Conflict of Interest in Academia—Straining the Public’s Trust

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Conflict of Interest - Example

- Professor learns of novel prevention strategy
- Conducts single arm study on 20 subjects
- Potentially lethal disease prevented in all 20
- Professor wishes to charge fee for others to use strategy
Conflict of Interest - Example

- 1799
- Benjamin Waterhouse
- Harvard Medical School
- Preventable disease - Smallpox
- Read Jenner’s work

From Martin and Kasper
NEJM 343: 1646, 2000
First, A Key Definition
Fiduciary

Of or relating to a confidence or trust. Power to be used to the benefit of another, based on specialized knowledge or expertise.
Conflict of Interest

“A set of conditions in which professional judgment concerning a primary interest (such as a patient’s welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).”

Quoted in Bekelman et al, JAMA 289:454, 2003
From Thomp sen, D, NEJM 329:573, 1993
Science in the Private Interest

(Has the lure of profits corrupted Biomedical Research?)

By

Sheldon Krimsky
3 Stages of Conflict of Interest (after Andrew Stark in “Conflict of Interest in Public Life” as quoted in Krimsky, p. 126)

- Antecedent Acts - factors conditioning the state of mind (gifts, equity, consultancies)   LEADS TO
- States of Mind – sentiments, proclivities or affinities affected (favoritism, bias)    LEADS TO
- Outcome behavior (decisions, behaviors)

Rules aimed at stage 3 would only find someone guilty if behavior could be linked to antecedent acts and states of mind.

Thus, stage 1 is the target of policies, regulations, or laws.
Why Now?
Environmental Factors in the Debate

- Decreasing revenues to academic medical centers
  - Managed care
  - Payor mix
  - Decreased Medicare reimbursement
  - Uninsured
- Bayh-Dole Act of 1980
  - The rise of technology transfer
- Everybody’s got a company
- Demand for science that benefits man (and woman) rather than mankind
- Uneasy and unclear permitted arrangements between pharma and academia
- Grant money harder to get, especially for clinical research
- Greed - personal, institutional
Some Parts of the Problem

- 1999 - $17.8B in NIH funding - mostly basic research
- 1999 - Top 10 pharmaceutical companies - $22.7B - mostly clinical research
- Half advisers to FDA have financial interests in companies whose interests rest on FDA decisions
The True Cost of New Drugs

- Amount usually quoted - $800M
- Activities included under R & D are unknown
- 2000 – industry claims $26B on R & D and 98 new drugs = $265M each (after tax cost $175M; R & D tax deductible at 34% corporate tax rate)
- Actual cost probably closer to $100M per drug

From Marcia Angell, M.D.
“The Truth About the Drug Companies”
What’s So New About New Drugs

- 2002 – 17 of 78 approved were actually new molecular entities (NME)
- 1998 – 2002 - 415 approved; 133 NME

From Marcia Angell, M.D. “The Truth About the Drug Companies”
Central Argument of Krimsky’s “Science in the Private Interest”

• Public policies and legal decisions have created new incentives for universities, their faculty, and publicly supported nonprofit research institutes to commercialize scientific and medical research and to develop partnerships with for-profit companies.

• The new academic-industry and non-profit-for profit liaisons have led to changes in the ethical norms of scientific and medical researchers.

• Secrecy has replaced openness.

• Privatization of knowledge has replaced communitarian values.
Central Argument of Krimsky’s “Science in the Private Interest” (cont.)

- Commodification of discovery has replaced the idea that university-generated knowledge is a free good.
- The rapid growth of entrepreneurship in universities has resulted in an unprecedented rise in conflicts of interest (COI).
- COI among scientists has been linked to research bias…the loss of disinterestedness
- Fewer opportunities will exist in academia for public interest science – a loss to society.
“The erosion of the public’s faith in the reliability of scientific findings may, in fact, be one of the greatest harms resulting from the strengthening of ties between industry and academia.”

Peter J. Harrington
J. of College and University Law 27:775, 2001
“University science becomes entangled with entrepreneurship; knowledge is pursued for its monetary value; and expertise with a point of view can be purchased.”

Sheldon Krimsky

“Science in the Private Interest” p.1
Is This Really Entrepreneurship?

Entrepreneur - “a person who organizes and manages any enterprise, especially a business, usually with considerable initiative and risk” - Random House Dictionary

“Even in cases where taxpayers have funded years of research, scientists can turn a discovery built on such research into a profitable drug. Many people, whose taxes funded the research and who are in dire need of the drug, now cannot afford it.”

“The irony cannot be avoided. Capitalism is supposed to operate on the principle that private risk yields private loss or private wealth. Philanthropy turns private wealth into social resources. But the idea that public risk should be turned into private wealth is a perversion of the capitalistic ethic.”

From Krimsky, p. 181
Dr. Marcia Angell Speaks

(NEJM – May 18, 2000)

“Is Academic Medicine for Sale?”

Financial ties of articles’ author so great, they cannot be summarized in print. (placed on NEJM website)
What Are the Financial Ties?

- Research support - grant/contracts
- Consultants
- Advisory Boards
- Speakers Bureaus
- Royalties, licenses
- Ghostwriting
- Promotion at sponsored symposia
- Gifts, trips
- Equity, options

From Angel, M.
NEJM - 5/18/2000
Industry Sponsors Can Legally Suppress the Publication of Research Supported by Them

Experts See Bias In Drug Data

By LAWRENCE K. ALTMAN

Suppression of a university scientist’s findings about a common thyroid drug by a company that paid

Medical Journal Cites Misleading Drug Research

By DENISE GRADY

Reports of research on drugs tend to exaggerate the drugs' benefits, making them sound better than they are. But Dr. Rennie attributed the problem not only to drug companies, but also to researchers and the institutions that allow shoddy research, sometimes publish the same data more than once, without letting on that it has ever been in print before. That may mislead doctors into thinking that fluconazole, a newer drug, is better than it is.

The literature is dominated by research reports of positive studies. Is this why?
Surveys of the medical literature indicate that positive reports are more likely when the research is industry sponsored.
What Industry Sponsors do to Influence Study Outcomes

(from Bodenheimer, NEJM; May 18, 2000)

- Opt not to do a post-approval study the results of which could negatively impact drug sales
- Study designs may favor the sponsor’s product – use of younger population than is targeted by the drug; dose of competitor’s comparison drug is too low
- Use of surrogate end-points that may not correlate with meaningful clinical results
What Industry Sponsors do to Influence Study Outcomes (cont.)

• Sponsor controls data – participants do not get to examine all results

• Sponsors may control publication including order of authorship and whether results get published at all

• Publications are “ghost-written” by company authors
Help From the Federal Government?
Not Really
Conflict of Interest

1. Part of objectivity in research
2. Applicability: PHS and NSF grant applications
3. Significant Financial Interest
   a) anything of monetary value
   b) exceptions
      equity <$10,000 – includes spouse and children
      <5% ownership
      payments <$10,000 over next 12 months
4. Must be written policy; investigators informed
5. Institution’s responsibility to monitor sub-awardees
6. Institutional official reviews disclosures of significant financial interests
   that would reasonably appear to be affected by research for which PHS
   funding is sought
7. Updating – annual and transactional
Conflict of Interest
Federal Rules – NIH / NSF 1995 (cont.)

8. Maintain records for 3 years
9. Certify above with each grant
10. Reporting of COI to PHS, but not details
11. Assure COI managed, reduced or eliminated
12. IO determines if COI exists and how it will be managed. Sole responsibility rests with institution.
13. PHS can suspend funding
14. NSF differences
   IO = reviewer
15. Nothing is strictly prohibited
Conflict of Interest
US FDA – 1998

1. Responsibility to disclose with sponsor who must seek disclosure from investigator

2. Disclosure “when covered clinical studies are submitted to FDA in support of product marketing”. Could be after research is done.

3. Disclose financial arrangement where compensation to investigator is affected by study outcome – more dollars for better outcome or from product sales

4. Significant equity interest cannot be determined (non-public stock) or >$50,000 value during study plus 1 year
   Also payment by sponsor to investigator or institution of >$25,000 (not counting costs of trial)

5. No financial interest – Form 3454
   Disclose on Form 3455
   Include steps to minimize bias
A. Bartlett Giamatti, President, Yale University (Science, 1982)

- “Doubt faculty member can devote time and energy to the university and a company”
- Conflict in norms governing dissemination knowledge. Two separate research programs; results of one widely disseminated, the results of other kept secret
- Risk of putting students and associates in ambiguous situations
Conflict of Interest in Clinical Research
A Unique Subset
“Gifts, hospitality, or subsidies offered to physicians by the pharmaceutical industry ought not to be accepted if acceptance might influence or appear to others to influence the objectivity of clinical judgment. The useful criterion in determining acceptable activities and relationships is: Would you be willing to have these arrangements generally known?”

From American College of Physicians
as quoted by Hutchison and Halperin in
Important Conflict of Interest Points from Goldner – J. Law, Medicine and Ethics 28:379, 2000

• The difference between practice and research – informed consent is not a professional treatment recommendation

• “The result of conflict of interest and bad research is that public confidence and trust in the entire research enterprise vanishes.”

• Abolitionist position – eliminate conflicts

• Absent political will to abolish, must manage
The Death of Jesse Gelsinger
The ‘Near Death” of Gene Therapy

How one death started an avalanche of investigating, finger-pointing and ill will
The NIH Failed to Adequately Oversee Gene Therapy Trials

- Of 691 serious adverse events experienced by patients, only 39 had appropriately been reported
- 652 were submitted following Mr. Gelsinger’s death
Gelsinger Case - Conflict of Interest Issues

• Genetic deficiency, but well controlled on drugs and diet
• Liver function not adequate for protocol
• FDA had not received AEs – monkey or human
• Toxicities not in consent document
• Director of Institute for Human Gene Therapy owned stock in sponsor
• Director and Dean had patents
• University received money for rights and had equity
• Law suit settled

From Goldner in J. Law, Medicine and Ethics 28: 379, 2000
The Cost of Marketing

- 2001 - $11B in “free samples”
- 88,000 sales reps
- 35% of revenues spent on marketing

From Marcia Angell, M.D.
“The Truth About the Drug Companies”
Institutional Conflict of Interest

Why control:

- Inappropriate decision-making by institutional decision-makers or IRB members
- Institutional conflict of interest can be transferred to others in institution
- Cause preferential treatment or resource allocation

“While entrepreneurship in academia has accelerated scientific innovation, on occasion it has also marred academia’s reputation as independent truth-seeker, reduced public trust in the research enterprise, and resulted in a burgeoning literature on conflicts of interest.”

From John et al.
JAMA 289: 741, 2003
Krimsky’s 3 Principles for Re-establishing the University’s Traditional Role

- Separate the producers of knowledge and those with a financial interest in the knowledge
- Separate clinical investigators from those with a financial interest in the drug being tested
- Separate those assessing the safety and efficacy of products from those with a financial interest in the product
  - The courts don’t run the prisons
  - Physicians shouldn’t earn income for each pill swallowed or each subject registered on a clinical trial
  - Members of Congress do not sit on boards of corporations
  - University scientists should not be corporate CEOs of for-profit companies
Dr. Angell’s Suggestions

1. Shift emphasis from “me too” - all new drugs must be compared with current, available ones. Minimize placebo-control trials.

2. Strengthen the FDA – no users’ fees. Increase public support including safety monitoring. Eliminate conflicts of interest on FDA panels.

3. New institution to oversee drug testing - within NIH

4. Curb monopoly marketing rights – patents don’t start until drug comes to market. No 6 month extension for pediatric trials. Close loopholes that extend exclusivity.

5. Get drug companies out of medical education

6. Open the industry’s books

7. Reasonable and uniform pricing

From Marcia Angell, M.D.  
“The Truth About the Drug Companies”
Health Industry Practices That Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers

Brennan et al, JAMA 295:429, 2006

- Prohibit all gifts
- Prohibit all free drug samples. Substitute with voucher system for low-income patients.
- Physicians on formulary committees may receive no gifts, grants, contracts, or stock from a drug company.
- No direct or indirect CME support from drug companies
- No direct travel grants from drug companies
- No faculty on drug company speakers’ bureaus
- All funds from drug companies must be for specific work and accompanied by a contract. “No strings” gifts are prohibited to individuals. Any such grants or contracts should be posted on an internet site.
- No “ghostwritten” articles allowed
“Because gifts of even minimal value carry influence and because disclosure is an inadequate safeguard, the guidance presently provided by the medical profession, the pharmaceutical industry, and the federal government fails to protect the best interests of patients and the integrity of physician decision making.”

Brennan et al., JAMA 295:429, 2006
“Without these policies and procedures, the academic institutions where most clinical research is based and their faculty members who perform the research are in grave danger of losing the support and respect of the public. Without this support and respect, trust in new medical discoveries and their applications will not be forthcoming. Without trust, medical research is doomed.”

Catherine D. DeAngelis, M.D.
Editor, JAMA
in JAMA 284: 2237, 2000