

WHEN EVIDENCE ISN'T: TRIALS, DRUG COMPANIES AND THE FDA

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THE EDITOR'S PRIVILEGED VANTAGE POINT

This article is written from my viewpoint as a professor of medicine at a large biomedical research institution, the University of California San Francisco (UCSF). This point of view is colored by my experience as a patient and a doctor, as well as by a lifetime climbing in the highest mountain regions in the world. But what has allowed me a uniquely useful perspective is that for the past 30 years I have been deputy editor either of the New England Journal of Medicine (NEJM), or of the Journal of the American Medical Association (JAMA).¹

A physician-researcher is not appointed deputy editor at the two most prominent and largest general medical journals, both of which are owned by medical societies, by being a wild radical. In various ways I and my fellow medical editors are seen as representing the establishment. So consider this. Indirectly, the issue of money's influence on researchers and physicians has over the past two decades eased the departure of several of the editors in chief of our major medical journals. My colleagues, Jerome Kassirer and Marcia Angell, both of the NEJM, and Richard Smith, editor of the British Medical

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¹ I emphasize that I in no way express JAMA policy, nor that of its owners, the AMA.

Journal, have all, the moment that they left their posts, written books bemoaning the appalling influence of pharmaceutical company money on the morals and practices of their profession.²

The editor's daily task is to examine large amounts of clinical research from research institutions. What has made my position so privileged and such an excellent vantage point is that these two general medical journals are magnets attracting the manuscripts of the best researcher-authors. Publication in one or the other can have an extraordinary effect on a researcher's career. The research doesn't exist until published, so a scientific manuscript is far more than simply letting one's colleagues know new facts. Winning the fight to get published has huge social consequence: publication in a large general medical journal, rather than a small specialty journal, is a much larger coin—a huge silver dollar—in helping a clinical researcher along the toll road to academic promotion. It represents everything to an investigator—fame and fortune.³ So there is hot competition, reflected in our 5-7 percent acceptance rate, and this translates into that mysterious and precious commodity “prestige.”

The fact that these two journals are the largest general medical journals in the world means that specialists are eager to try to publish their best work there, and only if they have been rejected at the general journals, will they then turn to a specialist journal. Journalists are well aware of the careful sieving that the NEJM and JAMA perform, so every week the major newspapers and media carry stories from both journals—something our authors are keenly aware of.

We editors try to determine the validity of clinical science, selecting and then improving the best 5 percent or so of the steady stream of 7,000 manuscripts coming in to JAMA yearly,

² See MARCIA ANGELL, *THE TRUTH ABOUT DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT*, (2004); JEROME KASSIRER, *ON THE TAKE: HOW MEDICINE'S COMPLICITY WITH BIG BUSINESS CAN ENDANGER YOUR HEALTH* (2005); Richard Smith, *The Trouble With Medical Journals*, ROYAL SOCIETY OF MEDICINE PRESS (2006).

³ See D. Rennie, V. Yank & L. Emanuel, *When Authorship Fails: A Proposal to Make Contributors Accountable*, 278 JAMA 579, 579-85 (1997).

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each describing clinical research, or reviewing what is known about a relevant clinical subject—a disease, a drug, an operation and so on. Publication marks the first time the work is formally and completely out of the research institution, to be scrutinized, and attempts made to test and replicate it. However, after publication challenges to an article's validity and sometimes honesty are directed at the editors. So editors sit at the hub of science, and those seats can become extremely hot.

Science is not set up like a bank checking system, on the assumption that fraud will be attempted. We cannot have cops, each presumably with a PhD, in every lab. A quicker way of inhibiting free thought and experimentation could not be devised. So we are forced to rely on trust. The editor, also a scientist, is part of this web of trust.

Indeed, when there's an allegation of, say, misconduct on the part of one of our authors at a research university, we editors are singularly helpless. We don't have the time, resources, forensic expertise, mandate or authority to investigate, adjudicate and punish. All we can do is refer the complaint back to the author's institution for formal investigation—and trust that the institution will follow through. Thus, the whole system is built on trust.

Trust depends on there being someone accountable. This is why Joshua Lederberg, the Nobel Laureate who was president of Rockefeller University, wrote, "Above all, the act of publication is an inscription under oath, a testimony."⁴ That is how I was taught science should operate and assumed it did until, in 1977, I became deputy editor of the NEJM. I soon learned from repeated, bitter personal experience that, when scientists had a great deal at stake, some were prepared, in the name of prestige, to take short cuts, falsify, fabricate, plagiarize, bamboozle, lie, cheat, and throw away their reputations simply to notch up more publications, advance their careers and, of course, make more money.

⁴ J. Lederberg, 7 *THE SCIENTIST* 10, 10-14 (1993).

I. RESEARCH MISCONDUCT

By chance, I became a medical editor just at the time when instances of scientific “fraud” were hitting the newspapers, and engaging academics in furious debate. Several flamboyant cases of fabricating scientists, some from important research institutions such as Harvard and Yale, publishing fabricated work in my journal and in others, occurred during the decade between 1979 and 1989. The scientific establishment professed shock and denial in equal amounts. To an editor like myself, it was clear that the problem was real and on-going.⁵

Eventually, scientists were forced to face reality by politicians, starting with then-Congressman Al Gore, and considerably assisted by the benign influence of wise individuals from the American Bar Association, whose everyday job was to confront and deal with fraud of every sort, and who were far less prone than my colleagues to believe that scientific degrees bestowed such attributes as honesty. In 1989 federal regulations were put in place that defined scientific misconduct, and set out a framework and process whereby allegations were to be handled and adjudicated by all research institutions. While these regulations were modified as cases occurred during the decade of the 1990s, handling of such cases became routine and the frenetic atmosphere surrounding such betrayals of their profession by scientists, and especially physician-scientists, calmed down.

Thus, when Eric Poehlman was recently sentenced to a year in prison because he included the results of his numerous falsified and fabricated reports in grant applications for NIH money, scant notice was paid by the media.⁶ This did not mean not that the problem of gross fraud had gone away, but that we, the profession and the public had learned that a certain small

⁵ See D. Rennie & C.K. Gunsalus, *Scientific Misconduct: New Definition, Procedures, and Office—Perhaps a New Leaf*, 269 JAMA 915, 915-91 (1993).

⁶ H.C. Sox & D. Rennie, *Research Misconduct, Retraction and Cleansing the Medical Literature: Lessons from the Poehlman Case*, 144 ANN. INTERN. MED. 609, 609-13 (2006).

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proportion of scientist/physicians will turn out to be crooks. . . No great surprise to lawyers, but apparently a revelation to scientists.

II. BIASED REPORTING OF RESULTS: DELIBERATE OR UNCONSCIOUS

After a year or so as an editor, it became obvious to me that such rare cases, the chainsaw massacres of science, were not the main problem. My eyes were first opened in 1978 at the NEJM when we published an article describing a break-through in developing a blood test to detect chronic paranoid schizophrenia.⁷ We were astonished, embarrassed and then angry to be told that on the day we had published our article another had appeared in the American Journal of Psychiatry. In the American Journal of Psychiatry's article the authors showed the complete absence of this marker in chronic paranoid schizophrenics.⁸ What upset us was that two of the authors appeared on the byline of both articles. When challenged, they disingenuously claimed that it was not their custom to refer to unpublished work in a publication, showing that to them authorship of a scientific article had meaning only in so far as it brought credit in the form of another publication. The other side of credit, responsibility, simply did not exist.

Authors would sign our forms testifying that they there was no substantive overlap between the manuscript they had sent us and any other paper they had in the works, yet happily publish almost identical articles in other journals. They would attest to a complete absence of financial conflicts of interest, but at the same time fail to tell us, for example, of relevant patents that they held, or that they had appeared as paid expert witnesses on the subject on dozens of occasions. Numerous other incidents of

⁷ See S.G. Potkin, H.E. Cannon, D.L. Murphy & R.J. Wyatt, *Are Paranoid Schizophrenics Biologically Different from other Schizophrenics?*, 298 N. ENGL. J. MED 61, 61-66 (1978) .

⁸ P.A. Berger, R.A. Ginsburg, J.D. Barchas, D.L. Murphy & R.J. Wyatt, *Platelet Monoamine Oxidase in Chronic Schizophrenic Patients*, 135 AM. J. PSYCHIATRY 95, 95-99 (1978).

failure to accept accountability in the race for promotion, which, had I not been an editor, I would never have known about, made me increasingly skeptical.

III. MONEY

For clinical science, and so for us editors, everything changed with the passage of the Bayh-Dole Act in 1980.⁹ This Act allowed universities, for example, to retain intellectual property control of their inventions made while conducting federally funded research. The Act smoothed the process whereby researchers working on government contracts or grants could, with their institutions, share in the action, and profit from their discoveries. This had the desired effect: a massive influx of venture capital into universities, and a stimulus to researchers, a few of whom became rich, and it probably shortened the gap between bench and bed-side for some new drugs.

However, a predictable consequence of this huge influx of money was to compete for the interest of the researchers. Researchers became more secretive, less willing to share, and the sponsorship of clinical studies became a crucial issue.¹⁰ During the late 1970s and early 1980s, I never once was involved in an editorial discussion about funding and conflicts of interest. In contrast, nowadays it would be very rare at the twice weekly JAMA manuscript selection meetings for the subject not

⁹ Bayh-Dole University and Small Business Patent Act (codified as 35 U.S.C. §§ 200-212; implemented by 37 C.F.R. 401(1980)).

¹⁰ See J.E. Bekelman, Y. Li & C.P. Gross, *Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review*, 289 JAMA 454, 454-65 (2003); J. Lexchin, L.A. Bero, B. Djulbegovic, & O. Clark, *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, 326 BMJ 1167, 1167-70 (2003); B. Als-Nielsen, W. Chen, C. Gluud & L.L. Kjaergard, *Association of Funding and Conclusions in Randomized Drug Trials: A Reflection of Treatment Effect or Adverse Events*, 290 JAMA 921, 921-28 (2003); L.A. Bero, A. Galbraith & D. Rennie, *The Publication of Sponsored Symposia in Medical Journals*, 327 N. ENGL. J. MED. 1135, 1135-40 (1992); N.K. Choudhry, H.T. Stelfox & A.S. Detksy, *Relationships Between Authors of Clinical Practice Guidelines and the Pharmaceutical Industry*, 287 JAMA 612, 612-17 (2002).

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to come up, our skepticism often taking this sort of form: “It seems like a good paper. Can we believe a word of it?” Are the authors so influenced by the money they receive from their commercial sponsors that they either deliberately distort the evidence, or are unconsciously biased to do so?

IV. THE EVIDENCE THAT THE EVIDENCE WAS BAD

We editors are clinical investigators, and we are used to weighing scientific evidence. So what is the evidence that indicates that scientific evidence is suspect?

In the 1980s, faced by the challenge of trying to make sense of, and boil down, the massive and rapidly increasing literature on the effect of “interventions”—of drugs, surgery and other therapies—the science of meta-analysis was developed. Meta-analysis is a rigorous technique whereby all the literature concerning a particular drug could, using new methods of searching, be identified, and studied for relevance and quality. Then, after considerable winnowing, the efficacy of the drug in all comparable high quality trials, could be worked out. Meta-analysis began to be applied on a large scale, and as, for the first time, rational and systematic ways to sort the wheat from the chaff, so for the first time all sorts of problems with the literature began to emerge.

First, it was found that companies were paying physician scientists to publish the same results of the same trials in different journals, under different authors’ names, with no cross-referencing. Since they were also paying scientists to publish only the positive results, and bury the negative ones, this systematic obfuscation had the effect of creating artificial scientific support for a drug, both before regulatory agencies, and, of course, to impress the prescribing physician.¹¹

¹¹ See, e.g., P.C. Gøtzsche, *Multiple Publication of Reports of Drug Trials*, 36 EUR. J. CLIN. PHARMACOL. 429, 429-32 (1989). See also P. Huston & D. Moher, *Redundancy, Disaggregation, and the Integrity of Medical Research*, 347 LANCET 1024, 1024-26 (1996); M.R. Tramer, D.J.M. Reynolds, R.A. Moore & H.J. McQuay, *Impact of Covert Duplicate Publication on Meta-Analysis: A Case Study*, 315 BMJ 635, 635-40 (1997).

It was then found that some physician had so far forgotten their professional ethics that, again at the behest of their sponsors, they were getting the results their sponsors wanted in drug trials by hobbling the other horse in the race, the competitor's drug, which in the trials was administered in the wrong dose by the wrong route.¹²

Meanwhile, it became apparent that many trials, though ostensibly coming from impartial and prestigious research universities, were actually set up, designed, conducted, and the data analyzed by the companies themselves, or their dependent subcontractors who wrote the reports of the trials.¹³ These were the manuscripts that we editors received in good faith, only to discover, sometimes years later, that the "authors" had been anointed as such when everything but the final draft of the manuscript had been completed by the company, their sole function being to lend their scientific and institutional prestige to the trials, and make them credible to the profession.¹⁴

Ethical investigators, outraged by what was happening, began sending me letters that they had received from firms acting for drug manufacturers offering them tens of thousands of dollars simply to add their own names to reviews of a drug's efficacy—reviews they had never seen before and which were always favorable to the new drug¹⁵. Meanwhile sponsoring companies threatened the researchers to prevent them from

¹² H.K. Johansen & P.C. Gøtzsche, *Problems in the Design and Reporting of Trials of Antifungal Agents Encountered During Meta-Analysis*, 282 JAMA 1752, 1752-59 (1999); D. Rennie, *Fair Conduct and Fair Reporting of Clinical Trials*, 282 JAMA 1766, 1766-68 (1999).

¹³ See R. Winslow, *Drug Company's PR Firm Made Offer to Pay for Editorial, Professor Says*, WALL ST. J., Sept. 8, 1994, at B-12; D. Rennie & A. Flanagin, *Authorship! Authorship! Guests, Ghosts, Grafters, and the Two-Sided Coin*, 271 JAMA 469, 469-71 (1994); T. Hornbein, L. Bero & D. Rennie, *The Publication of Commercially Supported Supplements Statement*, 81 ANESTH. ANALG. 887, 887-88 (1995).

¹⁴ See L.A. Bero & D. Rennie, *Influences on the Quality of Published Drug Studies*, 12 INT. J. TECHNOL. ASSESS. HEALTH CARE 209, 209-37 (1996).

¹⁵ T. Brennan, *Buying Editorials*, 331 N. ENGL. J. MED. 673, 675 (1994).

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publishing unfavorable results.¹⁶

Soon scientists began to investigate the phenomenon. In every one of the many scores of such studies of published trials, an overwhelming bias was found in favor of the sponsors' drugs, a bias that was not present when the trials were performed by investigators free of commercial funding.

When my colleagues and I recently studied reviews drugs used in a widespread, serious and treatable condition, hypertension, we found that, on the basis of the same data, the reviews sponsored by manufacturers placed a far more positive spin on the data than did independent reviews.¹⁷ Recently, the situation reached its worst when some scientists published a paper that showed that in numerous head-to-head comparisons, drug A was better than drug B; drug B better than drug C; and drug C better than drug A.¹⁸ The only factor that explained this was the funding of the various trials.

V. THE \$2,000 ASPIRIN

Just how widespread this distortion of the evidence has become was illustrated starkly in the case of two classes of drug, the new pain-relievers, the COX-2 inhibitors, and the psychoactive drugs used in depression, the SSRIs.

The COX-2s inhibit an enzyme associated with inflammation, and there was reason to think that they would be

¹⁶ D. Rennie, *Thyroid Storm*, 277 JAMA 1238, 1243 (1997); J.O. Kahn, D.W. Gherng, K. Mayer, H. Murray & S. Lagakos, *Evaluation of HIV-1 Immunogen, An Immunologic Modifier, Administered to Patients Infected with HIV Having 300 to 549 106/L CD4 Cell Counts*, 284 JAMA 2193, 2193-02 (2000); D.G. Nathan & D.J. Weatherall, *Academic Freedom in Clinical Research*, 347 N. ENGL. J. MED. 1368, 1638-71 (2002).

¹⁷ V.A. Yank, D. Rennie & L.A. Bero, *Financial Ties and Concordance Between Results and Conclusions in Meta-Analyses* (forthcoming 2007 in BMJ).

¹⁸ S. Heres, J. Davis, K. Maino, E. Jetzinger, W. Kissling & S. Leucht, *Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics*, 163 AM. J. PSYCHIATRY 185, 185-94 (2006).

better than aspirin and all the others pain-relievers, and, being extremely expensive, would make billions for the manufacturers. A key claim made by the manufacturers to persuade physicians to prescribe these expensive new drugs was that these COX-2s caused less inflammation and bleeding in the stomach than the standard drugs. At the same time, since the enzyme that was inhibited tended to decrease clotting mechanisms in blood vessels, the makers needed to show that the COX-2s did not increase the risk of blood clots and heart attacks.

The big trials, done at the behest of the manufacturers, that showed these crucial findings were all published in prominent medical journals: one in JAMA¹⁹ two in the NEJM²⁰ and one in the Annals of Internal Medicine.²¹ Over the next few years, and partly because of lawsuits, it became clear that in every case the authors either could not take full responsibility for their trials, or there were distortions of the evidence that seriously weakened

¹⁹ F.E. Silverstein et al., *Gastrointestinal Toxicity with Celecoxib vs Nonsteroidal Anti-Inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis: The CLASS Study: A Randomized Controlled Trial*, 284 JAMA 1247, 1247-55 (2000). See also J.B. Hrachovec, *Reporting of 6-month vs 12-month Data in a Clinical Trial of Celecoxib*, 286 JAMA 2398 (2001); J.M. Wright, T.L. Perry, K.L. Bassett & G.K. Chambers, *Reporting of 6-month vs 12-month Data in a Clinical Trial of Celecoxib*, 286 JAMA 2398 (2001).

²⁰ C. Bombardier et al., *VIGOR Study Group: Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343(21) N. ENGL. J. MED. 1520, 1528 (Nov. 23, 2000). See also R.S. Bresalier et al., *Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators: Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial*, 352 N. ENGL. J. MED. 1092, 1102 (2005), Epub Feb. 15, 2005, Erratum in 355(2) N. ENGL. J. MED. 221 (Jul. 13, 2006); S.W. Lagakos, *Time-to-Event Analyses for Long-Term Treatments: the APPROVe Trial*, 355 N. ENGL. J. MED. 113, 117 (2006); Merck and Co Inc., News Release, *Merck Corrects Description of a Statistical Method Used in APPROVe Study* May 30, 2006, available at http://www.merck.com/newsroom/press_releases/corporate/2006_0530.html (last visited Aug. 6, 2006).

²¹ J.R. Lisse et al., ADVANTAGE Study Group, *Gastrointestinal Tolerability and Effectiveness of Rofecoxib Versus Naproxen in the Treatment of Osteoarthritis: A Randomized, Controlled Trial*, 139(7) Ann. Intern. Med. 539, 529-46 (Oct. 7, 2003).

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the conclusions of the trials that such drugs did not cause cardiovascular disease.²² The stock of Merck, the makers of Vioxx, lost \$29 billion in one night when they withdrew it from the market because of its effects on the heart.²³ I believe that, had the results been presented in a forthright manner from the start, Vioxx might still be on the market.

VI. PUBLICATION BIAS AND TRIAL REGISTRATION

When the selective serotonin re-uptake inhibitors (SSRIs) were introduced, they were thought to herald a new dawn in the treatment of disorders of mood, including depression. The parents of children who had been prescribed these drugs, arguing that the SSRIs had precipitated the suicides, sued the makers, and the discovery process revealed the existence of unpublished trials, with far less favorable results from those that had appeared in the medical journals, as well as instances of suicide in children given SSRIs. It is well-known that at the time when a child's depression is so bad that he or she has to be taken to see a physician, suicide is a real possibility, so there is legitimate scientific debate on the issue of whether these drugs increase that likelihood.

The tendency of "positive" trials to be written up, sent to journals and published before "negative" trials, is called "publication bias"—bias, because only one side is ever known to physicians and their patients. It has emerged as a massive distortion of the clinical evidence because the makers are the biggest sponsors of trials and they rarely publish the negative

²² P. Jüni, A.W.S. Rutjes & P.A. Dieppe, *Are Selective COX 2 Inhibitors Superior to Traditional Non Steroidal Anti-Inflammatory Drugs?*, 324 *BMJ* 1287, 1288 (2002); D.J. Graham, *Cox-2 Inhibitors, Other NSAIDs, and Cardiovascular Risk: The Seduction of Common Sense*, 296 *JAMA* 1653, 1656 (2006).

²³ Merck and Co Inc., News Release, *Merck Announces Voluntary Worldwide Withdrawal of Vioxx*, Sept. 30, 2006, available at http://www.merck.com/newsroom/vioxx/pdf/vioxx_press_release_final.pdf (last visited Aug. 4, 2006).

results.²⁴ A good preventive strategy is to register all trials at inception, so that anyone reviewing the evidence can know about unpublished trials, and get the results, or, if they are withheld, draw their own conclusions.²⁵ Representatives of the industry refused to agree to this in 2000, claiming that the very existence of trials was a trade secret, a position which I, as a physician, a researcher, and, above all, as a patient and an experimental subject in clinical trials, regard as entirely unethical.²⁶

However, on June 2, 2004 Eliot Spitzer, then the attorney general for the State of New York, recognizing that no one knew whether or not SSRIs increased the risk of suicide, but aware that failure to reveal the existence of trials was at the very least unfair to the parents and patients, sued a large manufacturer, GSK, to reveal the existence of such trials. I have summarized the events that have followed, in brief, as part of a settlement, the company agreed to register all trials publicly.²⁷

Within a few days, several other drug companies agreed to comply and on August 26, 2004, Spitzer announced a settlement whereby GSK committed to putting summaries of the results of all GSK-sponsored clinical trials of drugs into a clinical trials register, posted on the Internet and conspicuously identified on the home page of the GSK website.²⁸

²⁴ K. Dickersin, S. Chan, T.C. Chalmers, H.S. Sacks & H.J.R. Smith, *Publication Bias and Clinical Trials*, 8 CONTROLLED CLIN. TRIALS 343, 353 (1987). See also P.J. Easterbrook, J.A. Berlin, R. Gopalan & D.R. Matthews, *Publication Bias in Clinical Research*, 337 LANCET 867, 867-72 (1991); K. Dickersin, *The Existence of Publication Bias and Risk Factors for its Occurrence*, 263 JAMA 1385, 1385-89 (1990); K. Dickersin, R. Scherer & C. Lefebvre, *Identifying Relevant Studies for Systematic Reviews*, 309 BMJ 1286, 1286-91 (1994).

²⁵ K. Dickersin, *Why Register Clinical Trials? Revisited*, 13 CONTROL CLIN. TRIALS, 170, 177 (1992); K. Dickersin & D. Rennie, *Registering Clinical Trials*, 290 JAMA 516, 516-23 (2003).

²⁶ I. Chalmers, *Underreporting Research is Scientific Misconduct*, 263 JAMA 1405, 1408 (1990).

²⁷ D. Rennie, *Trial Registration—A Great Idea Switches from Ignored to Irresistible*, 292 JAMA 1359, 1259-362 (2004).

²⁸ Office of New York State Attorney General Eliot Spitzer, Press Release, Settlement Sets New Standard for Release of Drug Information,

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Using the blunt instrument of the law, Spitzer accomplished in a month what I and my colleagues had failed to do over more than two decades. Meanwhile, the International Committee of Medical Journal Editors announced that, for the journals they represented, trials would have to be registered before they could be considered for publication.²⁹ Though there have been numerous attempts by manufacturers to subvert trial registration, while at the same time seeming to comply, (trials are registered as being of “an investigational drug,” for example), the system now seems to be beginning to work reasonably well.

VII. WHERE IS THE FDA IN ALL OF THIS?

A function of the FDA is to guard the health of the public, so it is striking to discover that the FDA was entirely absent from the debate over trial registration, even though that bears directly on information available to patients and their physicians. In like manner, it is reasonable to ask why the FDA did not correct what appeared in the journals when results were published that directly conflicted with what the FDA knew to be the true facts. The FDA had the facts, provided under law by the manufacturers, since a drug’s approval is contingent on such provision, but claimed they have no mandate actually to inform the public.

Just as Bayh-Dole in 1980 changed the culture of clinical research, and the relationships between sponsors, researchers and journals, so changes in the law have affected the FDA’s relationships. The Prescription Drug User Fee Act (PDUFA) was passed in 1992,³⁰ and revised in 1997 and 2002. The object of PDUFA was to speed up the approval process for drugs, and it provided the means to do this by mandating user-fees. Manufacturers had to pay towards the costs of the approval

Aug. 26, 2004, available at http://www.oag.state.ny.us/press/2004/aug/aug26a_04.html (last visited Aug. 27, 2004).

²⁹ *Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors*, 292 JAMA 1363 (2004).

³⁰ The Prescription Drug User Fee Act (PDUFA I), Public Law 102-571, Oct. 29, 1992. The Act is currently up again before the Congress.

process. The Act was effective in cutting down the time to approval.³¹ In the process, the PDUFA changed the entire culture at the FDA as well as its relationships with the pharmaceutical companies and the American people. The FDA used to have one client: the American people. The fact that the companies it regulates pay user-fees for the service has meant that the only clients on the FDA's case are drug company representatives. This is so even though the speeded up process results in profits that vastly exceed the fees, and even though the actual contribution of industry to the finances of the FDA is a fraction of that provided by public monies. The FDA now behaves as if the manufacturers are the only clients worth serving.

A telling example of this behavior, and illustration of this relationship, has just been described by Ross.³² The FDA knew that numerous severe violations (four referred for criminal investigations) had occurred in the trial performed by the maker of the antibiotic ketec. Indeed, the FDA's own criminal investigators had recommended examining the manufacturers to determine whether there had been systematic fraud—an examination that the FDA never followed through by doing. At the very least, these facts put the integrity of the whole database into question. Yet the data were, despite this, still presented to the experts for ketec's approval, and those experts voted for its approval without knowing that the data were highly suspect. Subsequently, the FDA helped to retain the drug's approval rating by allowing foreign data on safety to be considered despite the known unreliability of such data.

In the case of medical devices, the FDA is even more company-friendly. A review on a device to ease severe depression had already become a poster child for what is wrong with medical publishing. The academics who appeared as authors of the definitive review on the effectiveness of a vagal

³¹ The Department of Health and Human Services, Food and Drug Administration, Prescription Drug User Fee Act, Public Meeting, 72 Federal Register 1743-53 (Jan. 16, 2007).

³² D.B. Ross, The FDA and the Case of Ketec, 356 N. ENGL. J. MED. 1601, 1604 (2007).

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nerve stimulating (VNS) device were later all revealed to have close financial ties with the makers, none of which were mentioned in the article.³³ The review was actually ghost-written by an individual employed by the makers. Finally, the first “author” on the by-line was the editor of the journal that published it.

The approval process for the device was handled by the FDA in an even more extraordinary fashion,³⁴ the approval being granted, as Senator Charles Grassley, ranking republican on the Senate Finance Committee, noted:

based upon a senior manager overruling more than 20 Food and Drug Administration scientists, medical, and safety officers, as well as managers, who reviewed the data on VNS. The high-level official approved the device despite a resolute conclusion by many at the FDA that the device did not demonstrate a reasonable assurance of safety and effectiveness.³⁵

The FDA chooses not to exercise the powers it possesses. Given that it has the power to force a manufacturer to withdraw a drug from the market, this timid approach is astonishing, and, of course, directly harms patients. In addition, the FDA grants waivers to advisory committee members with disabling conflicts of interest since they are paid by a drug’s makers to decide about the approval of the maker’s drugs.³⁶ Add to that the fact that the FDA fails to tell the public, let alone the journals, when the agency possesses data that show authors are distorting the evidence; and that the FDA is complicit with companies in

³³ C.B. Nemeroff et al., *VNS Therapy in Treatment-Resistant Depression: Clinical Evidence and Putative Neurobiological Mechanisms*, 31 NEUROPSYCHOPHARMACOLOGY 1345, 1355 (2006), Epub Review Apr. 19, 2006, Erratum in 31 NEUROPSYCHOPHARMACOLOGY 2329 (2006).

³⁴ M. Schuchman, *Approving the Vagus-Nerve Stimulator for Depression*, 356 N. ENGL. J. MED. 1604, 1607 (2007).

³⁵ U.S. Senate Committee on Finance. Review of the FDA’s approval process for the Vagus Nerve Stimulation Therapy System for treatment-resistant depression, S. 1388-1389 (Feb. 16, 2006).

³⁶ D. Cauchon, *FDA Advisers Tied to Industry*, USA TODAY, Sept. 25, 2000.

hiding trials and so in worsening publication bias. All in all, the FDA presents a classic picture of an agency captured by those it regulates.³⁷ The failure of a politically spineless FDA to regulate is especially unfortunate at a time when editors, the profession and the public are losing confidence in the integrity of the trials required by the FDA and needed by the profession and public.

VIII. POST-MARKETING SURVEILLANCE

Nothing illustrates the problem with the FDA's pro-industry, anti-public health stance better than post-marketing surveillance—the single most important function for any rational system for protecting the public against the dangers of harmful drugs.

Though it has for ten years been mandatory to register trials having to do with HIV infection and cancer (the only conditions regarded as “life threatening”) drug companies routinely ignored the law and were never punished by the regulators.³⁸ The FDA does not enforce requirements that companies perform the post-marketing studies on which their approval is conditioned; it puts post-marketing surveillance in the hands of those with the least incentive to find problems—those who handled pre-marketing approval; and the FDA has reduced surveillance to a very small group with little standing and prestige.

IX. WHAT IS A TRIAL?

The approval process starts with evidence gleaned from clinical trials. It might be instructive to compare the sort of

³⁷ See generally D. Henry & J. Lexchin, *The Pharmaceutical Industry as a Medicines Provider*, 360 LANCET 1590, 1595 (2002); J. Collier & I. Iheanacho, *The Pharmaceutical Industry as an Informant*, 360 LANCET 1404, 1409 (2002). See also J. Abraham, *The Pharmaceutical Industry as a Political Player*, 360 LANCET 1498, 1498-502 (2002); M. Angell, *Taking Back the FDA*, BOSTON GLOBE, Feb. 26, 2007; R. Moynihan, *Alosetron: A Case Study in Regulatory Capture, or a Victory for Patients' Rights?*, 325 BMJ 592, 592-95 (2002).

³⁸ E. Manheimer & D. Anderson, *Survey of Public Information About Ongoing Clinical Trials Funded by Industry: Evaluation of Completeness and Accessibility*, 325 BMJ 528, 531 (2002).

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trials with which clinical researchers are familiar with those that go on in the courts. It seems to me fundamental that the legal trial carries credibility and retains force and respect with the public because the various parties, judge, jury, opposing counsels, witnesses and police, are independent one from another.

A clinical trial can be different. In that process, it is very much in the interest of the drug's sponsor, or manufacturer, to make everyone in the process its dependent, fostering as many conflicts of interest as possible. Before the approval process, the sponsor sets up the clinical trial—the drug selected, and the dose and route of administration of the comparison drug (or placebo). Since the trial is designed to have one outcome, is it surprising that the comparison drug may be hobbled—given in the wrong dose, by the wrong method? The sponsor pays those who collect the evidence, doctors, and nurses, so is it surprising that in a dozen ways they influence results? All the results flow in to the sponsor, who analyses the evidence, drops what is inconvenient, and keeps it all secret—even from the trial physicians.³⁹ The manufacturer deals out to the FDA bits of evidence, and pays the FDA (the judge) to keep it secret. Panels (the jury), usually paid consultant fees by the sponsors, decide on FDA approval, often lobbied for by paid grass-roots patients organizations who pack the court (that trick is called “astro-turfing”). If the trial, under these conditions, shows the drug works, the sponsors pay subcontractors to write up the research and impart whatever spin they may; they pay “distinguished” academics to add their names as “authors” to give the enterprise credibility, and often publish in journals dependent on the sponsors for their existence. If the drug seems no good or harmful, the trial is buried and everyone reminded of their confidentiality agreements. Unless the trial is set up in this way, the sponsor will refuse to back the trial, but even if it is set up as they wish, those same sponsors may suddenly walk away from it, leaving patients and their

³⁹ A.W. Chan, A. Hrobjartsson, M.T. Haahr, P.C. Gøtzsche & D.G. Altman, *Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials: Comparison of Protocols to Published Articles*, 291 JAMA 2457, 2465 (2004).

physicians high and dry.⁴⁰

In short, we have a system where defendant, developers of evidence, police, judge, jury, and even court reporters are all induced to arrive at one conclusion in favor of the new drug.

But no issue could possibly affect our lives and health more than this. Moore and Cohen⁴¹ are among many physicians who have presented evidence about drugs that were withdrawn only after causing many thousands of deaths. It has been estimated by Graham that tens of thousands of Americans have died as a consequence of taking Vioxx.

Can we really afford to continue this broken model, pretending that patients can make informed choices when neither their physicians, nor the editors who vetted the trial reports, can access relevant evidence, or trust what evidence they can find?

I find none of this surprising. Drug companies behave as if run by marketers, and nothing the pharmaceutical industry does is more scientific than its marketing. The industry has established, by the application of vast amounts of money, a paradise for themselves on earth. Under the shaky (and unaudited) pretext that it costs at least \$800 million to put a new drug on the market,⁴² the industry has its way with the Congress, researchers, the FDA, physicians and the public.

⁴⁰ B.M. Psaty & D. Rennie, *Stopping Medical Research to Save Money: A Broken Pact with Researchers and Patients*, 289 JAMA 2128, 2131 (2003).

⁴¹ T.J. MOORE, *PRESCRIPTION FOR DISASTER* (Simon & Schuster 1998); J.S. COHEN, *OVERDOSE: THE CASE AGAINST THE DRUG COMPANIES* (Tarcher/Putnam 2001).

⁴² New Study Expected to Significantly Overstate Drug Industry R&D Costs, CITIZEN, Nov. 28, 2001, available at http://www.citizen.org/pressroom/print_release.cfm?ID=942 (last visited Dec 5, 2003); J. Love, *Reporting \$802: Opportunity Cost of Capital as a Drug Development Cost*. IP-HEALTH, Dec. 1, 2001, available at <http://lists.essential.org/pipermail/ip-health/2001-December/002486.html> (last visited Dec. 5, 2003); U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks, and Rewards*, OTA-H-522, Appendix D; Congressional Access to Proprietary Pharmaceutical Industry Data, Feb. 1993, <http://www.wws.princeton.edu/cgibin/byteserv.prl/~ota/disk1/1993/9336/933616.PDF> (last visited Dec 5, 2003).

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X. SO WHAT SHOULD BE DONE TO SALVAGE OUR FDA?

The FDA was set up to regulate drugs because of a popular belief that the safety and effectiveness of drugs was too important to be left to those who sold those drugs. Over the past two decades, we have seen steady erosion in the FDA's power and a transfer of that power to the drug companies. More importantly, together with increasing politicization of the agency, there has been conspicuous erosion in the FDA's willingness to exercise what powers it does possess to force compliance by the drug manufacturers with the law.

1. We should reaffirm our decision that we want drug regulation, and the first essential is to give the FDA strong, stable leadership. The lengthy succession of short-term acting commissioners is as much an insult to the American people as is the fact that the last such acting commissioner has recently pled guilty to a criminal indictment concerning financial conflicts of interest. Given that the pervasiveness of such conflicts has become the principal problem with the whole system, this is particularly shameful and emphasizes that strong ethical leadership is essential.

The first order of business for the new commissioner should be to restore morale, and ensure that the agency enforces the law.

2. User fees must end. They are profoundly corrupting and tilt the balance strongly for the manufacturers and against the public health. It is ludicrous to imagine that the FDA could truly work for the public if they continue to be paid not to.

3. Post-marketing surveillance. The Institute of Medicine and a good many individuals have drawn attention to the woeful state of post marketing surveillance.⁴³ I shall not repeat all their

⁴³ Institute of Medicine, Committee on the Assessment of the US Drug Safety System, *Promoting and Protecting the Health of the Public* (Baciu A, Stratton K, Burke SP, eds., National Academies Press, 2006); B.M. Psaty & S.P. Burke, *Protecting the Health of the Public—Institute of Medicine Recommendations on Drug Safety*, 355 N. ENGL. J. MED. 1753, 1755 (2006). See also G.D. Curfman, S. Morrissey & J.M. Drazen, *Blueprint for a stronger Food and drug Administration*, 355 N. ENGL. J. MED. 1821 (2006).

points, but concentrate on those that I have been pushing for several years.

First, at least as many resources must be devoted to surveillance as to pre-marketing approval. Second, surveillance must be given a separate department, of equal status to the approval arm of the FDA, and taken out of the hands of the same people who approved the drug, all of whom have a built-in conflict in finding problems with a drug they have just approved. Third, at present, our surveillance systems identify perhaps 1 percent of such harms due to drugs. I believe that all drugs must be approved for a specific probationary period, say two years, and during that time, every patient taking the new drugs must be entered into a database so that for the very first time we begin to get reliable incidence rates for drug reactions and other harms. The onus must be placed on the manufacturer to prove that the drug should then receive full approval. Fourth, if the post marketing studies demanded as a condition of approval are not performed in a timely fashion, the FDA must promptly withdraw the drug.

4. It makes no sense for the pharmaceutical companies to be the only ones developing the evidence. At present, those who have most to gain by finding positive results in clinical trials are often the only source of information about their drugs. We must separate the development of molecular entities from their later clinical trial in humans. I am enthusiastic about venture capital flowing to researchers and their institutions when they make new discoveries and develop promising new therapies. I am completely against the *testing* of these entities, the new drugs, being under the control of the makers, not simply because of failures and distortions of reporting, but because it is unethical to treat results of experiments done on patients as trade secrets.

To deal with this fundamental problem, we must set up a separate agency—an entirely federally-funded National Institute of Clinical Trials, separate in budget from the NIH. This institute would decide the trial agenda, and contract out the work to institutions. Clinical scientists engaging in these trials would receive all the funds through their institutions and not be allowed to receive other funds. The results would carry great credibility

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and, because they would be trials directed to answer clinically relevant questions, would be published fast by good journals. Medicare and managed care organizations would see a great advantage in having an agenda that pays more attention to the needs of patients than to the potential profits of the manufacturers. For the first time, they would get unbiased results and be able to conduct credible cost-effectiveness studies.⁴⁴ Others have proposed variants of this idea.⁴⁵

Drug companies would be allowed to conduct trials of their drugs, as at present, and to register and publish them. However, they will find that the public is prepared to give them less credibility and good journals will be leery of publishing them.

CONCLUSION

Over the past thirty years, we have come to realize that the scientific record may be fabricated and in other ways fraudulent. But having set up systems to deal with research misconduct, we are now discovering a vastly more important problem: the massive bias and distortion of the published evidence by researchers and their sponsors, both influenced by money.

All of us will benefit from systems that remove clinical testing from the hands of those with profound self-interest in the results, and all will benefit from a stronger, less political, FDA, entirely freed from pharmaceutical user-fee money.

The pharmaceutical companies, by their arrogant behavior and their naked disregard for the well-being of the public, have lost our trust. The FDA, by spinelessly knuckling under to every

⁴⁴ S.R. Tunis, D.B. Stryer & C.M. Clancy, *Practical Clinical Trials. Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy*, 290 JAMA 1624, 1624-32 (2003); J.P. Kassirer & M. Angell, *The Journal's Policy on Cost-Effectiveness Analysis*, 331 N. ENGL. J. MED. 669, 670 (1994); S. Hill, D. Henry & A. Mitchell, *Problems in Pharmacoeconomic Analyses*, 284 JAMA 1923, 1923-24 (2000); D. Rennie & H.S. Luft, *Pharmacoeconomic Analyses: Making them Transparent, Making them Credible*, 283 JAMA 2158, 2158-60 (2000).

⁴⁵ A.J.J. Wood, C.M. Stein & R. Woosley, *Making Medicines Safer—The Need for an Independent Drug Safety Board*, 339 N. ENGL. J. MED. 1851, 1851-54 (1998).

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whim of the drug companies, has thrown away its high reputation, and in so doing, also forfeited our trust. For both, winning this trust back will be a long and painful business. But all of us have too much at stake for them not to succeed.