra* note 91, at 792-794.
 98. Hilts, *id.*, at 280. Marcia Angell states bluntly that the drug regulatory agencies have become "big pharma's handmaiden." *Supra* note 12, at 243.
 99. S. Pomper, "Drug Rush: Why the Prescription Drug Market is Unsafe at High Speeds," *Washington Monthly* 32, no. 5 (2000): 31-37, available at <<http://www.washingtonmonthly.com/features/2000/0005.pomper.html>>.
 100. R. Eisenberg, "The Robert L. Levine Distinguished Lecture Series: Patents, Product Exclusivity, and Information Dissemination: How Law Directs Biopharmaceutical Research and Development," *Fordham Law Review* 72 (2003): 477-491, at 489.
 101. *Id.*, at 477. For a discussion of the effect of these statutory provi-

- sions, see also Angell, *supra* note 12, at 173-192.
102. *Orphan Drug Act of 1983*, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended in sections of 15, 21, 26 U.S.C.). See the discussion in McCabe, *supra* note 91, at 795-796.
103. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 15, 21, 28, 35 U.S.C.).
104. Pub. L. 105-115, 111 Stat. 2296 (1977).
105. See Eisenberg, *supra* note 100.
106. 21 C.F.R. 54 (1998).
107. See the discussion by M. Baram, "Making Clinical Trials Safer for Human Subjects," *American Journal of Law & Medicine* 253 (2001): 271-283, at 262 and 274.
108. The label determines the official purpose for which a drug can be prescribed. It does not prevent physicians from prescribing the drug for other use – opening the door to various promotional tactics for off-label use. Promotion of off-label prescription was one of the controversial practices in the case of Neurontin (see *supra*).
109. Baram, *supra* note 107, at 262.
110. *Id.* at 253.
111. Health Canada only gives access to the much less informative official product monograph. See J. Lexchin, "Secrecy and the Health Protection Branch," *Canadian Medical Association Journal* 159 (1998): 481-483, at 482-483.
112. See Angell, *supra* note 12, at 112.
113. See Healy, *supra* note 13 at 85.
114. E.J. Garland, "Facing the Evidence: Antidepressant Treatment in Children and Adolescents," *Canadian Medical Association Journal* 170 (2004): 489-492; C.J. Whittington *et al.*, "Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data," *The Lancet* 363 (2004): 1341-1345.
115. See Healy, *supra* note 13, at 83-90; and Angell, *supra* note 12, at 112-113.
116. See Healy, *id.*, at 116-119.
117. See Angell, *supra* note 12, at 210.
118. See *id.* and reference there. As mentioned, this is not unique to the drug regulatory agency. E. Marris, "Ethics Review Slams Government Panels Over Conflicts of Interest," *Nature* 431 (2004): at 3.
119. Lars Noah, for example, seems to have confidence in the current REC review system because of the existence of complementary regulatory regimes. See "Deputizing Institutional Review Boards to Police (Audit?) Biomedical Research," *Journal of Legal Medicine* 25 (2004): 267-293, in particular at 273-275.
120. See Krinsky, *supra* note 31, at 229.
121. Commission on the Future of Health Care in Canada, *Building on Values: The Future of Health Care in Canada, Final Report* (2002), in particular at 199-210, available at <http://www.hc-sc.gc.ca/english/pdf/romanow/pdfs/HCC_Final_Report.pdf
122. See Angell, *supra* note 12, at 244-247.
123. S. Neilson, "Healy and Goliath: The Creation of Psychopharmacology," *Canadian Medical Association Journal* 170 (2004): 501-502.
124. B. Dickens, "Conflicts of Interest in Canadian Health Care Law," *American Journal of Law & Medicine* 21, no. 2-3 (1995): 259-280, in particular at 273-274.
125. P.E. Kalb and K.G. Koehler, "Legal Issues in Scientific Research," *JAMA* 287 (2002): 85-91.
126. See Lemmens & Miller, *supra* note 50.
127. Jeffrey Krasner, "SEC focusing on drug makers: Full disclosure of tests called key," *Boston Globe*, September 27, 2004, at C-4.
128. E. Press and J. Washburn, "The Kept University," *Atlantic Monthly* (March 2000): 39-54, at 54.