

REVISITING THE PHYSICIAN/INDUSTRY ALLIANCE: THE
BAYH-DOLE ACT AND CONFLICT OF INTEREST
MANAGEMENT AT ACADEMIC MEDICAL CENTERS

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I. INTRODUCTION

Three decades ago the Bayh-Dole Act, also known as the Patent and Trademark Act Amendments of 1980¹, was enacted to promote the development of inventions and discoveries that came about through research funded by the federal government. Prior to Bayh-Dole, numerous valuable patents and unpatented discoveries were in the possession of the governmental agencies that sponsored the research (often through grants to researchers at academic medical centers), and thus, owned the rights for their development, marketing and licensing.² These agencies, however, lacked the resources, expertise and relationships with industry necessary to commercialize the products and other inventions created pursuant to various governmental research programs and, thus, owned by them.³ Furthermore, although the goal of the government was to make these discoveries available to anyone willing to invest the time and resources necessary to bring them to market, the absence of patent rights made it commercially unprofitable for industry sponsors to in-

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1. Bayh-Dole Act, Pub. L. No. 96-517, 94 Stat. 3019 (1980) (codified as 35 U.S.C. §§ 200-212 (2010)) (implemented by 37 C.F.R. 401 (2000)).

2. Office of Technology and Transfer and Economic Development. *What is the Bayh-Dole Act, What Prompted it, and Why is it important to University Technology Transfer?*, UNIVERSITY OF HAWAII, available at <http://www.otted.hawaii.edu/what-bayh-dole-act> (last visited Nov. 26, 2010).

3. *Id.*

vest the resources needed to develop and market products and technologies that would thereafter have no patent protection.⁴ Even the licensing was problematic since few commercial entities were willing to undertake the bureaucracy involved with licensing patents from the government. Indeed, when the Bayh-Dole Act was passed, less than 5% of the 28,000 patents held by the federal government had been licensed.⁵ With thousands of valuable patents in the possession of the various federal agencies that funded the research, it appeared the time had come to encourage the academic researchers and their universities where the patentable inventions were created to develop and commercialize their own discoveries.⁶

In order to accomplish this end, Congress was urged to enact legislation that would simultaneously accomplish two necessary goals: (a) to develop a reliable technology transfer mechanism that created an incentive for the researchers and their institutions to patent their inventions or sell their patent rights to commercial interests that had the ability to develop the discoveries; and (b) to enact a patent and trademark policy that would be uniform among all federal agencies that sponsor funded research.⁷ In furtherance of these goals, the federal government, previously unwilling to grant licenses to the private sector but without resources and expertise to develop and commercialize the inventions itself, would now transfer that obligation to those with a significant interest in seeing the inventions developed and commercialized. The key to the success of the Bayh-Dole Act was for the government to allow universities to obtain patents and grant exclusive licenses to their researchers' discoveries generated through federal funding, thus allowing the universities and faculty a genuine incentive, unencumbered by unwieldy governmental bureaucracy.⁸

Ten years after the enactment of the Bayh-Dole Act, the success of the legislation was hotly debated. On the one hand, there was an incontrovertible spike in the number of patents issued to universities: prior to 1981, approximately 250 patents were issued per year; in the ten years following Bayh-Dole, nearly 1600 patents per year were issued to universities, and nearly 80% of these derived from federally-funded research.⁹ Core technologies, notably

4. *Id.*

5. UNITED STATES GENERAL ACCOUNTING OFFICE, REPORT TO CONGRESSIONAL COMMITTEES, GAO/RCED-98-126, TECHNOLOGY TRANSFER: ADMINISTRATION OF THE BAYH-DOLE ACT BY RESEARCH UNIVERSITIES 3 (1998).

6. See generally Lynne G. Zucker & Michael R. Darby, *Star Scientists and Institutional Transformation: Patterns of Invention and Innovation in the Formation of the Biotechnology Industry*, 93 PROC. NATL. ACAD. SCI. 12709, 12709-16 (1996).

7. UNIVERSITY OF HAWAII, *supra* note 2.

8. David Blumenthal, *Academic-Industrial Relationships in the Life Sciences*, 349 NEW. ENG. J. MED. 2452, 2453 (2003).

9. The Bayh-Dole Act, Pub. L. 96-517, *A Review of Patent Issues in Federally Funded Research. Hearing before the Subcomm on Patents, Copyrights, and Trademarks of the Comm on the Judiciary*, 103rd Cong. 11, 42 (1994), available at <http://www.gao.gov/archive/1998/rc98126.pdf>.

biotechnology, flourished as a direct result of university inventions.¹⁰ On the other hand, the Bayh-Dole legislation spurred a flurry of new partnerships between academic medicine and industry partners, igniting an intense controversy over conflicts of interest as a result of industry's role in assuming greater control over research conducted within these new academic medical center/industry partnerships.¹¹

The Bayh-Dole Act impacted research in several ways: the sale of patents infused universities with a stream of income; industry became more interested in creating contracts with university-based researchers to purchase patent rights to their inventions; the researchers themselves had a new incentive to pursue their work; and commercial organizations could directly approach academic researchers to license patent rights without having to rely solely upon its own research staff.¹² However, the Bayh-Dole Act also set the stage for the industry, whose first obligation is the profit interests of its shareholders, to become enmeshed with academia and to extend its profit incentives to their research partners.¹³ It is these relationships that have come under intense scrutiny in recent years as data is presented spotlighting the visible influence of industry on research.

Nearly thirty years after the enactment of Bayh-Dole, academic medical centers and commercial industry have become substantially (but not entirely) mutually interdependent upon one another to discover, develop, market and commercialize new products and technologies. By some accounts, this symbiotic relationship has operated to invigorate technology and propel new discoveries, but it has also escalated the controversy over conflicts of interest and undue influence of industry partners to market particular products.¹⁴ This paper examines the legislative intent behind the Bayh-Dole Act, focusing specifically on the rationale that promotes interdependent relationships between academic medicine and industry. It explores the current climate of mistrust of physician-industry relationships. Finally, it concludes with some additional suggestions for safeguarding research integrity without entirely dismantling the partnerships that were instrumental in invigorating technological innovation nearly thirty years ago.

10. David C. Mowery and Bhaven N. Sampat, *The Bayh Dole Act of 1980 and University-Industry Technology Transfer: A Model of Other OECD Governments?*, 30 J TECH. TRANSFER 115, 116 (2005).

11. Bryan A. Liang and Tim Mackey, *Confronting Conflict: Addressing Institutional Conflicts of Interest in Academic Medical Centers*, 36 AM. J. L. & MED. 136, 153-54 (2010).

12. Annetine C. Gelijns & Samuel O. Their, *Medical Innovation and Institutional Interdependence: Rethinking University-Industry Connections*, 287 J. AM. MED. ASS'N 72, 73, 75-77 (2002).

13. Liang & Mackey, *supra* note 11, at 156.

14. *Id.*

II. THE BAYH-DOLE ACT: LEGISLATIVE INTENT

Although there are good reasons to be wary of some of the university physician-industry relationships that were spawned as a result of the Bayh-Dole Act, few challenge the value of the significant medical advancements that developed as a result of such relationships. Passed at a time of overwhelming concern about U.S. economic decline, the Bayh-Dole Act accelerated the transfer of vital technology, thus stimulating a slow economy, increasing the availability of medical and scientific inventions to the public, and forging new alliances between academic medical centers and industry.¹⁵ Indeed, Congress' primary intent in passing Bayh-Dole was to promote collaboration between industry and non-profit organizations such as academic medical centers.¹⁶ These new university physician-industry relationships allowed Congress to turn the government's investment in academic research into substantial economic and public health advancements. Academia, with an ability to draw on its large patient base, extensive laboratory facilities, and highly-trained physician scientists, traditionally served as a major source of high-quality research and research tools.¹⁷ Industry, with the ability and facilities to further develop the research and quickly transfer it into therapeutic interventions, became a major source of economic stimulus and medical development.¹⁸ With the efficient transfer of research from academia to industry, Bayh-Dole promised not only collaboration between the two sectors but also acceleration of the economy with respect to the pace of therapeutic interventions reaching the public.¹⁹

Importantly, Congress was not alone in concluding that the collaboration between academic physicians and industry would prove fruitful. At the time the Bayh-Dole Act was enacted, the scientific community itself believed that valuable benefits would flow from university-industry relationships:

The country as a whole would benefit from improved substantive relations between universities and industry. Innovation should be significantly accelerated by reestablishing the role of market motivation in stimulating research and in enhancing the linkage between the development and application of new knowledge. Furthermore, the strengthening of both the academic and industrial sectors would enhance the quality and relevance of research, the stability and robustness of the research enterprise, the breadth and problem-solving ca-

15. Donald S. Siegel et al., *Toward a Model of the Effective Transfer of Scientific Knowledge from Academicians to Practitioners: Qualitative Evidence from the Commercialization of University Technologies*, 21 J. ENGINEERING TECH. MGMT. 115, 116, 121 (2004).

16. Bayh-Dole Pub. L. 96-517; 35 U.S.C. § 200 (1980).

17. Stossel, *infra* note 45.

18. *Id.*

19. Gelijns & Their, *supra* note 12.

pabilities of university graduates, and the competitiveness of the U.S. industrial sector.²⁰

While the scientific community accurately predicted that “substantial institutional and attitudinal barriers” to academic-industrial relationships would exist, it also believed that “the potential benefits are sufficiently compelling to engender confidence that those barriers can be surmounted.”²¹ Nearly thirty years later, many of the benefits of academic-industry relationships have been realized. Indeed, medical innovation has become extensively linked to alliances between academia and industry. From the research in genetics and molecular biology that spawned the biotechnology industry, to research in physics and the material sciences that revitalized the medical device industry, academic scientists working with industry have been responsible for significant healthcare achievements. Today academic physician-industry relationships continue to foster therapeutic innovation in many areas by efficiently translating academic insight into clinical advancement.²²

Despite the high degree of medical innovation and translational research that has resulted from academic physician-industry collaboration, it is unclear that the predicted barriers have been, or can be, surmounted. Escalating concerns about consequences directly attributable to the financial conflicts of interest and the undue influence of industry on academic physicians has chilled the response to such relationships.²³ In 2005, the Food and Drug Administration (FDA) convened a meeting of an advisory committee to discuss the cardiovascular risk associated with the Cox-2 inhibitors (painkillers) that included Vioxx, Bextra and Celebrex.²⁴ As a result, all three products remained on the market despite the substantial morbidity and mortality that would eventually be associated with the drugs. Shortly thereafter, the Center for Science in the Public Interest examined the industry relationships of the scientists serving on the FDA advisory board and discovered that 10 of the 32 FDA members had affiliations with manufacturers of the Cox-2 inhibitors and another 17 had ties to other drug manufacturers.²⁵ An analysis of the vote conducted by the *New York Times* suggests that had the 10 advisory

20. Denis J. Prager & Gilbert S. Omenn, *Research, Innovation, and University-Industry Linkages*, 207 *Sci.* 379-80 (1980).

21. *Id.* at 384.

22. Gelijns, *supra* note 12.

23. *Id.*

24. U.S. Food & Drug Administration, *Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee* (2005), available at <http://www.fda.gov/oc/advisory/accalendar/2005/cder12532ddd0216171805.html>.

25. CENTER FOR SCIENCE IN THE PUBLIC INTEREST, CONFLICTS OF INTEREST ON THE COX-2 PANEL: RESEARCH FROM CSPI'S INTEGRITY IN SCIENCE PROJECT (2005), available at <http://www.cspinet.org/new/200502251.html>.

committee members with the industry affiliations been excluded, the drugs would not have been recommended for remaining on the market.²⁶

The pharmaceutical industry has also begun to withdraw from collaboration with academic medical centers, instead outsourcing clinical trials to for-profit contract research organizations (CROs) and site-management organizations (SMOs), citing more efficient institutional review board (IRB) approval and data management.²⁷ While the expediency of utilizing CROs and SMOs is evident, so are the risks of partnering with these organizations. These include a dangerous abundance of commercial interests and increasing public (as well as physician) skepticism of drug trial results.²⁸ The prospect of foregoing academic physician collaboration and the resulting translational research is also of concern as academic medical centers offer clinical expertise and experience in designing and conducting trials as well as a diverse patient population. These contributions of academic physicians increase the quality, outcomes and cost effectiveness of clinical trials.²⁹ At the same time, the IRBs that review the protocols play an important role: more efficient IRB policies should translate into more rigorous safeguards and more confidence in the research.³⁰

The real and potential conflicts of interest posed by physician-industry collaboration have earned the intense scrutiny garnered in recent years. Physician participation in high-visibility marketing abuses such as those represented by the historic \$2.3 billion Pfizer settlement (including criminal fines) in 2009 concerning the marketing of certain pharmaceutical products.³¹ Pfizer settled with the government to resolve charges that it planned and executed schemes to illegally market those drugs. The periodic reemergence of these industry abuses, often coming to light only through whistleblower actions, make it clear that close oversight and vigilance is warranted. With the necessary oversight, the question is whether it is nevertheless possible to achieve many of the Bayh-Dole objectives despite the abuses.

26. Gardiner Harris & Alex Berenson, *10 Voters on Panel Backing Pain Pills Had Industry Ties*, N.Y. TIMES, Feb. 25, 2005, at A1, available at <http://www.nytimes.com/2005/02/25/politics/25fda.html>.

27. Geljns & Their, *supra* note 12, at 74.

28. Thomas Boedenheimer, *Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry*, 432 NEW ENG. J. MED. 1539, 1543 (2000).

29. Geljns, *supra* note 12, at 74.

30. *Id.*

31. *See Pfizer To Pay \$2.3B in Largest Health-care Fraud Settlement*, BOSTON HERALD, Sept. 2, 2009, available at <http://www.bostonherald.com/business/healthcare/view.bg?articleid=1194925>.

III. DISTINGUISHING INDUSTRY “MARKETING” AND “RESEARCH” RELATIONSHIPS

Conflicts of interest were defined nearly two decades ago as a condition in which a physician’s judgment regarding a primary interest is unduly influenced by a secondary interest. Concerns about conflicts of interest that haunt modern-day academic medicine often view industry-branded gifts in the same light with industry-sponsored research, resulting in a combination of abuses that subject academic physician-industry relationships to intense scrutiny.³² Today most academic medical centers acknowledge that physician-industry interactions intended primarily to market industry products create conflicts with physicians’ commitment to patient care.³³ Indeed, the effort and expense devoted to physician marketing has been vast, accounting for an estimated 90% of the \$21 billion pharmaceutical marketing budget.³⁴ This includes complimentary pens, mugs, lunches, reference tools, books, hospitality and travel.³⁵ While it is still possible to debate the conflicts of interest created by such gifts,³⁶ today academic medical centers routinely prohibit faculty from receiving such gifts.³⁷ The more challenging question is whether the issues ingrained in the complimentary gifts are legitimately distinguishable from the abuses that have plagued industry-sponsored research. It is notable that pharmaceutical marketing budgets are consistently reported to be larger than the budgets for the research and development itself.³⁸

The line between research and marketing, however, is far from distinct. Indeed, it is more of a continuum wherein academic physicians, including those who conduct research, are also engaged in marketing industry products by presenting their research at the behest of industry sponsors, often under the influence of such sponsors.³⁹ Speakers’ bureaus have come under intense

32. Dennis Thompson, *Sounding Board Understanding Financial Conflicts of Interest*, 329 NEW ENG. J. MED. 573, 573 (1993).

33. Gelijns, *supra* note 12.

34. Troyen Brennan et al., *Health Industry Practices That Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers*, 295 JAMA 429, 430 (2006).

35. Catherine Marco et al, *Gifts to Physicians from the Pharmaceutical Industry: An Ethical Analysis*, 48 ANNALS EMERGENCY MEDICINE 513, 517 (2006) (Social science research continues to demonstrate that acceptance of even token gifts often produces a powerful impulse to reciprocate to the gift-giver in a way that biases physicians’ drug therapy decisions).

36. *Id.* at 514.

37. See e.g. TUFTS UNIVERSITY SCHOOL OF MEDICINE, 2010 REVISED POLICY ON INDUSTRY CONFLICTS OF INTEREST, *available at* http://www.tufts.edu/med/docs/about/faculty/COI_Policy.pdf; BOSTON UNIVERSITY, FACULTY HANDBOOK: GIFT POLICY, *available at* <http://www.bu.edu/handbook/ethics/gift-policy/>.

38. See generally Marcia Angell, *The Pharmaceutical Industry – To Whom is it Accountable?* 342 NEW ENG. J. MED. 1902 (2000).

39. Troyan A. Brennan, David J. Rothman, Linda Blank, David Blumenthal, Susan Chimonas, Jordan J. Cohen, Janlori Goldman, Jerome P. Kassirer, Harry Kimball, James Naugh-

scrutiny in recent years and most academic medical centers now have taken steps to discourage faculty members from their participation.⁴⁰ There has also been ongoing and legitimate concern about undue industry influence on the research itself. But does this necessarily require that research-based relationships and marketing relationships be viewed in the same light? Further, despite the flurry of recent criticism, not everyone agrees industry relationships with academic medicine are as harmful to patient care, or as devastating to public trust, as critics have suggested.⁴¹

In 2008, the Association of American Medical Colleges (AAMC) recommended that academic medical centers adopt policies that would prohibit gifts from the pharmaceutical industry, including free drug samples.⁴² In part, these procedures were recommended in order to sustain public trust in physicians' therapeutic decisions.⁴³ More importantly, the AAMC intended that addressing these marketing issues would facilitate the continued public trust in research partnerships between academia and industry.⁴⁴ Indeed, public polls demonstrate that physicians still enjoy a trusted position in society and that research subjects still eagerly volunteer for clinical trials.⁴⁵

Some of the current criticism of academic-industry research relationships has shifted the focus of evaluating research results from objective outcomes to subjective motives, utilizing isolated cases of scientific misconduct as circumstantial evidence of corruptness due to industry involvement. While there are a small, albeit significant, number of misconduct cases involving the dishonesty of academic researchers at the hands of industry, these outliers are not representative of the majority of academic-industry partnerships.⁴⁶ It is also not clear that misconduct is more likely to occur when industry funds the research than when the government provides the funding. The question of whether industry-funded research is more vulnerable to influence or bias is a

ton, Neil Smelser, *Health industry practices that create conflicts of interest: a policy proposal for academic medical centers*, 295 JAMA 429, 429-33 (2006), available at http://www.nhmrc.gov.au/_files_nhmrc/file/health_ethics/hrecs/Health_Industry_Practices_that_create_conflicts_of_Interest.pdf.

40. *Id.* See generally Steven L. Dubovsky, David L. Kaye, Cynthia A. Pristach, Paula Del-Regno, Linda Pessar, Keith Stiles, *Can Academic Departments Maintain Industry Relationships While Promoting Physician Professionalism?*, 85 ACADEMIC MEDICINE 68 (2010).

41. Thomas Stossel, *A Biopsy of Financial Conflicts of Interest in Medicine*, 143 SURGERY 193, 196 (2008).

42. Darrell Kirch, *A Principled Partnership Between Academic Medicine and Industry*, 10 MEDSCAPE J MED. 198, 198 (2008).

43. *Id.*

44. *Id.*

45. Thomas Stossel, *Regulating Academic-Industrial Research Relationships – Solving Problems or Stifling Progress?*, 350 NEW ENG. J. MED. 1060, 1063 (2005).

46. William Heisel, *Antidote: New Ways to Investigate Untold Health Stories: Researcher Regrets Ghostwritten Hormone Therapy Review*, REPORTING HEALTH, Aug. 24, 2009, <http://www.reportingonhealth.org/blogs/researcher-regrets-ghostwritten-hormone-therapy-review>.

difficult one, both in terms of studying it and finding reasonable recourse. The recent cases involving misrepresenting the effectiveness of specific medications highlight the problem of industry participation in slanting research findings.⁴⁷ While the desire to curry favor with research sponsors may be intuitive, it is not limited to academic or industry-sponsorship, and may impact equally governmental and private foundation sponsorship, both of whom scrutinize research results when making decisions about ongoing funding.⁴⁸ Today's researchers, however funded, advocate passionately for their discoveries and ideas and seek ongoing research sponsorship.⁴⁹ In many cases, replicable results continue to emerge.⁵⁰

Some studies that have sought to prove that academic-industry collaboration results in more positive research findings than government-sponsored research have also had their own methodological shortcomings. For example, Leopold et al. found that industry funding was positively associated with publication of favorable product outcomes, but did not distinguish between industry's research support and other types of industry incentives such as royalties, stock options and employee status.⁵¹ Other studies that do distinguish industry research support and other personal financial ties have found that personal financial conflicts such as royalties and stock options are associated with higher rates of positive findings, but that industry sponsorship of research is not.⁵² The current data is still unclear as to whether industry-sponsored research is more vulnerable to bias than private or government-sponsored research.

IV. THE DATA IS THE DATA

There was a time when randomized, double-blind studies were thought to be impervious to even subtle bias, but that notion has been challenged in recent years.⁵³ In particular, concerns have been raised about the handling and reporting of research data by industry sponsors. In August 2009, Merck & Co. settled two lawsuits with third-party payers and patients totaling over \$120 million for allegedly withholding unfavorable clinical trial results involv-

47. Benedict Carey, *Antidepressant Studies Unpublished*, N.Y. TIMES, Jan. 17, 2008, http://www.nytimes.com/2008/01/17/health/17depress.html?_r=1&ex=1358312400&en=e71783fa9fd98172&ei=5088&partner=rssnyt&emc=rss.

48. Stossel, *supra* note 45, at 1063.

49. *Id.* at 195.

50. *Id.*

51. Seth S. Leopold et al., *Association Between Funding Source and Study Outcome in Orthopaedic Research*, 415 CLINICAL ORTHOPEDICS & RELATED RESEARCH 293, 296-97 (2003). See also Kanu Okike et al., *Conflict of Interest in Orthopaedic Research: An Association Between Findings and Funding in Scientific Presentations*, 89 J. BONE & JOINT SURGERY 608, 608-09 (2007).

52. Kanu Okike et al., *Conflict of Interest in Orthopaedic Research: An Association Between Findings and Funding in Scientific Presentations*, 89 J. BONE & JOINT SURGERY 608, 612 (2007).

53. See generally Sheila M. Gore, *Assessing Clinical Trials-Double-Blind Trials*, 283 BRIT. MED. J. 122 (1981).

ing Vioxx⁵⁴ and Vytorin.⁵⁵ There is also a current ongoing investigation alleging Wyeth engaged ghostwriters to generate literature supporting the use of Premarin and Prempro hormone replacement therapy.⁵⁶ And in 2006 Pfizer was accused of failing to inform consumers and medical professionals about the serious side effects associated with Lipitor.⁵⁷

It is also alleged that industry sometimes carefully selects for publication the research data that will boost sales. Vioxx documents from the Merck & Co. litigation reportedly demonstrate that the company reported only the on-treatment analysis of Vioxx to the FDA, which minimized the apparent mortality risk previously discovered in the company's internal intention-to-treat analyses.⁵⁸ Shah et al. report having found that positive study results emerged from industry funded studies 3.3 times as often as from studies with non-industry funding sources.⁵⁹ Another review comparing FDA and industry studies of 12 antidepressants found that 94% of the published studies were generally positive, while only 51% of the FDA studies came to the same conclusion.⁶⁰

It is, of course, much easier to get positive studies published, and very difficult to get negative studies published. So, while the investigators may have submitted the negative studies to journals, they may not have succeeded in getting them accepted for publication. This additional complicating factor does not necessarily reflect industry bias. The most selective journals publish 8% of all manuscripts submitted for review and even those with lower selectivity only publish up to about 30%, which means that 70% of manuscripts are rejected.⁶¹ Methodological criticism of industry studies is also frequent,

54. Peter Loftus, *Merck: See \$80 million Vioxx Settlement*, WALL ST. J., Aug. 3, 2009, at Health Section (noting also the 2007 \$4.85 billion Vioxx personal injury settlement).

55. Peter Loftus & Jonathan D. Rockoff, *Merck, Schering to Settle Cholesterol Lawsuits*, WALL ST. J., Aug. 6, 2009, at B4.

56. In re Prempro Products Liability Litigation, No. 4:03-CV-1507-WRW, 2009, 2010 WL 5058653 (E.D. Ark. July 24, 2009), available at <http://dida.library.ucsf.edu/lawsuits.jsp>. See also Duff Wilson, *Wyeth's use of medical ghostwriters questioned*, N. Y. TIMES, Dec. 12, 2008, available at <http://www.nytimes.com/2008/12/13/business/13wyeth.html>.

57. See *Southern Illinois Laborers' & Employers Health & Welfare Fund v. Pfizer Inc.*, Civ. A. No. 08 CV 5175 (KMW), slip op. at 2, (S.D.N.Y. Sept. 30, 2009). The lawsuit, filed as a class action by a third-party payer, was ultimately dismissed; see also, Aaron Smith, *Pfizer Sued Over Alleged Lipitor Side Effects*, CNN, June 8, 2006, for a similar action filed in 2006, available at <http://money.cnn.com/2006/06/08/news/companies/lipitor/>.

58. Bruce M. Psaty & Richard A. Kronmal, *Reporting Mortality Findings in Trials of Rosiglitazone for Alzheimer Disease or Cognitive Impairment: A Case Study Based on Documents From Rosiglitazone Litigation*, 299 JAMA 1813, 1816 (2008). See *Cona v. Merck*, 949 A.2d 223, 229, 277 (N.J. 2008); *McDarby v. Merck and Co.*, 949 A.2d 223, 229, 277 (N.J. 2008).

59. Rahul V. Shah et al., *Industry Support and Correlation to Study Outcome for Papers Published in Spine*, 30 SPINE 1099, 1101 (2005).

60. Erick H. Turner et al., *Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy*, 358 NEW ENG. J. MED. 252, 254-55 (2008).

61. ACCURATE COMMUNICATIONS FOR PUBLISHERS, AMERICAN MEDICAL ASSOCIATION, <http://www.accucoms.com/libraries/AMA.htm>. (last visited Nov. 26, 2010).

particularly for the overuse of placebos or the use of inferior comparative therapies.⁶² This is where the issue of study design dictated by the Food and Drug Administration (FDA) may be most important. If the product is eligible for FDA approval, the FDA may specify the comparators and the study design.⁶³ The industry sponsor has no control over this factor if it wants its product reviewed and approved.

In general phase IV studies, after approval by the FDA, have protocols that should be designed by the investigator (rather than its industry sponsor).⁶⁴ However, the sponsor may still be saddled with questions raised by the FDA at the time of review and approval that require further study, and may effectively result in the FDA dictating populations, comparators, study design or endpoints.

It is also sometimes the case that the protocols are set by the industry sponsor in ways that transform research studies into what are actually marketing studies by massaging the interpretation of clinical trial data to paint a more marketable picture. The criticism is that manufacturers sometimes report conclusions that are not entirely supported by the data.⁶⁵ For example, one study of industry-supported non-steroidal anti-inflammatory drug (NSAID) trials reportedly revealed consistent claims of superior efficacy and diminished toxicity, even though such claims were not supported or were incompletely supported by the trial data.⁶⁶ Indeed, a systematic review of the NSAID studies found that the drug being studied was always better than the comparator, resulting in all NSAIDs better than all other NSAIDs, which, of course, is impossible.⁶⁷ Notwithstanding some relatively few notorious matters such as this, the vast majority of studies, however funded, *are*, in fact, supported by the data.⁶⁸

Why would respected and accomplished scientists risk their credibility to present their findings in a more favorable light? Is it because they aspire to be prestigious, promoted, tenured and well compensated?⁶⁹ Do those who are funded by industry alter their findings more frequently than those sponsored

62. Benjamin Djulbegovic et al., *The Uncertainty Principle and Industry-Sponsored Research*, 356 LANCET 635, 637 (2000).

63. Alec B. O'Connor, *Building Comparative Efficacy and Tolerability Into the FDA Approval Process*, 303 JAMA 979, 979-80 (2010).

64. *Id.*

65. See generally R.A. Davidson, *Source Of Funding And Outcome Of Clinical Trials*, 1 J. GEN. INTERNAL MED. 155, 155-58 (1986).

66. Paula A. Rochon, et al. *A Study of Manufacturer-Supported Trials of Non-Steroidal Anti-Inflammatory Drugs in the Treatment of Arthritis*, 154 ARCHIVES INTERNAL MED. 157, 157-63 (1994).

67. See Igor Kissin, *The Development of New Analgesics Over the Past 50 Years: A Lack of Real Breakthrough Drugs*, 110 ANESTHESIA & ANALGESIA 780, 780-89 (2010).

68. J Lexchin, LA Bero, B Djulbegovic, O. Clark, *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*. 326 BMJ 1167, 1167-70 (2003).

69. Jerome P. Kassirer, *Financial Conflicts of Interest: An Unresolved Ethical Frontier*, 27 AM. J. L. & MED. 149, 157-59 (2001).

by private or governmental funders? Academic researchers are certainly “not immune to the bad judgment, bad luck, and disagreeable behavior that afflict all human endeavors.”⁷⁰ Indeed, Dr. John Eden expressed the particular burden of academic researchers in his admission to authoring a paper that had actually been written by Wyeth and a ghostwriter from DesignWrite, noting the “...pressure to ‘publish or perish.’”⁷¹ Although not all examples of misconduct are as clear, the “fine line” between statistical manipulation of the data and falsification of data to improve its importance may be thicker than some have argued.⁷² In many respects, this may indicate a need for revisiting and reworking the Bayh-Dole Act so as to set forth stricter rules and regulations that minimize the likelihood of running afoul of conflicts of interest. At the same time, academic institutions may need to clean house and foster a different reward system that does not encourage such activities as ghostwriting in the service of being published.

The National Office of Research Integrity (ORI) was established in 1993 by Congress to respond to allegations of scientific misconduct.⁷³ Despite ORI jurisdiction being limited to research supported by Public Health Service funds, its basic definition of scientific misconduct has been largely adopted by the private sector.⁷⁴ Fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results, is generally acknowledged as scientific misconduct.⁷⁵ Other activities that may constitute “research misconduct” are less well-defined.⁷⁶ The federal regulations that provide guidance are clear, however, that it is only such activities as making up data or results, changing or omitting data or results (such that the research is not accurately represented in the research record) and appropriation of another person’s ideas, processes, results, or words without giving appropriate credit that constitute research misconduct. Further, to find research misconduct, there must be a *significant* departure from accepted practices of the relevant research community and the misconduct must be committed intention-

70. Stossel, *supra* note 45, at 1063.

71. Heisel, *supra* note 46, at 1.

72. Dolores J. Lamb, *When the Quest for Truth Falts: The Issue of Scientific Misconduct*, 179 J. UROLOGY 11, 11-12 (2008).

73. National Institutes of Health Revitalization Act of 1993, Pub. L. No. 103-43 § 161 (codified as amended 42 U.S.C. § 289(b) (2000)).

74. 42 C.F.R. § 93.220 (2005). The Public Health Service unit includes the Agency for Healthcare Research and Quality, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Food and Drug Administration, Health Resources and Services Administration, Indian Health Service, National Institutes of Health, Substance Abuse and Mental Health Services Administration, and the offices of the Regional Health Administrators. See generally Chris B. Pascal, *The Office of Research Integrity: Experience and Authorities*, 35 HOFSTRA L. REV. 795 (2006); Lamb, *supra* note 72.

75. 42 C.F.R. 93.103.

76. Douglas L. Weed, *Preventing Scientific Misconduct*, 88 AM. J. PUB. HEALTH 125, 125-29 (1998).

ally, knowingly, or recklessly.⁷⁷ This invites a large number of unorthodox practices to slide under the radar.

In the absence of outright fraud, such as reporting data that is never collected, the suggestion that legitimate researchers can nevertheless “spin” research data to favor an industry product appears difficult to support in light of the current controls on the collection and reporting of data. FDA procedures require that it must be given *all* of the raw data and that it conduct its own review within its own structure and protocol (including conducting its own statistical analysis) – impervious to any sponsor influence.⁷⁸ Assuming blinded, randomized studies, local Principal Investigators (PIs) are generally unaware of their own results since they, like the patients, are blinded. They are only given data from all the sites after the data have been adjudicated and data lock has been accomplished followed by data analysis.⁷⁹ Thus, there appears to be little opportunity to “spin” data, absent actual fraud.

It is noteworthy that selective *publication* of positive research findings and even the statistical “massaging” of data (to the extent possible, in light of the vigilant oversight of the FDA) obtained from studies are largely absent from regulation. The Celebrex studies were only discovered through a review of FDA files that were reported as part of its oversight responsibilities. These criticisms, which are the most common concerning industry research, often do not rise to the level of research “misconduct,” and have been alleged in the medical literature for decades.⁸⁰ Of course, the issues are certainly not limited to industry-funded studies but are shared with prominent government agencies,⁸¹ cooperative groups⁸² and journal editors⁸³ alike. Indeed, the FDA itself has become a repository of unpublished randomized clinical trials.⁸⁴ Rather than withholding information or delaying publication, as had happened in the

77. 42 C.F.R. 93.104 (2005) (emphasis added).

78. Part 58-Good Laboratory Practice for Nonclinical Laboratory Studies, 21 C.F.R. § 58.

79. Weed, *supra* note 76. See also GUIDANCE FOR INDUSTRY: E2C CLINICAL SAFETY DATA MANAGEMENT: PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (1996), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073102.pdf>.

80. See, e.g. Robert J. Simes, *Publication Bias: The Case for an International Registry of Clinical Trials*, 4 J. CLINICAL ONCOLOGY 1529, 1529-41 (1986); David J. Slasburg, *The Religion of Statistics as Practiced in Medical Journals*, 39 AM. STAT. 220, 221-22 (1975); Jan P. Vandenbroucke, *Passive Smoking and Lung Cancer: A Publication Bias?*, 296 Brit. Med. J. 391, 391-92 (1988).

81. An-Wen Chan et. al., *Outcome Reporting Bias in Randomized Trials Funded by the Canadian Institutes of Health Research*, 171 CAN. MED. ASS'N. J. 735, 735-40 (2004).

82. Monika K. Krzyzanowska et al., *Factors Associated with Failure to Publish Large Randomized Trials Presented at an Oncology Meeting*, 290 J. AM. MED. ASS'N., 495, 495-501 (2003).

83. Alison Thorton & Peter Lee, *Publication Bias in Meta-analysis: Its Causes and Consequences*, 53 J. CLIN. EPIDEMIOLOGY 207, 207-08 (2000).

84. Derrick Bennett & Andrew Jull, *FDA: Untapped Source of Unpublished Trials*, 361 LANCET 1402, 1402-03 (2003).

past,⁸⁵ a more recent study found that industry sponsorship was a significant predictor of eventual publication, which may also be due to selective submission of positive studies or selective bias in the research.⁸⁶ The investigators must determine primary and key secondary results, and those definitions can lead to selective bias in the research.⁸⁷ Industry sponsored research was also found to be published faster than comparable studies with non-industry sponsors.⁸⁸ Indeed, in 2004, Merck committed itself to publishing the primary and key secondary results of its registered trials, regardless of trial outcome.⁸⁹ In its 2009 revision of its Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results, the Pharmaceutical Research and Manufacturers Association (PhRMA) committed itself to similar transparency.⁹⁰

V. RECOMMENDATIONS FOR ACADEMIC MEDICAL CENTERS CONFLICT OF INTEREST MANAGEMENT TO ADDRESS LEGITIMATE CONCERNS AND STILL BE CONSISTENT WITH THE LEGISLATIVE INTENT OF THE BAYH-DOLE ACT

In light of the legislative intent of the Bayh-Dole Act to facilitate productive collaborations between industry and academia, along with reported concerns about research integrity and full reporting of all studies and results, many academic medical centers are proceeding cautiously with their relationships with industry partners.⁹¹ To that end, most are developing comprehensive Conflict of Interest (COI) policies to address disclosure of industry relationships and limit faculty participation in activities that compromise their ability to speak candidly about industry products, research protocols and interpretation of results.⁹² In addition to setting forth such provisions in COI policies, academic medical centers can make further provisions for candor and integrity concerning faculty participation in research in their consulting agreements and sponsored research contracts, which are negotiated with industry partners. Specific recommendations are set forth below. Although

85. David Blumenthal et al., *Withholding Research Results in Academic Life Science: Evidence From a National Survey of Faculty*, 277 J. AM. MED. ASS'N 1224, 1224-28 (1997).

86. Krzyzanowska, et al., *supra* note 82.

87. *Id.*

88. *Id.*

89. MERCK, MERCK GUIDELINES FOR PUBLICATION OF CLINICAL TRIALS AND RELATED WORKS, available at http://www.merck.com/mrl/swf/clinical_trial_publication_guidelines.swf (last visited Sept. 1, 2009).

90. PHARMA, PRINCIPLES ON CONDUCT OF CLINICAL TRIALS AND COMMUNICATION OF CLINICAL TRIAL RESULTS, <http://www.clinicalstudyresults.org/primers/2004-06-30%201035.pdf> (last visited Sept. 1, 2009).

91. Stossel, *supra* note 45.

92. DANIEL R. LEVINSON, DEPARTMENT OF HEALTH & HUMAN SERVICES, OFFICE OF INSPECTOR GENERAL, HOW GRANTEEES MANAGE FINANCIAL CONFLICTS OF INTEREST IN RESEARCH FUNDED BY THE NATIONAL INSTITUTES OF HEALTH i, 2-3, 15 (2009), available at <http://oig.hhs.gov/oei/reports/oei-03-07-00700.pdf>.

some of these strategies are related primarily to marketing efforts, the continuum from product research to publication of manuscripts, to speaking about published results and ultimately to promotion and marketing of the products, makes it clear that conflict of interest COI policies, contractual consultant arrangements and negotiated sponsored research agreements must manage all phases of research and marketing of products. With the following provisions in place, the interests of the public can be protected from undue industry interference in research reporting, and the fruits of the Bayh-Dole Act can still be harvested.

Most COI policies now contain and should contain the following provisions:

1. Prohibition of faculty participation in research where industry or contract research organizations (CRO) ghostwrite the articles stemming from research;
2. Prohibition of faculty participation in industry-sponsored speaking, whether or not defined as a “Speakers’ Bureau,” where the content of the presentation is determined by the industry sponsor, the presentation of data is prepared by the industry sponsor or there is any other arrangement that indicates inappropriate control over information presented by the industry sponsor;
3. Limitations on faculty participation in continuing medical education to those programs that comply with standards set forth by the Accreditation Council for Continuing Medical Education (ACCME), whether or not the programs are actually accredited.

If not provided in the COI policy, academic medical centers may include the following additional provisions in their sponsored research contractual arrangements with industry partners to better protect the reporting and transparency of research results (building upon the Institute of Medicine’s 2009 Consensus Report on conflicts of interest)⁹³:

- A. In investigator-initiated, single-center sites, sponsored research agreements that require the Principal Investigator (PI) to have full participation in the design of the clinical trials, including blinding procedures, subject selection, dosing, aims, methods, endpoint selection and analysis of the data, to ensure the methods are free of undue industry influence.
- B. In single-center sites, sponsored research agreements that ensure the PI has access to, and control over, all trial data collection and interpretation.
- C. In multicenter trial sites, sponsored research agreements that ensure the data are controlled and reported to the FDA by a steering

93. INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMIES, CONFLICTS OF INTEREST IN MEDICAL RESEARCH, EDUCATION AND PRACTICE 2-3 (2009), *available at* <http://www.iom.edu/Reports/2009/Conflict-of-Interest-in-Medical-Research-Education-and-Practice.aspx>.

committee and/or safety monitoring committee that is independent of any industry sponsor.

- D. Sponsored research agreements that ensure the PI has a guaranteed right to submit the study for publication. Sponsors may be allowed reasonable pre-publication review but cannot insist on edits, including use of their own statistical analysis, or delay publication;
- E. Sponsored research agreements that prohibit industry sponsors from publishing competing articles concerning the investigator's research within a certain period of time specifically including reinterpretation of statistical analyses.
- F. Sponsored research agreements that limit industry sponsors' ability to prematurely terminate a study or suppress results solely for financial or public relations reasons.
- G. Sponsored research agreements that require clinical trials to be registered so that unfavorable as well as favorable primary and secondary results are not ignored and risk information is not distorted.

Finally, academic medical centers can urge their states to allow them to take the lead in devoting more outreach resources to "academic detailing" – unbiased, academic physicians providing practitioners with balanced and unbiased information about the costs, benefits, risks and effectiveness of various prescription products.⁹⁴ This source of reliable and authoritative information provides physicians with an alternative to pharmaceutical detailers for information that improves health outcomes for their patients.

94. Stephen B. Soumerai & Jerry Avorn, *Principles of Educational Outreach ('Academic Detailing') to Improve Clinical Decision Making*, 263 J. AM. MED. ASS'N 549, 549-56 (1990).