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Drug Development and the Public Health Mission: Collaborative Challenges at the FDA, NIH, and Academic Medical Centers

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In creating a regime of food and drug regulation, Roosevelt and Congress were establishing the principle that it was now the job of government not just to champion commerce but also to intervene when it got out of hand.¹

Given the pervasive concerns about the influence of industry over government, drug safety assessment might flourish better in a freestanding non-governmental organization.²

INTRODUCTION

Allegations of “coziness” between the U.S. Food and Drug Administration (FDA) and the pharmaceutical industry tend to accompany times of crisis at the agency. The opposing dynamics reflected in the quotes above are symptomatic of a longstanding struggle over the FDA’s relationship with the powerful industrial sectors it regulates. Less obvious are the layers of overlapping relationships that link the broader biomedical research community, the pharmaceutical industry, and the FDA.

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A recent confluence of events involving prescription drugs has once again triggered concerns that the FDA's regulatory culture has forced the Agency's public health mandate onto the back burner, favoring the interests of pharmaceutical manufacturers. The events in one way or another involve sensitive topics intimately linked to broader public health issues. For example, anxiety was provoked by, among other things, protracted discussions and perceived delays in controversial labeling changes for antidepressant drugs and a potential link to adolescent suicides; by a survey report from the Department of Health and Human Services Inspector General suggesting FDA scientists at times feel overwhelmed by application review timelines, and pressured to recommend approval of new drugs despite reservations about safety, effectiveness or quality; and most recently by a series of drug safety concerns linked to widely used prescription medications that suggested passivity and lapses in the FDA's oversight of marketed products. Proposals for an independent office

3. See FDA, Merck and Vioxx: Putting Patient Safety First?: Hearing Before the S. Comm. on Fin., 108th Cong. (2004) (opening statement of Sen. Chuck Grassley, Chairman, Sen. Comm. on Fin.) ("It also looks like the FDA allowed itself to be manipulated by Merck on labeling changes that became necessary after a review by Merck that's known as the VIGOR trial. . . . One of my concerns is that the FDA has a relationship with drug companies that is too cozy."); Gardiner Harris, Drug Regulators are Trying to Quash Study, Senator Says, N.Y. TIMES, Feb. 12, 2005, at A13; Kathleen Kerr, New FDA Board Has Its Critics (Feb. 16, 2005) ("FDA critics questioned whether the new Drug Safety Oversight Board would be independent and have real clout, with some charging the agency remains too close to industry."), at http://www.newsday.com.


of drug safety, as well as more severe criminal penalties for concealment of adverse drug events, were once again on the table. On April 27, 2005, Senators Dodd and Grassley introduced a bill, The Food and Drug Administration Safety Act of 2005, that would create a new safety center within FDA, increase surveillance of medical devices, provide additional civil penalty authority, and grant authority to restrict direct to consumer promotion of newly approved drugs.

The high profile nature of the controversies and their occurrence over a relatively concentrated period served to reinvigorate criticisms of the FDA's regulatory culture.

7. See Pharmaceutical Research and Manufacturers Accountability Act of 2005, H.R. 870, 109th Cong. (2005) ("To amend the Federal Food, Drug, and Cosmetic Act to provide enhanced criminal penalties for certain violations of the Act involving knowing concealment of evidence of a serious adverse drug experience, and for other purposes."); Avorn, supra note 2, at 373 (suggesting an allocation of functions that would separate the regulating agency from the organization that investigates questions of safety, similar to the model seen in the separation of the Federal Aviation Administration (the regulator) and the National Transportation Safety Board (the safety investigator)). See generally Brian L. Strom, Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions, 292 JAMA 2643 (Dec. 1, 2004). The FDA responded by announcing the creation of a new Drug Safety Oversight Board, which will consist of medical experts from government agencies appointed by the FDA Commissioner. See CTR. FOR DRUG EVALUATION AND RESEARCH, FDA, MANUAL OF POLICIES AND PROCEDURES (May 4, 2005), available at http://www.fda.gov/cedt/mapp/4151-3.pdf; Memorandum from Senator Chuck Grassley, Chairman, United States Senate Committee on Finance (Apr. 7, 2005), available at http://finance.senate.gov/press/Gpress/2005/prg040705.pdf. The Board will be part of the FDA's Center for Drug Evaluation and Research. See id.

Questions surfaced from consumer advocates and members of Congress about the essential nature of the agency-industry relationship, reflecting a nagging sense of unease that the FDA had become too entangled in the interests of its regulated constituencies, and in the process had short-changed public health interests. FDA officials themselves have queried whether their independence may have, in some way, been compromised by the need to work more closely with industry.

Given the nature of the concerns and the inherent implication that the FDA-industry alliance has been tainted in some way, it seems fair to ask what might constitute "coziness" in the context of the FDA's work, and what institutional parameters guide interactions between the FDA and the industrial sectors over which the agency exercises broad regulatory authority. These questions are not new. Since the earliest days of federal drug regulation in the U.S., similar inquiries have emerged as part of what has been described as a "virtual tidal wave" of 


10. See Susan Okie, What Ails the FDA? 352 N. ENG. J. MED. 1063 (Mar. 17, 2005); Jim Drinkard, Label Quibble Helped Cause Vioxx Lapse, USA TODAY, Mar. 2, 2005, at 8D (reporting on the congressional testimony of Sandra Kweder, Deputy Director, Office of New Drugs, FDA, before the U.S. Senate Committee on Health, Education, Labor, and Pensions, Mar. 1, 2005, in which she indicated there was a "lapse" in the system that prevented prescribing physicians from promptly receiving notice of serious adverse drug reactions); Murray M. Lumpkin, Accelerating Drug Development: Regulatory Initiatives in the USA, Presentation at the Drug Information Association (DIA) Euromeeting in Nice, France (Mar. 9, 2000), available at http://www.fda.gov/cder/present/dianice2000/dianice1/. Among other questions posed at the DIA Euromeeting by Dr. Lumpkin, then Deputy Center Director, FDA's Center for Drug Evaluation and Research, were the following: "Is FDA a tax-payer funded drug development consulting firm?" and "At what point has FDA been co-opted into the development program such that it affects FDA's ability to be objective in its regulatory oversight decisions at later point in time – like when the NDA is submitted for review?" Lumpkin, supra, at 14-15.

11. Peter Barton Hutt, Progress in New Drug Regulation, 5 CLINICAL RES. PRACT. & DRUG REGULATORY REGULATION 307, 310 (1987). The article describes six broad categories of events or concerns effectively triggering the inquiries:
investigations and recommendations related to the agency's work. The FDA has been called "the most closely watched federal regulatory agency," and its regulatory activities "the most thoroughly investigated and studied program of government regulation in history." The FDA-industry dynamic has figured prominently in a number of these inquiries, in some instances reflecting concerns that the agency was dominated by industry, and in others, that the agency was insufficiently cooperative and interactive with industry.

The FDA of 2005, however, is a very different enterprise than it was even fifteen or twenty years ago. Cumulatively over the past two decades, the agency has been required to respond to an unrelenting series of challenges: the emergence of AIDS and bioterrorism; the increased volume and complexity of an expanding workload; the need to develop regulatory pathways for novel technologies emerging in the biosciences, and by drug safety; ethical issues; FDA administration and resources; advisory committees; the FDA review process; and competitiveness issues. See id.


additional statutory obligations that have placed rigorous demands on its resources. The new programs are infused with mandates and initiatives that invite, and at times require, a new level of partnership between FDA and industry. The inherent complexities of this collaborative enterprise have become more obvious and potentially problematic as the agency has implemented new statutory programs, including the prescription drug user fee scheme, and a range of other initiatives designed to speed the development and review of prescription drugs. These changes in the late 1980s and 1990s, together with prompts from Congress for the FDA and pharmaceutical firms to work more closely, may have created an inherently weaker FDA, and as a consequence, new public health problems.

The process of drug development is multi-tiered, with a host of actors influencing the outcome at various stages. The work product contained in a new drug application ultimately received by the FDA has numerous sources, many of them overlapping in intriguing, often indirect, alliances. As the FDA has changed over the past twenty-five years, so have members of the broader biomedical research community. Much of the initial development of new drug therapies takes place at the National Institutes of Health (NIH) and academic medical centers. Industry collaboration with researchers in the development process
also has been the result of a changing statutory landscape during this period, a time notable for its great productivity in terms of new therapies, patents, and revenue sources. More recently, however, there has been concern that collaboration with industry has morphed into its own form of coziness, and that the risks to scientific objectivity, data integrity, and patient safety threaten to undermine the public health mission of NIH, academic medical centers, and the FDA, which relies on their work.

This paper examines the overlapping and potentially conflicting roles assumed by the FDA, FDA Advisory Committee members, the pharmaceutical industry, and researchers at NIH and academic medical centers responsible for the laboratory (pre-clinical) and clinical research that constitute the foundation of marketing applications submitted to the FDA. Part I reviews several of the institutional forces and statutory initiatives that compel FDA-industry alliances and render ongoing dialogue an essential ingredient of the process, but which may simultaneously contribute to a blurring of roles. Part I concludes with a discussion of the influence exerted indirectly by drug companies through the FDA Advisory Committee system, as the conflict of interest of panel members continues to threaten the credibility of committee recommendations. Part II moves to the role conflicts that arise when scientists and their institutions have an entrepreneurial stake in therapy development. The nature of collaborative interests among NIH, its scientists and industry is discussed in the context of recent public scrutiny regarding scientists' financial remuneration by industry, along with the newly issued regulations addressing these interests. Part II then examines similar relationships that researchers in academic medicine and their institutions have with the pharmaceutical industry, as well as current and proposed methods for managing conflicts of interest.
A. Regulatory Culture

Like all modern administrative agencies, the FDA exists within a statutory environment. Its work is circumscribed by the legislative authorization granted by Congress in the FDA's organic statute, the Federal Food, Drug, Cosmetic Act (the FFDCA), other general laws applicable to administrative actions, regulations promulgated under those statutes, guidance documents, and internal programs and policies. Using the language and constructs of the statute creatively, the agency has adapted to the enormous changes in science, health policy, and technology.

A useful starting point in thinking about the work of the FDA is the core directive setting out the Agency's mission. Codified in 1997, the mission statement requires the agency to promote and protect the public health through prompt and efficient review of clinical research, and by ensuring that marketed products meet statutory and regulatory standards. The mission directive and the common sense demands of the process anticipate collaboration at the most fundamental levels of drug development. When appropriate, the agency is required to consult and cooperate with external groups, including manufacturers. FDA officials have promoted this concept of partnership with industry. The precise parameters of

25. See The Food and Drug Administration Modernization Act § 406 (amending the FFDCA to integrate an agency mission statement for the first time in the history of the FDA).
26. See id.
27. See id.
the anticipated collaboration or working relationship inevitably shift in response to pressures from Congress, industry, and consumer groups. Given the essential nature of the joint undertakings, what safeguards or firewalls, other than basic ethical guidelines, disclosure of financial interests, and professional standards, are in place to protect the agency's core public health mission and the integrity of the process?29

Empirical studies have examined bureaucratic decision-making in regulatory agencies, but offer little consensus on the key influencing factors.30 However, in the case of the FDA, the science-based nature of the work clearly is a powerful factor shaping its operational, policy, and procedural mechanisms.31 The observation that information is the life-blood of regulatory policy has intriguing implications in the context of the FDA.32 The complexity of

29. See 5 C.F.R. §§ 2635.101-.902 (2005) (establishing uniform rules of ethical conduct applicable to all executive branch personnel); 5 C.F.R. § 5501.101 (2005) (establishing supplemental standards of ethical conduct and financial disclosure requirements for employees of the Department of Health and Human Services, revising the definition of “significantly regulated organization” and requiring an annual reporting by all employees of financial and other information concerning outside activities and a supplemental disclosure by all FDA and NIH employees with respect to prohibited financial interests); 21 C.F.R. § 19 (2004) (establishing standards of conduct and conflicts of interest applicable to all FDA employees).

30. See Mary Olson, Substitution in Regulatory Agencies: FDA Enforcement Alternatives, 12 J.L. ECON. & ORG. 376, 377 (1996) (examining the impact on FDA enforcement actions of feedback from external groups, including Congress, consumers, and industry); William F. Pederson, Contracting with the Regulated for Better Regulation, 53 ADMIN. L. REV. 1067 (2001) (advocating the use of regulatory reform contracts to avoid the regulatory dysfunction that results from the failure of agencies to distinguish between the ends a regulatory program seeks to achieve and the means used to achieve them); Joseph P. Tomain & Sidney A. Shapiro, Analyzing Government Regulation, 49 ADMIN. L. REV. 377, 391 (1997) (noting that although an agency's capacity to act is affected by its institutional framework and legal constraints, non-legal factors such as bureaucratic culture and agency resources come into play). The authors advocate a model that balances policy, political and institutional factors as opposed to a public choice model in which regulatory decisions serve the interests of the regulated industries.


32. See Cary Coglianese et al., Seeking Truth for Power: Informational
the FDA's job is heightened by the agency's dependence on scientific data and information provided predominantly by the companies it regulates. Along with this dependency comes the potential for the manipulation of data and for companies to withhold or minimize negative information about their drugs.\textsuperscript{33} The ability of FDA officials to detect problematic data and subtle biases has been questioned for some time.\textsuperscript{34} The notion of agency "capture" is never far from the surface.\textsuperscript{35} The partnership construct carries with it an implication of influence and bias, the risk of regulatory capture, and results in regulatory policy that favors the interest of industry.\textsuperscript{36} Coglianese and his colleagues argue that the push for increased transparency in the regulatory process results in an information deficit due to industry's reticence to share information in a more open fashion.\textsuperscript{37} They argue that although transparency may be one way to combat the dangers of cozy relationships between regulators and industry, it also makes it more difficult for agencies to most effectively work with individual

\textit{Strategy and Regulatory Policymaking}, 89 MINN. L. REV. 277 (noting that regulators need detailed and accurate information about the operations of private business enterprises to understand the scope and cause of regulatory problems, and to craft effective solutions to them). The authors also point out that the regulated firms have an incentive to share favorable, self-serving information. \textit{See id.} at 278-79.

33. \textit{See} Thomas O. McGarity, \textit{Beyond Buckman: Wrongful Manipulation of the Regulatory Process in the Law of Torts}, 41 WASHBURN L.J. 549, 564 (2002). "Fraud on the FDA" is a litigation theory argued in state courts alleging FDA approval had been granted on the basis of misleading data filed by the sponsoring company, in the absence of which no FDA approval would have been forthcoming. \textit{See} Buckman Co. v. Plaintiff's Legal Comm., 531 U.S. 341 (2001), in which the Supreme Court ruled that private FDA fraud allegations in state tort litigation conflicted with the FDA's regulatory authority to police compliance. \textit{See also} James M. Beck, 'Fraud on the FDA' Liability?, \textit{UPDATE FOOD & DRUG L. REG. & EDUC.} 33 (Jan./Feb. 2004); Bean, \textit{supra} note 27, at 892 (providing case studies of two drugs (Rezulin and Fen-Phen) approved on the basis of misinformation and manipulation of FDA officials). Often the fraud remains undetected until post-marketing problems emerge. \textit{Id.} at 891.


35. McGarity, \textit{supra} note 33, at 564.

36. \textit{See} Coglianese, \textit{supra} note 32 (arguing that the push for increased transparency in the regulatory process results in an information deficit due to industry's reticence to share information in a more open fashion).

37. \textit{Id.} at 334.
companies, to exploit asymmetries of interest, and to engage in informal interactions, which may be the source of the most salient information. Given the informational dependence, interactions and collaborations at various levels of drug development may result in biases and informational deficits that are further exacerbated by initiatives to move drugs to market faster.

B. Risk Privatization: Initiatives to Speed Drugs to Market

Beginning in the mid-1980s, a period dominated by the initial confrontation with AIDS and by the need to respond to demands from advocates for AIDS patients, the FDA formally implemented two sets of initiatives to ease and expand access to certain drugs for the treatment of serious and life-threatening conditions. The AIDS crisis essentially gave the FDA political license to move in new directions, with Congress directing the FDA to develop a partnership with pharmaceutical companies to expedite the review of AIDS drugs. Responding to what one FDA official referred to as "a strong sense of hurry-up," drug development protocols that deviated from traditional practices were designed not only for AIDS therapies, but also for a range of drugs for life threatening or seriously

38. Id. at 341. The authors point out that "virtually no analytic attention has been paid to the way regulators play the regulatory game to overcome their informational disadvantage." See Coglianese, supra note 32, at 342.

39. See generally, JACOB S. HACKER, THE DIVIDED WELFARE STATE 23, 36, 48 (2002). Risk privatization is a concept used by Hacker in the economic context to refer to the gradual erosion of protective government programs and the simultaneous decline in the economic vitality of middle income individuals due in part to longer periods of unemployment, more problematic access to health insurance, and more vulnerable pensions. See id. The term has been adopted here to refer to the erosion of the FDA safety net, and the transfer to patients of greater risk and uncertainty about the safety and efficacy of new drugs.


41. Bean, supra note 20, at 881.

The regulatory schemes represent the emergence of an important historical phase in drug development in the United States. Both are characterized by earlier and more intense collaboration between FDA and industry, and by marked privatization of drug-associated risk. The end product of an abbreviated development period is a less well-developed safety and effectiveness profile, and a more uncertain risk-benefit analysis that ultimately shifts a greater degree of risk to seriously ill patients. In fact, it has been argued that as a result of the expedited processes, political influence, and a too-cozy relationship between the FDA and corporations, a new public health crisis has been created.

The first set of initiatives are those that provide for the distribution of certain investigational drugs outside of, but concurrent with, traditional clinical trial protocols (such as the treatment IND and parallel track programs). The intent reflects a treatment-research duality to make promising investigational drugs available to patients for treatment purposes earlier in the development process, and to obtain additional data on the drug's safety and effectiveness. Although the practice of releasing investigational drugs for treatment purposes was not new in 1987, the programs represented an expansion and

43. See Sheila R. Shulman, Maria J. Wood-Armany, Accelerating Access to Cancer Drugs, 2 J. BIOLaw & BUSINESS 38 (1999). In 1996, after a decade in which the regulatory focus favored AIDS drugs, the FDA designed an initiative ("Reinventing the Regulation of Cancer Drugs") specifically directed toward early access and accelerated approval for investigational cancer therapies. See id.

44. See Shulman, supra note 43, at 503.

45. See generally HACKER, supra note 39, at 36, 48.

46. See Bean, supra note 20, at 886 (asserting that the traditional FDA approval process, while slower was more effective at delivering safer medicines to the public).


49. Shulman, supra note 43, at 505.
codification of existing procedures. The second set of initiatives provides mechanisms to expedite both drug development (Subpart E procedures) and FDA review (Accelerated Approval). The former provides for the telescoping of phases two and three of clinical development; the latter permits FDA marketing approval on the basis of a change in a surrogate endpoint, such as a blood cell count or tumor reduction, representing the sharpest deviation from the evidentiary requirements for FDA marketing approval. To further flesh out a drug's portfolio, post-marketing or phase four studies to validate the surrogate or clinical endpoints may be requested at the time of FDA approval. Although failure to comply with this request may result in the expedited withdrawal of the drug from the market, the FDA has not exercised its discretion to do so even though the studies are more often not completed.

Major amendments to the FDCA in 1997 codified the treatment investigational (IND) expanded access program, and the accelerated (fast track) approval

53. See FFDCA § 505(d) (establishing the evidentiary standard for FDA approval of prescription drugs to require substantial evidence from "adequate and well-controlled" clinical trials that the drug will have the effect it is represented to have). The safety standard is satisfied by the conduct of "adequate tests by all methods reasonably applicable" to show the drug is safe for the intended use. Id.
55. See id.
initiative. For drugs designated as fast track products, ongoing dialogue, protocol review, and frequent meetings are intrinsic to the process. Although industry-FDA dialogue has become a more formalized feature of the drug development process generally, the joint FDA-industry investment in fast track drug development calls for intensive contact through meetings and written communications with the FDA reviewing division. The goal here is to improve the efficiency of preclinical and clinical development, and to achieve early agreement on the design of the major clinical efficacy studies needed to support approval. However, timing expectations, a critical variable in this process, together with the joint agency-industry development commitment for fast track drugs, hold the potential for not only a shift in the relationship equilibrium between FDA and industry, but also for investment bias and a more profound informational deficit.

The fragility of the new regulatory pathways recently became evident following problematic events with two drugs approved under the accelerated approval regulations. Tysabri, a drug for the treatment of multiple sclerosis was withdrawn after only three months on the market, following the deaths of two patients from a rare brain

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59. Fast tracking is a development pathway designed to ease and expedite the development and marketing of drugs intended for the treatment of serious or life-threatening conditions for which therapeutic agents are nonexistent or, if available, may be less than optimally effective. FFDCA § 506, 21 U.S.C. § 356 (2005).


62. See FDA PRESS RELEASE GUIDANCE, supra note 60.

63. See id.
infection. Additionally, in post-approval studies, Iressa, a drug for small-cell lung cancer, failed to demonstrate an ability to prolong survival rates in patients when compared with a placebo. The signal here is that it may be time for Congress and the agency to reassess the shift in FDA operational culture and norms that have stretched traditional evidentiary standards for approval. For drugs lacking confirmatory evidence of a clinical benefit—an initial feature of most drugs approved under accelerated approval or the fast-track program—additional post-approval safeguards may be needed if these expedited pathways are to remain among the available regulatory options.

C. Quid Pro Quo: User Fees and FDA Performance Goals

Discussions of coziness between the FDA and the pharmaceutical industry often “follow the money.” Under the authority of The Prescription Drug User Fee Act of 1992 (PDUFA I), checks for substantial sums, representing statutorily imposed user fees, must accompany marketing applications submitted to the FDA by drug manufacturers. Drug user fees will pump $1.2 billion into

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65. See Press Release, FDA, FDA Statement on Iressa (Dec. 17, 2004). Iressa was approved on the basis of data from small clinical trials without placebo controls showing the drug had an effect on a surrogate endpoint—tumor shrinkage. Id. In ten percent of patients, tumors decreased in size. Id. The post-marketing study was done to investigate whether the drug actually prolonged life. Id.


the agency over the five year period from 2002 to 2007.68 Some worry that what essentially amounts to payment for FDA services has been accompanied by a commensurate increase in the influence industry exerts on agency procedures and policies and by a decline in the agency's objectivity and independence.69

Authority for the imposition of user fees is found in Title V of the Independent Offices Appropriation Act of 1952,70 permitting a federal agency to charge for services it provides when those services confer a special benefit on an identifiable recipient. The United States is not unique in shifting a portion of the cost of the drug approval process to the regulated industry. The Medicine Control Agency in the United Kingdom has levied user fees since the early 1980s, and since April 1989 has derived all of its funding from this source.71 In January 1995, the European Parliament approved regulations establishing the structure and amount of fees to be paid by companies seeking marketing authorization from the European Medicines Evaluation Agency.72 The following year, Canada, through its Drug Directorate, implemented a cost-recovery user fee plan.73

PDUFA I, signed into law by former President George H. W. Bush on October 29, 1992, introduced a new dynamic into the FDA process and signaled the start of an unprecedented phase in the history of the FDA.74 The 1992 collection of user fees for certain animal drug applications, certain animal drug products, manufacturing establishments, and investigational animal drug submissions.


72. Id.


74. Shulman, supra note 71, at 122.
legislation authorized an initial five-year program of user fees; Congress subsequently reauthorized the legislative scheme in 1997 (PDUFA II)\textsuperscript{75} and 2002 (PDUFA III),\textsuperscript{76} for additional five-year terms. Three categories of fees are assessed: application, establishment, and product. The total revenue to be collected for each of the three fee categories is stipulated by statute; however, an annual adjustment is made to account for inflation and workload based on the estimated number of applications anticipated during the relative fiscal period.\textsuperscript{77} Over the thirteen years since the implementation of the program, user fee revenues have increased by more than 700%. In Fiscal Year (FY) 1993, prescription drug user fees generated $36 million;\textsuperscript{78} the anticipated revenue for 2005 totals $274,377,607\textsuperscript{79} and the 2006 FDA budget proposal estimates $382 million of its $1.9 billion budget to come from the same user fee source.\textsuperscript{80} The application fee, by far the most significant component of the three categories of fees, has risen from $100,000 in FY 1993 to $672,000 in 2005.\textsuperscript{81}

A quid pro quo arrangement was key to the drug companies buy-in on the user fee package. The result forced a concentration of agency resources on faster drug reviews, with no parallel increase in post-marketing oversight.\textsuperscript{82} In 1992, following lengthy negotiations between the FDA, Congress, and the pharmaceutical and biotechnology industries, an essential agreement was forged that

\textsuperscript{75} See The FDA Modernization Act of 1997.


\textsuperscript{81} Id.

\textsuperscript{82} Avorn, supra note 2, at 93. See also, Editorial, Half a Step on Drug Safety, N.Y. TIMES, Feb. 17, 2005, at A26.
overcame industry's longstanding resistance to a user fee program. Several factors were critical: first, the FDA signaled a willingness to link user fees to a set of performance goals that initially involved dedicating the funds to improving the efficiency of the FDA review and approval process and, among other things, hiring some six-hundred new review staff; and second, the fees would be added to existing FDA appropriations rather than replacing them. The performance goals, which targeted issues of longstanding concern to industry, including application review times, backlogged overdue applications, and certain organizational and management issues, were developed in consultation with and received the endorsement of the pharmaceutical industry.\(^8\) Each of the subsequent user fee reauthorizations had its own set of quid pro quo FDA performance targets. In 1997, the PDUFA II goals shifted from the FDA review and approval phase to the clinical development phase, implementing collaborative strategies that included requirements for more formal dialogue and written agreements between industry and FDA reviewers.

In 2002, PDUFA III goals continued to target FDA review times for original and resubmitted applications.\(^8\) Other performance targets stipulate specific procedures and timelines for meetings between FDA officials and company representatives and for major dispute resolution. Two pilot programs have been agreed to involving Fast Track drugs or biologics.\(^8\) In one such project, the FDA may enter into an agreement with the company sponsor to initiate a formal program of frequent scientific feedback and interactions regarding the development of the drug. This could take the form of regular meetings between the FDA and company

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85. Section 506 of the FFDCA authorizes designation of drug or biologic as a Fast Track product when it is intended to treat a serious or life-threatening condition for which no effective therapeutic agent exists. FFDCA, 21 U.S.C. § 356 (2005).
representatives, and regular written feedback on development plans and clinical protocols.

The quid pro quo arrangement of user fees in exchange for FDA commitments to speed the drug development and review phases generally has been applauded. However, some twelve years and two congressional reauthorizations later, some might ask, applauded by whom? Certainly, the agency has met its review commitments. In 2003, the median time to market approval for priority-rated drugs was 6.7 months compared to 14.9 months in 1993.86 For standard-rated drugs, approval times fell from 27.2 months in 1993 to 15.9 months in 2002.87 The months saved translate into a longer effective patent life and increased revenues for the sponsoring companies. Although the FDA has hired hundreds of additional review staff and has been applauded for its greater efficiency, the downside of the review juggernaut may now be surfacing. Hints of a frenetic atmosphere in which safety considerations may be shortchanged were reported by the General Accounting Office (GAO) in 2002.88 The GAO also reported a resource shift away from other activities including post-marketing surveillance.89 An aura in which the demands and needs of industry as "the customer" threatens to cloud the agency's work.90 In addition, the intersection of the fast-track and user fee initiatives means that for priority-rated fast-track drugs, the FDA review time must meet the abbreviated user fee goal of six months. With a truncated development

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86. FDA's Center for Biologics Evaluation and Research categorizes drugs to be reviewed on the basis of therapeutic value. FDA, From Test Tube to Patient: Improving Health Through Human Drugs (1999), available at http://www.fda.gov/cder/about/whatwedo/testtube-full.pdf. Those allocated to priority status offer significant therapeutic benefit over existing therapies; those with a standard rating offer little or no therapeutic value over currently available drugs. Id. at 31.


89. See id.

90. See Okie, supra note 9, at 1064.
period, less than certain outcome measures for efficacy, diminished time for the emergence of safety issues, and pressures to meet user fee performance goals, FDA reviewers may be more vulnerable to and disadvantaged by a greater than usual information deficit and by a potentially bias-inducing collaborative investment with industry.

D. "Innovation or Stagnation:” Critical Path Analysis

An additional collaborative initiative involving the FDA, industry, and academia was announced by the FDA in March 2004. Termed “critical path” analysis, the new partnership is a response to perceived roadblocks in the product development process, manifest by a “slowdown” in innovative new drug, biologic, and medical device applications, or by what has been referred to as “sputtering” biomedical innovation in the United States. This dismal outlook is attributed to three factors: the complexity of novel drug development; the trend toward company mergers resulting in the abandonment of some drug development projects; and out-dated regulatory standards. The FDA has highlighted a perceived disconnect between the highly innovative work in the basic sciences and the application of these new scientific principles to the technology development process. At issue is the relevance and utility of traditional mechanisms of drug development, which have changed little over the past decades, within the context of emerging, novel fields such as gene therapy, bioinformatics, the development of predictive biomarkers and new vaccines. The goal here is the development of a new “product development toolkit” to eliminate or reduce the hazards that cause drugs to fail FDA standards, as well as to stimulate innovation in the biomedical sciences.

91. See generally INNOVATION AND STAGNATION, supra note 61.
92. Id.; see also Usdin, supra note 68.
94. Id.
95. See INNOVATION OR STAGNATION, supra note 61, at 7, 9, 11, 13.
This is not an entirely new role for the FDA, nor is it inconsistent with the agency’s mission to promote the public health; it does, however, anticipate intense information sharing among the agency, industry, and academic partners to identify problematic points in the “critical path,” and to design adaptive tools. It heightens FDA’s involvement in advancing innovation, and expands its collaborative efforts to include the most fundamental levels of drug development. The overlapping public health interests of the key parties are obvious. However, for industry, a successful outcome of the process suggests considerable benefit in terms of time and R & D investment. One study has estimated that the critical path initiative may reduce drug development times from fifteen years to five, saving nearly $500 billion in drug development costs.

Regardless of the universally shared public health goals of the critical path initiative, it is reasonable to anticipate that the traditional complexities and nuances inherent in regulator–industry collaborations will emerge here as well. Information exchange will be central to achieving the purposes of the program. The FDA will need industry participants who are forthcoming with detailed and accurate information to understand the nature and source of development problems, and to craft effective rules and policies in response. The process would seem to call for a level of transparency that could challenge industry participation. As Coglianese and colleagues have pointed out, the best source of information about the feasibility of different technologies is the firms the agency regulates. The potential exists for proprietary interests to infringe, effectively hindering or reshaping the conversation to suit the parameters established by the regulated firms.

96. See Raymond L. Woosley & Glenn Rice, A New System for Moving Drugs to Market, 21 ISSUES IN SCI. AND TECH. 63, 65 (Winter 2005).


98. Coglianese, supra note 34, at 278.

99. Id.
E. Conflicts-of-Interest and FDA Advisory Boards

FDA's reliance on an agency-wide system of expert advisory committees has been traced back to a precedent established in 1908 with the appointment of the Referee Board, made up of leading scientists of that era.\(^\text{100}\) As the volume and complexity of the agency's work have increased, so too has its reliance on the advisory function of the committees.\(^\text{101}\) These scientific advisory panels, now an integral part of the FDA process, are generally perceived as broadening the agency's access to specific areas of expertise, while at the same time enhancing the stature of the FDA's decisions.\(^\text{102}\) Currently, there are twenty-one scientific advisory boards, organized according to specific therapeutic categories, that may be convened by either the FDA's Center for Drug Evaluation and Research (sixteen)\(^\text{103}\) or the Center for Biologics Evaluation and Research (five),\(^\text{104}\) to consider and make recommendations on a broad range of issues related to drug development, safety, and approval.

In 1997, Congress removed FDA's discretion with respect to the use, formation, and makeup of Advisory Boards by mandating a role for the Committees, setting out member qualifications and requirements for committee diversity through the inclusion of consumer and industry representation.\(^\text{105}\) The statute also addressed a seemingly intransigent problem by requiring public disclosure of all conflicts of interest members have with respect to the specific questions assigned by the FDA, and mandating

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100. See Peter B. Hutt, The Transformation of United States Food and Drug Law, Address at the Centennial Meeting of the Association of Food and Drug Officials (June 16, 1996).


102. Hutt, supra note 100, at 91.


105. See Food and Drug Modernization Act of 1997 (codified as amended at 21 U.S.C. § 355 (2005)). The statute also requires education and training of committee members, and sets out a timeline for the FDA's response to Advisory Board recommendations. Id.
recusal in those instances where committee members or their immediate families may gain financially as a result of committee recommendations.\textsuperscript{106}

The conflicts problem may be attributable, in part, to the experiential statutory requirements for panel membership. Individuals must be "qualified by training and experience to evaluate the safety and effectiveness" of the class of drugs to be considered by the committee, and "possess skill and experience in the development, manufacture, or utilization" of those drugs.\textsuperscript{107} Not surprisingly, many of those who meet these qualifications have former or current ties to pharmaceutical firms as consultants, expert witnesses, or clinical trial investigators, or they hold stock in either the company whose product is under consideration or in a competitor's company.\textsuperscript{108} In a 2003 survey of advisory board members and individual attendees at board meetings, eighty-eight percent agreed that some conflict of interest among panel members was unavoidable to ensure access to the best expertise in the field.\textsuperscript{109} FDA also has argued that the pool of individuals from which to draw the requisite specialized knowledge is unavoidably similar to that called upon by industry, leaving little choice but to select those with dual roles. Others disagree: "It defies credulity to suggest that this large country does not contain enough highly qualified scientists and clinicians to serve as totally independent arbiters of the scientific questions posed to advisory panels."\textsuperscript{110}

Waiver of conflicts is an option under section 505(n)(4) of the FDCA, and 18 U.S.C. § 208 (Acts Affecting a Personal

\textsuperscript{106} Id. (codified as amended at 21 U.S.C. § 355 (n)(4) (2005)).

\textsuperscript{107} Id. § 505(n)(3)(a).

\textsuperscript{108} See Elizabeth R. Glode, Advising Under the Influence?: Conflicts of Interest Among FDA Advisory Committee Members, 57 FOOD & DRUG L.J. 293, 294 (2002) (noting that a decrease in government funding for medical research makes scientists more likely to rely on industry support).


\textsuperscript{110} Letter from Merrill Goozner, Center for Science in the Public Interest, to Dr. Lester Crawford, Acting Commissioner, Food and Drug Administration, (Mar. 10, 2005), at http://www.cspinet.org/new/200503101.html.
Financial Interest, applicable to all federal government employees) when the expertise of the committee member is deemed essential to the committee’s deliberations.\textsuperscript{111} Waiver must be accompanied by disclosure of the conflict when the committee deliberations are product specific. In a Draft Guidance published in January 2002, FDA sets out a new policy governing disclosure of the nature and magnitude of a conflict of interest that has been waived under those circumstances.\textsuperscript{112}

FDA’s attempts to more effectively regulate the conflicts issue continue to reveal shortcomings. Most recently, twelve consumer groups, including the Center for Science in the Public Interest, zeroed in on the conflict of interest matter in correspondence to Dr. Lester Crawford, Acting FDA Commissioner and the President’s nominee to assume the post permanently. The letter, dated March 10, 2005, requested closer scrutiny of FDA Advisory Committee members and their links to companies whose products are the subject of committee deliberations.\textsuperscript{113} The letter,

\textsuperscript{111} Id. A waiver is expressly prohibited when a committee member’s scientific work is to be considered. The granting of a waiver must be accompanied by public disclosure of the conflict. The extent of disclosure is the subject of a Draft Guidance issued by the FDA in February, 2002. See U.S. FOOD AND DRUG ADMIN., DRAFT GUIDANCE ON DISCLOSURE OF CONFLICT-OF-INTEREST FOR SPECIAL GOVERNMENT EMPLOYEES PARTICIPATING IN FDA PRODUCT SPECIFIC ADVISORY COMMITTEES, (Jan. 2002), available at http://www.fda.gov/oc/guidance/advisorycommittee.html.

\textsuperscript{112} See U.S. FOOD AND DRUG ADMIN., supra note 111. Details of the nature and magnitude of the conflict that has been waived are required to be disclosed in the form of a declaration read into the record prior to the advisory committee meeting. See id. The information disclosed should adequately enable a reasonable person to understand the nature of the conflict and the degree to which it could be expected to influence the recommendations the panel members will make. See id.

\textsuperscript{113} See Letter from Merrill Goozner to Dr. Lester Crawford, supra note 110. The letter proposed six specific measures to restore “fairness and credibility” to Advisory Committee deliberations including: prohibiting members with relevant conflicts of interest from serving as panel members and end the practice of granting waivers that permit conflicted members to serve; barring from committee meetings any doctors or researchers who have a direct financial relationship to companies that would be affected by the committee’s recommendations; increasing transparency by posting biographies of proposed panel members thirty days prior to a meeting, rather than the seventy-two hours prior, which is the current practice; allowing public comment on proposed members; and posting the final roster and questions to be considered by the panel on the FDA website at least seventy-two hours before the start of the
requesting immediate reform of the committee process, targeted the longstanding issue of conflicts of interest that result from intellectual investments, and from current or past financial relationships with drug companies (or with their competitors) that are affected by a Committee’s recommendations. Six specific reforms were advocated, including a proposal to “limit the number of panel members with any industry ties to no more than half the committee” to ensure balance and compliance with “the letter and spirit” of the Federal Advisory Committee Act (FACA). Among the mandates of the FACA is one that requires that the advice and recommendations of advisory committees reflect independent judgment, and are not “inappropriately influenced by the appointing authority or any special interest.”

The letter was precipitated by a high profile three-day Advisory Committee meeting convened to consider questions related to safety issues and continued marketing of several Cox-2 inhibitor drugs. Following the meeting, the Center for Science in the Public Interest, in response to a request from The New York Times, published an analysis meeting. See id.

114. See id.

115. See Letter from Merrill Goozner to Dr. Lester Crawford, supra note 110; Federal Advisory Committee Act § 2, 5 U.S.C. App. 2 (2001). The FACA, which governs all advisory committees established by the President, federal agencies, or Congress, reflected increasing concern about the influence of advisory committees on the regulatory process and the committees’ lack of accountability. See Federal Advisory Committee Act § 2(b)(4). The FACA, which among other things, made the process more transparent by opening committee meetings to the public, sets out standards and procedures for all committees, requiring committee membership to be balanced in terms of views and perspectives. Federal Advisory Committee Act § 5(b)(2). All records, minutes, reports, and other documentation related to committee meetings must be available for public inspection, subject to the exemptions of the Freedom of Information Act, 5 U.S.C. § 552. See also, Glode, supra note 108, at 298.


of panel members' industry affiliations. Drawing on disclosures in medical journals and other public documents, the Center concluded that ten of the thirty-two panel members had past financial ties to one of the three companies (Merck, Pfizer, or Novartis) directly affected by the panel's determinations. A review of the votes taken at the conclusion of the meeting showed that committee members with financial ties to the companies were ten times more likely to vote in favor of the companies than were members without such ties. At the start of the meetings, FDA issued a blanket waiver of the conflicts, sidestepping its usual procedure of announcing the names of panel members with relevant conflicts, stating that the work of the committees involved "issues of broad applicability" with no product approval questions to be determined.

The obvious conflicts emerging from the dual roles of panel members have plagued the FDA's advisory committee process for years. In 1978, the U.S. Department of Justice issued a restrictive interpretation of federal conflict of interest laws that would have disqualified advisory committee members in any matter in which they or their institutions had received research support from a company with an interest in that matter, even if the research support was wholly unrelated. In a 1992 report, prepared at the request of the FDA, the Institute of Medicine addressed


119. See id.


121. Id.


123. See Peter Barton Hutt, Investigations and Reports Respecting FDA Regulation of New Drugs (Part II), 33 CLINICAL PHARMACOLOGY & THERAPEUTICS 674, 678 (1983); Correspondence from Attorney General John Harmon to FDA Chief Counsel Richard Cooper (June 29, 1978); RICHARD A. MERRILL, UNIV. OF ROCHESTER CTR. FOR THE STUDY OF DRUG DEV. (NOW THE TUFTS CTR. FOR THE STUDY OF DRUG DEV.), PROBLEMS INVOLVING FEDERAL CONFLICT OF INTEREST RESTRICTIONS ON MEMBERS OF FDA ADVISORY COMMITTEES AND AGENCY OFFICIALS, PS 8032 (1980).
issues of conflict of interest, waivers, and intellectual bias. The report called for improved education on conflict issues for committee members and FDA staff, and for the development of criteria and procedures to identify potential bias, to protect objectivity and impartiality. The FDA responded through the publication of several Guidance Documents addressing conflict of interest issues, the granting of waivers, and the extent of public disclosure that must accompany a waiver.

The decision not to disclose the conflicts-of-interest of the Advisory Committee members prior to the February 2005 meeting highlights the continuing dilemma. A reexamination of the agency's conflict-of-interest policies seems timely. The European Medicines Evaluation Agency (EMEA) recently revised its policy in this area as part of an effort to achieve a more robust and transparent system. The policy includes criteria to assess what is referred to as a "risk level" associated with a given conflict. The risk level, assessed from one through three, is then used to determine the extent of the expert's participation in committee activities. A risk level of three will result in the exclusion of the expert from committee deliberations.

124. See Institute of Medicine, Committee to Study the Use of Advisory Committees by the FDA, FDA, U.S. Dep't of Health and Human Servs., Food and Drug Administration Advisory Committees (1992).


128. See id. at 2. Some of the criteria used to determine the risk level are the following: background of the expert; nature of the declared interest; availability of alternate experts; nature of the input needed from the expert; and the role of the expert or the phase during which involvement is required. See id. at 3.

129. Id.
other than in those instances when no suitable alternative expert can be found. In such a case, a waiver may be granted, and the expert’s risk level will be considered to be at level two, thus circumscribing the expert’s involvement. Perhaps more interesting is the degree of public access to information about committee members’ conflicts-of-interest. A list of experts is published on the EMEA’s homepage together with all Declarations of Interest submitted by chairpersons and members of EMEA Scientific Committees. Although the Declarations have always been available on request and in person, posting the statements on the Internet for public scrutiny in advance of committee deliberations not only expands transparency and accessibility, but also serves to inject a measure of good faith and accountability supportive of a more objective process.

Part II

A. NIH Scientists and Collaboration with Industry

The NIH is the federal government’s primary means for conducting and funding medical and behavioral research. The scientists and administrators within its twenty-seven institutes and centers have a broad range of responsibilities including: prioritizing funding for research, conducting basic (preclinical) research on disease mechanisms and potential therapeutic agents, designing clinical trials in which therapeutic agents are tested in humans, and assimilating results from clinical trials into treatment recommendations. Fellow scientists, regulators, and ultimately the public depend on the NIH and its scientists to conduct their work with scientific objectivity and the

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131. See EMEA POLICY, supra note 127, at 2.

132. See, e.g., About NIH, at http://www.nih.gov/about/ (last visited Apr. 30, 2005). NIH’s mission statement lists the four goals of NIH including, “exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.” Id.
highest professional standards so that the results can be trusted as valid and reliable.

Unlike the FDA, the NIH is not a regulatory agency. Yet, it is recognized that NIH scientists are influential because of their role in directing extramural research (NIH-funded grants for research typically at academic medical centers and universities) and developing practice guidelines (e.g., treatment criteria and methods for specific diseases).133 Outside of their official duties, many NIH scientists are influential because of their contributions to the field and, to a lesser extent, the agency they represent.134 It is not surprising, therefore, that the expertise of these scientists is in demand by the pharmaceutical industry, advising regarding nascent technology, designing clinical trials, and sitting on boards of startup biotechnology companies.135 The pharmaceutical industry has much to offer in return, particularly in providing significant capital for pre-clinical research and bringing novel technologies to market, and the opportunity for scientists on government pay scales to earn additional pay through consulting.136

Collaboration among industry, government, and scientists (NIH as well as scientists in academic medical centers, as discussed later) was not permitted under existing patent laws. The Federal Technology Transfer Act of 1986137 ("Technology Transfer Act"), and the Bayh-Dole Patent and Trademark Amendments of 1980138 ("Bayh-Dole


134. See Hamilton Moses III et al., Collaborating with Industry—Choices for the Academic Medical Center, 347 NEW ENG. J. MED. 1371 (2002). Biotechnology firms find it easier to attract venture capital investors to projects affiliated with scientists, such as those with NIH affiliation. See id. at 1372.

135. Their expertise is also more highly compensated by the pharmaceutical industry, as NIH scientists with a current salary cap of $200,000 earn in salary as little as one-third of their counterparts in the private sector. See Steinbrook, supra note 133, at 328.

136. See id. at 330.


The Bayh-Dole Act modified patent law to permit inventions developed using federal funding to be held by the organization responsible for the development. Prior to the Bayh-Dole Act, the federal government owned the rights to inventions developed with federal funds. Any discoveries by government scientists or by university-based scientists using federal funding belonged to the government. The government's patent rights were not easily assigned (e.g., to the university that made discovery) and federal licensing of the technology was done on a nonexclusive basis, consistent with the philosophy that research findings should be shared widely with the scientific community.

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142. Thomas N. Bulleit, Jr., Public-Private Partnerships in Biomedical Research: Resolving Conflicts of Interest Arising Under the Federal Technology Transfer Act of 1986, 4 J.L. & HEALTH 1, 5 (1989/1990). Prior to the Bayh-Dole Act, the most that a licensor of federal technology could obtain was a nonexclusive license, of much less commercial value.

Under the Bayh-Dole Act, scientists from the NIH or from universities are authorized, even encouraged, to protect rather than share new technology and to partner with industry to exploit the commercial value of discoveries, and "become part-time entrepreneurs." The Bayh-Dole Act has been criticized as leading to hoarding of information by scientists either because of contractual restrictions or from the drive to ensure maximum commercial benefit. Nevertheless, the increase in productivity in biomedicine has been noted during the years since its passage, and many credit these market incentives for the increase.

The Federal Technology Transfer Act was built on previous legislation, particularly the Bayh-Dole Act, to authorize federal scientists, such as those at the NIH, to collaborate with industry so that technology from government owned and operated laboratories can be commercialized. Specifically, federal employees may participate in Commercial Research and Development Agreements (CRADAs) in which private companies finance research within government laboratories in exchange for patent rights on developments. The Technology Transfer Act specifies that there can be no conflicts of interests under CRADAs, so scientists with financial interests or consulting arrangements with specific private companies must divest of these before participating in CRADAs with those companies.

144. Id.
146. See id. at 2454 (noting data from the 1990s showing that private-academic partnerships are more efficient at technology transfer than traditional scientific publications and meetings, among other indicators of productivity).
148. See id.
149. See Steinbrook, supra note 133, at 328. The NIH currently has about
More recently, NIH scientists were allowed to expand to consulting and directing biomedical firms (other than companies with which they participated in CRADAs), and to receive payment in money as well as stock or stock options for their consulting work.\textsuperscript{150} Prior to 1995, NIH's policies regarding outside activities were more restrictive than those of other executive agencies. In 1995, the Director of NIH, Dr. Harold Varmus, relaxed the NIH conflicts policies to be consistent with then existing policies by the Office of Government Ethics (OGE).\textsuperscript{151} The goal in relaxing NIH conflicts of interest policies at that time was to improve scientist recruitment and retention, recognizing that NIH competes with private industry for skilled scientists.\textsuperscript{152}

The 1995 changes in NIH conflicts policies affected all staff with the exception of presidential appointees. Institute and center directors had been limited in the types of outside activities they could perform; these restrictions were removed. All employees had been limited to outside earnings of $25,000 from a single source and $50,000 from all sources combined; these limits were removed. After 1995, employees could accept payment in the form of stock


\textsuperscript{152} See Steinbrook, supra note 133, at 329.
or stock options as well as money, and laboratory employees could work for an outside organization, as long as they did not have direct official business with the organization. All of these policy changes were done with the oversight and approval of the OGE, and were consistent with policies applied to other executive agencies. The resulting increased collaboration among NIH scientists and industry has been credited for new drugs, such as Videx, a Bristol-Myers Squibb drug used to treat Human Immunodeficiency Virus infections, and Fludara, a Berlex drug used to treat chronic lymphocytic leukemia. Increased collaboration between industry and NIH scientists is also credited with improving recruitment and retention of NIH scientists, because of both the atmosphere of innovation and the potential for income outside the government pay scale.

B. Role Overlap and Conflicts of Interests

The legislative initiatives and changes in NIH’s conflict of interest policy resulting in commercialization of what had previously been public domain, together with market forces favoring development of new technologies, has been credited with creating “a cozy space for interaction between industry and other “stakeholders.” The implication is that as industry and NIH and academic scientists become more cozy, the rest of us should feel less comfortable because scientists’ judgment may be compromised and their institutions can lose their public health mission when there are profits to be had from biomedical development.

Specific areas of concern include: giving one drug company unfair competitive advantage over another, failing to report complete data, exposing human subjects to

153. See id. at 327-29.
155. Lemmens, supra note 143, at 645. Lemmens aptly notes that by harnessing market forces, federally funded research focuses less on cost-effective public health measures and more on patentable products. See id.
unacceptable hazards, and inaccurate interpretation and reporting of results of clinical trials.\textsuperscript{156}

Indeed, many regard as intuitive the notion that financial relationships with pharmaceutical and biotechnology companies unduly influence professional judgment of researchers, whether the researchers intend it or not.\textsuperscript{157} What has become clear at the highest levels of the NIH, however, is that "coziness," even if scientifically defensible, undermines the perception of the validity of the protocols, research, and recommended standards developed by NIH scientists.

Public perception of the relationship of NIH scientists with pharmaceutical companies was sensitized by various \textit{Los Angeles Times} articles, casting the overlapping roles of scientist, consultant, and entrepreneur in a different light.\textsuperscript{158} The series highlighted several instances in which the objectivity of NIH scientists could be questioned, casting doubt on the validity of assessments about certain therapies as well as the safety of patients participating in clinical trials.\textsuperscript{159} One of the most prominent examples given was that of H. Bryan Brewer Jr., a scientist at the National Heart, Lung, and Blood Institute (NHLBI) within NIH.\textsuperscript{160} Dr. Brewer reportedly consulted four manufacturers of a class of cholesterol-lowering drugs, statins, earning $114,000 from 2001 to 2003.\textsuperscript{161} During this period, Dr. Brewer contributed in his official NIH capacity to patient treatment guidelines that made statins the standard of care, and in May 2001, urged more aggressive treatment...

\textsuperscript{156} Dennis F. Thompson, \textit{Understanding Financial Conflicts of Interest}, 329 \textit{NEW ENG. J. MED.} 573-76 (1993).
\textsuperscript{157} See id.
\textsuperscript{160} See id.
\textsuperscript{161} See id.
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with statins. Dr. Brewer also authored a 2003 publication in which he interpreted data as showing that the benefits of Crestor (a statin) outweighed its risks. This publication in the American Journal of Cardiology did not mention his financial relationship with the drug’s manufacturer, AstraZeneca, but did identify Dr. Brewer as an NIH employee. Since that time, the drug’s safety has been questioned, and a similar statin with related risks has been pulled from the market. The Los Angeles Times series included several other examples of consulting fees and stock options among NIH scientists, several of which have been disputed by the NIH scientists mentioned in the series. An OGE investigation of 100 NIH scientists for improprieties alleged in the Los Angeles Times series and elsewhere found that as many as 80% of the scientists investigated had done nothing wrong.

Following the Los Angeles Times series, U.S. Senate and House of Representatives subcommittees held oversight hearings on conflicts of interest within NIH. Members of


163. H. Bryan Brewer, Benefit-risk Assessment of Rosuvastatin 10 to 40 Milligrams, 92 (4B) AM. J. CARDIOLOGY 23K-29K (2003). Note that rosuvastatin is the generic name for Crestor. See id. at 23K.

164. See id.


168. For an excellent resource about these House and Senate hearings, see NATIONAL INSTITUTES OF HEALTH, U.S. DEP'T OF HEALTH AND HUMAN SERVS., CONFLICT OF INTEREST INFO. AND RESOURCES, at http://www.nih.gov/about/
Congress disparaged the practice of permitting senior NIH scientists to consult with industry and generally recommended that senior NIH officials and scientists be prohibited from working with industry while employed by NIH.\textsuperscript{169} Though current NIH Director, Elias Zerhouni, denied that there is any evidence that patients were harmed because of any scientist’s relationship with industry, he stated that he had “reached the conclusion that drastic changes are needed” to protect the public trust and the integrity of NIH and its scientists.\textsuperscript{170}

During this period, Dr. Zerhouni had requested that an independent Blue Ribbon Panel study the issue and recommend appropriate policy changes.\textsuperscript{171} The Blue Ribbon Panel adopted as its single guiding principle:

“NIH employees must avoid conflicts of interest incompatible with the proper exercise of their authority and the proper performance of their duties. Employees in a position to influence the financial interests of an outside entity such as a current or possible future recipient of an NIH grant or contract should neither receive


financial benefits from that organization nor have significant financial interests in it."172

Though relatively few NIH employees (approximately 120 of 17,500) had outside consulting agreements with biomedical companies at the time of the investigation, there were also honoraria and awards received from industry that were not considered outside employment and had not been reported.173 The Panel noted the tension caused when NIH scientists are encouraged to pursue individual financial interests at the same time as public scientific interests, and its recommendations reflected the desire to improve morale at NIH and ensure the public’s trust in and support of the work of NIH.174

After the Panel issued its report, the Department of Health and Human Services (DHHS), with the concurrence of the OGE, issued supplemental ethics regulations for NIH scientists, adopting most of the recommendations.175 The interim final regulation became effective on publication on February 3, 2005.176 The threat to the integrity and public esteem of NIH posed by outside employment or financial relationships with biotechnology or pharmaceutical companies was, therefore, sufficient to prompt a ban on most outside employment, divestiture of equity assets by many scientists and other restrictions, though less drastic approaches had been under consideration.177 The rule,


173. See id. Inconsistent enforcement of existing reporting rules was also noted by the U.S. Office of Government Ethics finding that 40% of the 155 outside payments to NIH employees it sampled randomly had not been approved in advance or accounted for within the agency. See id.

174. See id. at 11-12.

175. See id. at 19.


177. In his June 22, 2004 testimony before the U.S. House of Representatives Oversight and Investigations Subcommittee of the Committee on Energy and Commerce, Dr. Zerhouni stated that he planned to prohibit the
effective on publication, represents a significant shift in the acceptability of overlapping roles of NIH employees, particularly the scientists.

C. NIH's New Supplemental Regulations for Conflicts of Interest

The regulations (to be codified at 5 CFR 5501 et seq.) apply, to one degree or another, to all 17,500 NIH employees and focus on three areas in particular: activities (work, speeches, writing) outside NIH; financial holdings in biomedical companies; and awards.\textsuperscript{178} All NIH employees are prohibited from outside employment with “substantially affected organizations,” broadly defined as including biotechnology, pharmaceutical, and medical device companies.\textsuperscript{179} Employment with other organizations (e.g., teaching at a university; providing medical care in a separate practice) using the expertise of the NIH scientist must be approved in advance, consistent with NIH policy prior to the supplemental regulations and other regulations on outside employment.\textsuperscript{180} Writing in professional publications and speaking at continuing education seminars is still permitted (with advance approval), even if wholly or partly funded by pharmaceutical or biotechnology companies, as long as funding is unrestricted (i.e., not contingent on inclusion of specific content or speakers) and there is no editorial control by the funding company.\textsuperscript{181}

Restrictions on investments in substantially affected companies vary with the type of disclosure required of the NIH employee: “confidential” filers (approximately 25,000 employees, based on pay levels) and “public” filers

\begin{itemize}
\item most senior scientists from consulting with pharmaceutical and biotechnology companies, but permit other NIH employees to do so, provided there were controls in place. Zerhouni, supra note 171, at 4.
\item 178. See Supplemental Standards, supra note 176, at 5558. NIH employees were informed of the recommendations of the NIH Blue Ribbon Committee as of July 2004, with the knowledge that the supplemental regulations would be drawn from the Committee's report.
\item 179. 5 C.F.R. § 5501.109(b)(8)(i) (2005).
\item 180. See, e.g., 5 C.F.R. § 2635.603(a) (2005) (prohibiting work outside the NIH that is the same as official duties and work for an organization that has business with the agency in which the employee participates).
\end{itemize}
(approximately 1,000 employees at the highest levels within NIH). All NIH employees filing either of these financial disclosure reports, as well as their spouses and minor children, must divest of stocks in any companies involved in research, development, or manufacture of medical devices, biotechnology or pharmaceuticals. Even the majority of NIH employees who are not required to file such disclosure reports are limited to a total of $15,000 in any one company held by the NIH employee, spouse, and minor children combined. There are certain exceptions, such as stocks held in mutual funds or in employment retirement vehicles established prior to NIH employment. The divestiture requirement, similar to that required of FDA employees, was implemented by DHHS to avoid the appearance that industry holdings could affect the scientific judgment of its most influential scientists. This requirement may appear overbroad, requiring divestiture even if the senior NIH employee has no official business related to the specific company. It is, however, a reflection of the nature of the pharmaceutical and biotechnology industry when today's startup is tomorrow's subsidiary of a parent company with numerous spin-off companies.

Finally, senior employees are prohibited from accepting most awards of more than $200 from any entity that has business with NIH, or seeks official action from NIH. The


184. See id. § 5501.110(d)(i). De minimis levels may be adjusted, and are cross-referenced to the level set for all executive branch employees. See id. §2640.202(a).

185. See 5 C.F.R. § 5501.110(e).

186. Comments accompanying the regulation state that DHHS "has determined that the acquisition or holding of these financial interests would cause a reasonable person to question the impartiality or objectivity with which NIH programs are administered." Supplemental Standards, supra note 176, at 5543-57 (to be codified at 5 C.F.R. pt. 5501).

187. See 5 C.F.R. § 5501.111(b) (2005). Senior employees include the Director, Deputy Director of the NIH, the Directors (Scientific and Clinical) of
regulations do not change requirements for non-senior employees, also limited to $200 aggregate award unless it is a bona fide meritorious award. Awards are reviewed in advance by an independent NIH advisory committee to the Director, and it is up to the Director or the Secretary of DHHS to grant the exception. For permitted awards, a cooling-off period of one year following the award disqualifies the NIH employee from participating in official matters relating to donor organization.

The supplemental regulations avoid running counter to existing statutes, including the Technology Transfer Act. NIH employees are prohibited from engaging in the sale or promotion of products of biomedical companies, except when that employee owns the patent to the product. The regulations do not affect the potential for employees to earn royalties on their inventions, either through direct licensing or through CRADAs; however, as before, the NIH employee may not be involved in negotiating a CRADA with a biomedical company if the employee has an existing financial relationship with that company.

The mechanism for employee reporting and Institute enforcement remains the same as before the supplemental regulation and is the same for all federal employees. The increased reporting is not without costs, however, as the OGE personnel devoted to DHHS has already increased from eleven to twenty-five to accommodate demand for disclosure review. Of course, each employee retains ultimate responsibility for compliance with the

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188. See Supplemental Standards, supra note 176, at 5552.
189. See id. at 5553-54.
190. See 5 C.F.R. § 5501.112.
191. See Supplemental Standards, supra note 176, at 5547. As previously, any invention developed while in the employment of NIH is assigned to NIH unless the NIH waives its patent rights, in which case the employee may elect to pursue the patent and hold all rights to the invention. See id.
192. 5 C.F.R. § 5501.109(c)(1)(iii).
193. See Swindell, supra note 182.
supplementary regulations and with other rules applicable to all federal employees.\textsuperscript{194}

The question remains, however, whether a ban on equity holdings and consulting arrangements for higher-level scientists and officials is desirable. A ban has the virtue of being clearer than previous policies, and, therefore, easier to enforce. Greater clarity is achieved both by defining "substantially affected organizations" and by linking reporting requirements and investment/honoraria restrictions to existing financial disclosure levels.\textsuperscript{195} Initial reactions have varied, but some feel that these measures, though more strict than necessary to avoid conflicts, were needed to rebuild the public's trust in the NIH.\textsuperscript{196} It is worthwhile to note, however, that Dr. Zerhouni is already seeking changes in the rules, prompted in part by opposition by NIH personnel in the stock divestiture requirements.\textsuperscript{197}

Yet a ban is probably the least likely means to achieve the goal of promoting trustworthiness in human subjects research.\textsuperscript{198} Robert Gatter argues persuasively that a ban on specific financial relationships promotes an inaccurate message among scientists that others are acting out of self-interest, and results in lower compliance with report and conflicts avoidance goals.\textsuperscript{199} Gatter states that it is

\begin{flushleft}
\textsuperscript{194} See 5 C.F.R. § 5501.104(a) (2005).
\textsuperscript{196} See generally Robert Gatter, Walking the Talk of Trust in Human Subject Research, 52 EMORY L.J. 327 (2003) (recommending an approach similar to that suggested by DHHS). Gattner describes the benefits of creating "a general standard of fidelity" (disclosures) with a "risk of liability" for conduct deviating from the acceptable collaboration, rather than a general ban which invites individuals to find ways around it. Id. at 397-98.
\textsuperscript{198} See generally Gatter, supra note 196 (recommending an approach similar to that suggested by DHHS). Gatter describes the benefits of creating "a general standard of fidelity" (disclosures) with a "risk of liability" for conduct deviating from the acceptable collaboration, rather than a general ban which invites individuals to find ways around it. Id. at 397-98.
\textsuperscript{199} See id. at 390-91.
\end{flushleft}
preferable to clarify expected norms, for example, promoting a general message that scientists or officials should not conduct human subjects research or take official action if they have significant financial interests at stake.\textsuperscript{200}

Gatter's approach fits the situation at NIH, as there were few NIH scientists who benefited from undisclosed industry deals, and existing reporting mechanisms were underused.\textsuperscript{201} The behavioral norm that should be expressed is that stated by the Blue Ribbon Panel: avoiding conflicts that interfere with official duties and benefiting financially from the results of clinical research. Congress has made it clear in its legislation related to technology that productivity with integrity is the goal in biomedical research, and the objective of the Bayh-Dole Act and related legislation is to avoid conflicting interests, not interaction with industry. To ensure that the NIH maximizes self-regulatory behavior, Gatter's approach would avoid a broad ban (which invites individuals to find ways around it) and instead create a general standard of fidelity with disclosure and institutional oversight.\textsuperscript{202}

The short-term and long-term impact of the supplemental regulations will be assessed by DHHS over the coming year, particularly with regard to scientist recruitment and retention.\textsuperscript{203} The results of this assessment, along with public comments on the regulation, will be used in developing the final regulation.\textsuperscript{204}

In addition to focusing on NIH personnel issues, it would be useful for DHHS to consider the impact of supplemental regulations on the public perception of NIH's

\textsuperscript{200} See id. at 368-69.

\textsuperscript{201} See Weiss, supra note 167.

\textsuperscript{202} Gatter, supra note 196, at 397-98.


\textsuperscript{204} Supplemental Standards, supra note 176, at 5543.
scientific integrity. Though it could not be evaluated in the short term of one year, it would also be useful to track surrogate measures of productivity, such as CRADAs established or patents generated. It would be much more difficult to assess the impact of the regulations where the impact matters most: on the validity of research and on the safety of research subjects, just as it has been impossible to assess the effect on these two areas of the relationships between scientists and private biomedical entities. There is nothing in the supplemental regulation or accompanying discussion to suggest that the NIH approach should be adopted by academic medical centers, however, it would be informative to track the impact, if any, on the conflicts of interest policies at academic medical centers.

D. Academic Medical Institutions—Collaboration and Conflicts of Interests

Like government scientists, researchers at academic medical centers have become more entrepreneurial, accepting support form, and providing expertise to for-profit entities developing pharmaceuticals, devices, and other fruits of biomedical research. As discussed above, the Bayh-Dole Act encouraged collaboration among researchers, their academic institutions, and commercial entities to bring promising innovations from the laboratory bench to market.\textsuperscript{205} The primary mechanism for encouraging collaboration is found in patenting and exclusive licensing rights granted the inventor and the inventor’s institution.\textsuperscript{206} Private sector biomedical firms have the option of investing in promising research (paid in money, stock, or stock options) in exchange for these patent and licensing rights. In this way, private sector companies can own the technology developed under federal funding at academic medical centers. As a result, private sector funding for academic-based research has increased dramatically over the past twenty-five years.\textsuperscript{207} The

\begin{footnotes}
\item 205. See \textit{supra} notes 140-48 and accompanying text.
\item 206. See \textit{id}.
\item 207. See Blumenthal, \textit{supra} note 145, at 2452, 2455 (2003).
\end{footnotes}
increase in private sector funding began at a time when there was considerably less financial support for basic and clinical from the federal government through NIH.\textsuperscript{208}

As with government researchers, overlapping roles of academic researchers have aroused concern, though many stakeholders view a "principled partnership" between academia and industry as essential in continuing medical progress.\textsuperscript{209} Among preclinical scientists (i.e., laboratory scientists), the concern is that commercial interests may reduce the scientific objectivity of researchers, either intentionally or unintentionally. When researchers who are also patient care providers have relationships with industry, there are two areas of concern. As with preclinical scientists, there is the potential for bias in study design and result reporting, rendering results unreliable.\textsuperscript{210} There is also significant concern about the safety of patients and healthy volunteers because of the risk that patient accrual may be inappropriately zealous or that experimental drugs are used in humans without sufficient safeguards.\textsuperscript{211}

Potential conflicts of interests may affect an individual researcher, similar to the experience of NIH researchers, in which an investigator has a financial tie to the sponsor of the research, such as consulting agreements, or equity in the company. Unlike federal research facilities, however, academic institutions themselves may have vested interests in research outcomes. Institutions may have direct financial ties to commercial research sponsors.\textsuperscript{212} More problematic, however, are the conflicts that arise when the institution develops (and, therefore, owns) the technology (shared with the inventor as provided by the Bayh-Dole Act) and

\begin{itemize}
  \item \textsuperscript{208} See id.
  \item \textsuperscript{210} Blumenthal, supra note 145.
  \item \textsuperscript{211} See id.
  \item \textsuperscript{212} Academic medical centers receive varied support from for-profit biotechnology companies in addition to equity holdings. Examples include financial support of graduate students or fellows, joint patents and licensing with the academic medical center, and donations to affiliated universities. See id. at 2452.
\end{itemize}
conducts clinical testing of the therapy.\textsuperscript{213} The well-known case of Jesse Gelsinger, an 18-year-old who died during the course of experimental gene therapy at the University of Pennsylvania, is an example of institutional conflicts of interests.\textsuperscript{214} The university and the co-investigator conducting the earliest study of the drug in humans (Phase I toxicity) held equity in the company that would commercialize the therapy.\textsuperscript{215} Investigation following the death of Mr. Gelsinger by the FDA focused on the institution’s failure to disclose adverse effects in earlier primate experiments and in other patients.\textsuperscript{216} In discussions that have followed, the case has been used as an example of the potential for financial benefits to an academic medical center and its researchers to overwhelm ethical scientific and clinical judgment.\textsuperscript{217}

Just as with NIH investigators, academic researchers and their institutions’ financial interests in technology do not necessarily result in compromised research or threats to patient or human subject safety. Like the NIH, academic

\begin{itemize}
\item \textsuperscript{213} Mark Barnes and Patrik S. Florencio, Investigator, IRB and Institutional Financial Conflicts of Interest in Human-Subjects Research: Past, Present and Future, 32 Seton Hall L. Rev. 525, 529-30 (2002).
\item \textsuperscript{214} Id. at 525.
\item \textsuperscript{215} Mr. Gelsinger’s parents filed a complaint alleging wrongful death, strict product liability, and other liabilities, noting that the University of Pennsylvania and its researchers had various financial interests with the therapy’s commercial sponsor, Genovo, Inc. See Compl. for Plaintiff, Gelsinger v. Tr. of the Univ. of Pa. (filed Sept. 19, 2000), available at http://www.sskrplaw.com/links/healthcare2.html. The case has since been settled under undisclosed terms. See Federal Case Is Settled Over Death of Research Subject, 20 Hum. Res. Rep. 1 (Apr. 2005).
\item \textsuperscript{217} Barnes, supra note 213, at 547.
\end{itemize}
institutions have sought to ensure confidence in their scientific work by limiting their researchers' roles as entrepreneurs through conflicts of interest policies. These policies have been highly variable and discretionary in the levels of financial interests requiring disclosure as well as the penalties for noncompliance. Recent guidance from the DHHS as well as industry groups, however, has given structure policies for handling conflicts of interest in human subjects research, with standards emphasizing disclosure, transparency, and oversight rather than prohibiting specific financial relationship.\textsuperscript{218}

E. Managing Conflicts of Interests in Academic Medical Centers

The area of greatest concern in human subjects research is patient safety, and recent actions taken in both the public sector and the private sector have provided some guidance regarding investigator and institutional conflicts of interest.\textsuperscript{219} Aside from regulations requiring and governing Institutional Review Boards (IRBs),\textsuperscript{220} there are regulations requiring investigators receiving PHS funds to disclose certain levels of financial interest to their institution.\textsuperscript{221} Investigators receiving PHS funding must disclose potential financial conflicts to the designated officer in their institution and it is up to the institution to ensure that financial interests do not adversely affect human subjects research.\textsuperscript{222} Until relatively recently, there have not been specific requirements for the review process or

\textsuperscript{218} See generally id. at 529-31.


\textsuperscript{220} HHS requires that PHS funded research involving human subjects conform to subject protection requirements codified at 45 C.F.R. pt. 46 (2004). Research conducted to fulfill requirements of the FDA must conform to comparable regulations at 21 CFR pts. 50, 56 (2005). These regulations specify, among other things, that IRBs must review all proposed research, ensure that the benefit to risk ratio is reasonable, patient selection is appropriate and equitable and patients freely consent. See id.

\textsuperscript{221} See 42 C.F.R. § 50.604 (2004).

\textsuperscript{222} Id.
appropriate corrective measures.\textsuperscript{223} Not surprisingly, this has resulted in considerable variability among academic medical centers in the content of their policies and their approaches to enforcement.\textsuperscript{224} On May 12, 2004, DHHS issued its final guidance document regarding financial conflicts of interest in human subjects research. In addition, the AAMC issued its guidelines for managing financial interests held by investigators and by institutions in 2001 and 2202, respectively. The focus of these public and private guidelines has been on the protection of patients, however, many of the recommendations described would serve to ensure the integrity of pre-clinical research as well.

In the public sector, DHHS' final guidance document, \textit{Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection}, replaces its interim guidance issued more than three years earlier.\textsuperscript{225} The guidance document augments existing regulations for institutions and investigators receiving Public Health Service funding (the majority through NIH or NAS), and applies to human subject research conducted or supported by HHS or regulated by the FDA.\textsuperscript{226} The guidance provides points for IRBs, institutions, and investigators to consider (e.g., “Given the financial relationships involved, is the institution an appropriate site for the research?”), but does not provide criteria for resolving questions and ensuring that financial interests do

\textsuperscript{223} See e.g., 42 C.F.R. § 50.604(f) requiring that the institution of the investigator seeking PHS funding “establish adequate enforcement mechanisms and provide for sanctions where appropriate.”

\textsuperscript{224} S. Van McCrary et al., \textit{A National Survey of Policies on Disclosure of Conflicts of Interest in Biomedical Research}, 343 New Eng. J. Med. 1621 (2000). See also Bernard Lo et al., \textit{Conflict-of-Interest Policies for Investigators in Clinical Trials}, 343 New Eng. J. Med. 1616 (2000). Lo and colleagues reviewed the policies of leading universities and found that, while all universities require disclosure of financial interests, there was variation regarding whom on the research staff was required to disclose and what levels of financial interests should be disclosed. See Lo, supra. Penalties for non-disclosure also varied and were discretionary. See id. at 1618.


\textsuperscript{226} See id.
not compromise the welfare of research subjects.\textsuperscript{227} Institutions are, however, encouraged to consider establishing a conflict of interest committee separate from the IRB to establish criteria and policies to deal with conflicts independently of the IRB.\textsuperscript{228} Additional guidance addresses IRB operations to ensure that members are free of conflicts of interest as well as actions that investigators should consider, including having an independent individual obtain consent.\textsuperscript{229} The guidelines do not seek to reduce relationships among industry, academia and investigators, only to examine them.

Likewise, the core principle underlying the recent reports and guidelines from the Association of American Medical Colleges is that financial interests in human subjects research are not categorically improper.\textsuperscript{230} Financial interests are, however, viewed as potentially problematic, and the AAMC recommends a specific process to handle researchers with potential conflicts of interest in human research, using an institutional conflict of interest committee.\textsuperscript{231} Central to this process is the principle that a significant financial interest creates a rebuttable presumption that the individual (and institution) may not conduct the research involving human subjects, regardless

\textsuperscript{227} See id. at 26,396. For example, institutions are directed to consider whether payments per research participant or incentive payments are reasonable without guidelines for reasonableness. See id.

\textsuperscript{228} See id. at 26,396-97.

\textsuperscript{229} See id.


\textsuperscript{231} See AAMC I, supra note 230, at 14-19. Institutional COI committees are required for recipients of PHS funding; AAMC advocates using the same committee to review all potential conflicts in human subject research, regardless of the funding source. See id.
of the source of the funding for the research. The AAMC recommendations envision a separate institutional conflict of interest committee to review financial interest disclosures before protocols are sent for IRB review. The institutional conflict of interest committee would be the forum for analyzing requests by financially interested researchers to rebut disqualifying presumptions. The committee would also ensure disinterested monitoring if conflicts are significant and extenuating circumstances require that the financially interested investigator conduct the research. Their recommendations would be communicated to the IRB responsible for ensuring patient safety for the study under review.

A more challenging dilemma is presented when the institution conducting the human subjects research has significant financial interests in the outcome of the research. This occurs when the institution has developed the therapy in the lab, holds the patent, and is conducting Phase I testing or other clinical testing, as was the case with the University of Pennsylvania in the research in which Mr. Gelsinger participated. Institutional conflicts also result from financial interests of senior management or trustees in research that might affect or reasonably appear to affect the institutional processes for the conduct, review, or oversight of human services research. The AAMC report for institutional conflicts of interest emphasizes the need for separation of human subjects research oversight from financial interests oversight. This is accomplished in many institutions by a separate department for technology transfer (i.e., transfer of laboratory bench research to therapeutic applications). In addition, foundations handling endowments should be separate legal

232. The definition of "significant financial interest is the same definition employed by PHS in requiring reporting disclosure at 42 C.F.R. § 50.604 (2004). Unlike the Supplemental Regulation applicable to NIH employees, any employee can hold equity and accept consulting fees lower than de minimus levels. See 5 C.F.R. § 5501.110(d).


234. Gatter, supra note 196, at 351.


236. See id.
entities. Even with these separations, however, certain financial interests require the same level of scrutiny as described for individual researchers. These circumstances include: assignment of royalties for the investigational product; any equity interests in non-publicly traded companies acquired through licensing institutional technology; equity interests greater than $100,000 acquired through licensing technology to a publicly traded company; or, when institutional officials hold significant financial interests in the product for which they have responsibility for overseeing research. The report also lists other potential conflicts unique to institutions (e.g., substantial donations or endowments from commercial sponsors; acquisition of major equipment from commercial entity).

If an institution or senior institutional officers (e.g., deans, chairs, department heads) have a financial interest in the outcome of research, their interests may be aligned with commercial interests, including industry sponsors. Since excess funds from commercial sponsors may be used for other socially desirable ends, it may be in the best interest to sever funding. Rather, dealings with for-profit biomedical firms should be at arm’s length, so that the goals of the commercial sponsor do not skew the research agenda of the institution.

As with individual conflicts of interest, the key is disclosure of interests and review. The AAMC recommends that institutions conducting human subject research maintain a standing conflicts of interest committee to review these conflicts. The AAMC strongly urged

237. See id. at 4.

238. See id. at 6-7.

239. See id. An institutional official has a “significant financial interest” if the relationship with the commercial entity meets the criteria established under PHS Rule (i.e., consulting fees or honoraria which, in aggregate, exceed de minimus levels, serve as an officer, director or board member, or serve on a scientific advisory board of a commercial sponsor with regard to research being conducted at the institution). See id.

240. See id. at 7-8.


242. AAMC II, supra note 230, at 9. Institutional conflicts of interest committee members should have sufficient seniority, expertise, and
institutions to consider forming institutional conflicts of interest committees separate from mechanisms to consider individual conflicts of interest. It is strongly recommended that at least one member of the committee be from outside the institution to “increase the transparency of the committee’s deliberations and enhance the credibility of its determinations.” Technology licensing should have reporting obligations to this committee when an institution is likely to take any equity or ownership interests or royalty payments from potential sponsors for HSR.

Ideally, then, financial conflicts on the part of investigators or institutions are reviewed and managed before related research protocols are reviewed by IRBs. In some cases, however, investigators or institutions will have direct financial interests in research outcomes. If so, the presumption is that these interests conflict with patient care and scientific integrity. The presumption may be rebutted when circumstances are compelling (e.g., there is limited expertise in conducting the type of research required) and the committee has approved an effective conflict management plan. Conflict management plans may include requiring disclosure of interests to study participants, obtaining patient consent using only disinterested investigators, and more frequent review of the research protocol by the IRB. This management plan is communicated to the IRB with jurisdiction over research. This saves already overburdened IRBs from shouldering the responsibility for evaluating conflicts of interest; rather, IRBs act as a second level of review for the conflict of interest committee’s review. The AAMC recommends that a second level review by an external IRB be considered, particularly when institutional conflicts are involved.

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244. See id. at 14.

245. Factors to be considered include: nature of the science, nature of the interest, how closely the interest is related to the research, the degree of risk that the research poses to human subjects, and the degree to which the interest may be affected by the research . . . unique qualifications of the institution and the experience and expertise of investigators.
The most essential component in a financial conflict of interest policy is complete, accurate and timely disclosure on the part of individual investigators to the individual or committee responsible for overseeing these issues. Patient safety and scientific integrity remain the priorities for all concerned and where there are significant financial interests in research outcomes on the part of investigators or institutions, the reviewers must presume that the research cannot be conducted without management of the conflict (e.g., through divestiture or reassignment of research tasks) and oversight. The conflicts presented where institutions and their investigators hold patent rights in therapeutic agent to be tested for toxicity and dosing in patients will remain the most difficult to manage. Recommendations that a separate institutional conflict of interest committee have at least one independent member from outside the institution may not be sufficient, unless there is an institution-wide (in fact, industry-wide) commitment to full disclosure with independent review of all such research.

CONCLUSION

The web of conflicting roles examined above may be an unavoidable consequence of modern medical research structures. The narrow and sophisticated areas of expertise demanded at all levels of drug development may of necessity circumscribe a limited pool of players. Effective, coherent regulation requires that the FDA and industry collaborate and strategize as partners, not adversaries. “Negotiate, don’t dictate” was the essence of the 1995 edict issued by President Clinton in which he directed all federal agencies to establish cooperative relationships with regulated parties. Enormous public health benefit has emerged from the research dialogue between the

246. DuVal, supra note 241. DuVal notes that high-level institutional officials may also need to make disclosures to an audit or other subcommittee of the institution’s Board of Trustees. See id. at 623.


pharmaceutical industry and academic researchers. The need for an effective working relationship between the FDA and industry seems patently obvious. However, intrinsic to this interactive, dynamic process are potentially overlapping roles and varying degrees of self-interest, both actual and perceived. Assuming these realities, conflict management is essential to effectively stem the erosion of public trust and minimize damage to the research work product. The specific flash points that tend to generate aggressive accusations of agency capture at times of crisis, such as fast-track approval, user fees, and tolerance of conflicts among advisory board members are unlikely to disappear. Nor is it foreseeable that laws creating joint interests in promising therapies by NIH / academic researchers and biomedical companies will be amended in any significant way.

Each of the institutions involved at all levels of the drug development enterprise could, however, be more proactive in analyzing and overseeing the so-called hot spots. For example, FDA’s efforts in moving important new drugs to market expeditiously will and should remain a priority; however, internal checks must exist to ensure that reviewers’ concerns about safety are not muted due to pressures to meet approval timelines. One question to be addressed is whether the lesser evidentiary burden applicable under the fast-track approval scheme has been allowed to spill over to the traditional drug approval process. Oversight on this issue lies squarely with the FDA. The agency’s ability to challenge a company’s submissions should not be constrained by industry-imposed approval schedules. Drug development is fraught with uncertainty and risk. Why then should rigid timelines be imposed on the FDA review and approval process, potentially hindering an appropriate assessment of that uncertainty and risk? Given the fiscal exigencies of the federal government, Congress is unlikely to amend the user fee scheme; however, the rigidity and apparent pressures imposed on FDA review staff by the performance goals, as reported by the DHHS Office of Inspector General, should provide sufficient incentive to recalibrate future user fee time commitments, and to provide additional resources for more rigorous post-marketing surveillance either within or
outside of the FDA’s Office of New Drugs. NIH and academic medical centers also have the necessary tools to ensure scientific integrity and patient safety by enforcing broad disclosure requirements and internal oversight when signals of conflict emerge. The Office of Government Ethics is ideally situated to use the disclosure and oversight process as an opportunity to define norms for ethical scientific behavior even if some of the prohibitions prove difficult or unworkable in practice.

The timeless logic of transparency would seem to provide a governing principle when reshaping policies directed to both institutional and personal conflicts. The model provided by the EMEA to deal with conflicts of interest among its Scientific Committee members recommends itself as one route the FDA could follow. Post-meeting revelations of FDA Advisory Committee members’ conflicts of interest are a consequence of a timid FDA policy on this issue, one that unnecessarily results in public challenge to the integrity of the process. Likewise, the experience of academic medical centers in applying AAMC recommendations for dealing with conflicts of interest, an emphasis on disclosure and oversight rather than prohibition of financial relationships, may be informative for DHHS as it evaluates its supplemental regulations for NIH scientists.

250. See FDA’s Review Process, supra note 5.