ing compliance and good will. The new policies lose their controversial character rather quickly. The faculty moves on—and this should encourage other AMCs to appoint their own task forces to design and implement change.

As change becomes embedded in medical centers, it will be vital to analyze outcomes both qualitatively and quantitatively. There are many important questions to be answered: Do attitudes and practices change over time? Do house staff and medical students experience the change in terms of an intensified commitment to professionalism? Do disclosure requirements affect appointments to formulary committees or teaching assignments? As visits from pharmaceutical representatives decline, do physicians' prescriptions for generics increase? What effect on research funding might occur? Does the pharmaceutical industry devise new strategies that undercut the policies, and if so, how do the AMCs respond?

Last, but certainly not least, will AMCs make sufficient progress to obviate the need for government intervention?

Financial Disclosures: None reported.

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Industry-Sponsored Clinical Research
A Broken System

Marcia Angell, MD

OVER THE PAST 2 DECADES, THE PHARMACEUTICAL industry has gained unprecedented control over the evaluation of its own products. Drug companies now finance most clinical research on prescription drugs, and there is mounting evidence that they often skew the research they sponsor to make their drugs look better and safer. Two recent articles underscore the problem: one showed that many publications concerning Merck's rofecoxib that were attributed primarily or solely to academic investigators were actually written by Merck employees or medical publishing companies hired by Merck[1]; the other showed that the company manipulated the data analysis in 2 clinical trials to minimize the increased mortality associated with rofecoxib.[2] Bias in the way industry-sponsored research is conducted and reported is not unusual and by no means limited to Merck.[3]

The problem is not so much the sponsorship itself but the terms. Before the 1980s, industry grants to academic institutions to fund studies by faculty members gave investigators total responsibility. The investigator designed the studies, analyzed and interpreted the data, wrote the papers, and decided where and how to report the results. Generally, neither the investigators nor their institutions had other financial connections to sponsoring companies.

In recent years, however, sponsoring companies have become intimately involved in all aspects of research on their products. They often design the studies; perform the analysis; write the papers; and decide whether, when, and in what form to publish the results. In some multicenter trials, authors may not even have access to all their own data. The Pharmaceutical Research and Manufacturers of America, the trade association of the industry, justified withholding data in this way: "As owners of the study database, sponsors have discretion to determine who will have access to the database."[4] At its extreme, investigators have become little more than hired hands, supplying patients and collecting data according to the company protocol.

Adding to the willingness of medical centers to tolerate these encroachments on their traditional responsibilities is the competition from a huge new for-profit research industry that vies with medical centers for pharmaceutical contracts. Called contract research organizations (CROs), these businesses organize networks of physicians to supply patients. Contract research organizations are only too ready to accede to drug company terms because their only clients are drug companies. Sponsors would still prefer that their important clinical research be conducted in academic medi-

Author Affiliation: Department of Global Health and Social Medicine, Harvard Medical School, Cambridge, Massachusetts.
Corresponding Author: Marcia Angell, MD, Department of Global Health and Social Medicine, Harvard Medical School, 651 Huntington Ave, Cambridge, MA 02115 (marcia_angell@hms.harvard.edu).

cal centers, in part because of the added prestige. With the new competition for contracts, academic centers feel pressured to accept drug company terms that would once have been unthinkable, and they sometimes join with CROs to carry out research.

In addition to grant support, faculty investigators often have other financial ties to the sponsors of their research. They serve as paid consultants and members of speakers' bureaus and advisory boards and sometimes even have equity interest in the companies. Such conflicts of interest would once have been prohibited by academic medical centers, but those institutions now have their own extensive financial ties to industry and are hardly in a moral position to object to their faculty behaving in the same way. A recent review found that about two-thirds of academic medical centers hold equity interest in companies that sponsor research within the same institution,[5] and a study of medical school department chairs found that two-thirds received departmental income from drug companies and three-fifths received personal income.[6] Medical school guidelines governing faculty conflicts of interest are highly variable, generally quite permissive, and loosely enforced.

Recently Sen Charles Grassley, ranking Republican on the Senate Finance Committee, alleged that Dr Alan Schatzberg, chairman of Stanford's psychiatry department and incoming president of the American Psychiatric Association, controlled more than $6 million worth of stock in Corcept Therapeutics, a company he cofounded that is developing mifepristone to treat psychotic depression. At the same time, Schatzberg was also the principal investigator of a National Institute of Mental Health (NIMH) grant that included research on mifepristone for this use. In a statement released June 25, 2008, Stanford professed to see nothing amiss in this arrangement, although the university had divested itself of its own stock in Corcept "pursuant to its policy on institutional conflict of interest."[7] The statement also said that Schatzberg, although principal investigator on the NIMH grant (it neglected to mention that he was also coauthor of articles on mifepristone), "has not had responsibility for any aspect of the conduct of the grant's research related to mifepristone,"[7] which raises its own set of questions about exactly what it means to be the principal investigator on a grant and a coauthor. (On July 31, 2008, Stanford University's general counsel notified the NIMH that it was temporarily replacing Schatzberg as principal investigator of the grant "to eliminate any misunderstanding.")

Given the conflicts of interest that permeate the clinical research enterprise, it is not surprising that industry-sponsored research has consistently been shown to favor the sponsor's drug—partly because negative results are often not published, partly because positive results are repeatedly published in slightly different forms, and partly because a positive spin is put on even negative results. A study of 74 clinical trials of antidepressants found that 37 of 38 positive studies were published. But of the 36 negative studies, 33 were either not published or published in a form that conveyed a positive outcome.[8] Some of the most important instances of suppression of negative results have been exposed during the discovery phase of lawsuits or during congressional investigations, not by the academic community. A case in point is GlaxoSmithKline's withholding of evidence that paroxetine was ineffective and possibly harmful to children and adolescents. According to an internal company document obtained by the *Canadian Medical Association Journal*, company officials decided to suppress negative results from one study because, in their words, "It would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine."[9]

Clinical research that *is* published is often biased, usually by designing the studies in ways that will almost inevitably yield favorable results for the sponsor. This can be done in many ways. For example, comparator drugs may be administered at a too-low dose, so that the sponsor's drug looks more effective, or at a too-high dose, so that the sponsor's drug has relatively fewer adverse effects. Other maneuvers include choosing a composite outcome so that a favorable outcome can be selected as the "primary" end point; publishing only part of the data, as in the case of the publication of results from just the first half of the CLASS study of celecoxib, when the data were positive[10]; and downplaying evidence of serious adverse effects, as in the case of the VIGOR trial of rofecoxib.[11] Very often bias takes the form of comparing a new drug with a placebo when the relevant question is how it compares with an existing drug.

Conflicts of interest may bias more than research. They may also affect influential practice guidelines issued by professional and governmental bodies, as well as decisions by the Food and Drug Administration (FDA). A study of 200 panels that issued practice guidelines found that more than one-third of the authors acknowledged that they had some financial interest in the drugs they recommended.[12] After the National Cholesterol Education Program, sponsored by the National Institutes of Health (NIH) in conjunction with the American Heart Association and American College of Cardiology, called for sharply lowering the desired levels of low-density lipoprotein cholesterol, it was revealed that 8 of 9 members of the panel writing the recommendations had financial ties to the makers of statins.[13] Of the 170 contributors to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition), 95 had financial ties to drug companies,[14] as did all contributors to the sections on schizophrenia and mood disorders. Perhaps most importantly, many members of the FDA's 16 standing committees that advise the FDA on drug approvals also have financial ties to drug companies. Although these individuals are supposed to recuse themselves from participating in decisions about drugs made by specific companies with which they have a financial relationship, that requirement is frequently waived by FDA authorities.

Looking at this picture altogether, it would be naive to conclude that bias is only a matter of a few isolated instances. It permeates the entire system. Physicians can no

longer rely on the medical literature for valid and reliable information. This is the conclusion I reluctantly reached toward the end of my 2 decades as an editor of the *New England Journal of Medicine*, and it has been reinforced in subsequent years. Clinicians just do not know anymore how safe and effective prescription drugs really are, but these products are probably nowhere near as good as the published literature indicates.

Physicians who would be quite skeptical about drug company advertisements and the pitch of sales representatives tend to trust the peer-reviewed medical literature. One result of the bias in this literature is that physicians learn to practice a very drug-intensive style of medicine. Even when lifestyle changes would be more effective, physicians and their patients often believe that for every ailment and discontent there is a drug. Physicians are also led to believe that the newest, most expensive brand-name drugs are superior to older drugs or generics, even though there is seldom any evidence to that effect because sponsors do not usually compare their drugs with old drugs at equivalent doses. And finally, physicians learn to use drugs for off-label uses without good evidence of effectiveness. Although it is illegal for companies to market drugs for off-label uses, faculty "thought leaders" on company speakers' bureaus regularly promote off-label uses in the guise of education or research.

In a strong editorial accompanying the 2 articles in *JAMA* cited at the outset,[1,2] DeAngelis and Fontanarosa called for major reform.[3] One of their proposals was that clinical research should not be left primarily or solely to sponsoring companies. I agree, and I have proposed that an Institute for Prescription Drug Trials be established within the NIH to administer clinical trials of prescription drugs, including the premarketing trials that will be submitted to the FDA as a part of new drug applications.[15] It is self-evidently absurd to look to investor-owned companies for unbiased evaluations of their own products. Yet many academic investigators and their institutions pretend otherwise, and it is convenient and profitable for them to do so. They should instead be at the forefront of efforts to reform the system of clinical research and not leave it to the government and legal profession. It is more than a matter of perception or appearances: it is a matter of public health.

Financial Disclosures: Dr Angell reported receiving royalties from her book *The Truth About the Drug Companies: How They Deceive Us and What to Do About It.*

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Industry Support of Medical Education

Arnold S. Relman, MD

Should professional medical institutions (medical schools and teaching hospitals) and their staff accept support from industry for their educational programs? This long-standing debate has become more urgent in recent years, particularly with respect to accredited continuing medical education (CME). With a budget now approaching $3 billion, CME is more than half supported by industry.[1] Currently, most industry support is distributed through medical education and communication companies (MECCs) that act as agents for the pharmaceutical manufacturers. Many more billions of drug industry largesse is expended on personal gifts, favors, and payments to the physicians on the staff of teaching institutions.[2]

The Accreditation Council on Continuing Medical Education (ACCME) accredits medical institutions and MECCs to provide CME and has promulgated voluntary guidelines

Author Affiliation: Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts.
Corresponding Author: Arnold S. Relman, MD, Channing Laboratory, 181 Longwood Ave, Fifth Floor, Room 571, Boston, MA 02115 (arelman@rics.bwh.harvard.edu).