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Interactions of the public and private sectors in drug development: Boundaries to protect scientific values while preserving innovation

ABSTRACT

Industry, academia, and government have developed highly interwoven relationships in the pursuit of biomedical research. Establishing and maintaining boundaries among the public and private sectors at both the institutional level and the individual level is critical to protect core scientific values, preserve innovation, and allow product development to thrive. This article reviews principles that guide the interactions of these different sectors, sharing principles in place at Eli Lilly and Company as an example.

Biomedical research and pharmaceutical development are best conducted in a collaborative environment sustained by both publicly and privately funded research and by public policies that promote innovation. Since the passage of the Bayh-Dole Act of 1980, relationships between academia and industry have become closely intertwined. Because of the potential for conflicts of interest arising from these relationships, boundaries among the public and private sectors must be defined and maintained.

This article offers a "real-world" perspective on public-private relationships in pharmaceutical development. This perspective has evolved from my 9 years of experience in industry and 30 years, including a decade as a department chair, at the University of Alabama at Birmingham, as well as from my work on committees for the National Institutes of Health (NIH) and National Academy of Sciences. This paper outlines basic principles for avoiding conflicts of interest and shares some boundaries established by Eli Lilly and Company as examples.

Acknowledgment: The author gratefully acknowledges helpful discussions with H. Heath, A. Norris, L.E. Van Campen, M.C. Jones, G. Geipel, and S.M. Paul of Eli Lilly and Company; E. Holmes of the University of California, San Diego; and M.G. Edwards of Recombinant Capital.

Dr. Cassell reported that she has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article apart from her employment with Eli Lilly and Company, through which she receives a salary, grant/research support, and stock options.

DRIVERS OF INNOVATION: AN INDUSTRY PERSPECTIVE

What drives biomedical innovation? From the perspective of industry, the most important motivators are:

- Market-based pricing
- Intellectual property protection
- A predictable, expeditious regulatory climate based on sound science and innovative leadership
- Sustained public support for basic research
- A public policy environment that protects the current complementary and synergistic roles of publicly and privately funded research.

Although the first four factors are frequently cited, the fifth and final factor is rarely mentioned and is probably the least understood by the public and policymakers. Yet effective interaction between the public and private sectors is critical to the successful discovery and development of new medicines.

Traditionally, scientists in academic and government institutions have performed mostly basic (ie, fundamental) research, whereas those in industry have been more involved in applied and translational research. However, the gap between fundamental and applied research is rapidly narrowing and the boundaries are becoming blurred. Perhaps the two most significant factors contributing to this blurring of boundaries have been (1) the founding of the biotechnology ("biotech") industry, with some of the first companies being based on technology licensed from universities (eg, Genentech in 1976), and (2) passage in 1980 of the Bayh-Dole Act, which facilitates technology transfer from the public sector to the private sector.

The influential business magazine *The Economist* has called the Bayh-Dole Act "possibly the most inspired piece of legislation to be enacted in America

over the past half-century."[1] Because of the impact of this legislation in the United States and the way it has been emulated by other countries, we are unlikely to return to the days when the commercialization process was stymied by slow technology transfer.

A 'TRIPLE HELIX'—INDUSTRY, ACADEMIA, GOVERNMENT

The two-stranded structure of DNA that codes the genome is popularly known as the double helix. Meanwhile, in the United States, the challenge of unlocking the secrets of human genetics—along with many other breakthroughs in biomedicine—depends on what some have called the "triple helix," an interconnected complex of relationships between individuals and institutions in three sectors: (1) the vast research and development networks of private life-sciences companies, (2) universities, and (3) the research, grant-making, and regulatory agencies of government.[2]

Most people did not imagine that the Bayh-Dole Act would change the nature and scope of the economic partnership among industry, academia, and government so far beyond its original intent. A highly interwoven relationship between the private and public sectors has now developed, extending to all levels of academia and the research enterprise—and even to state and federal policymakers, who are encouraging universities to earn more of their income by licensing, royalty fees, and company start-ups.

Equity ownership in start-up biotech firms has substantially outperformed licensing fees in generating revenue for academic institutions.

A plethora of potential conflicts

The new relationships between the public and private sectors produce a plethora of opportunities for conflicts of interest of all types. They arise for several reasons:

- The number and diversity of players and stakeholders
- The enormous financial stakes for both the public and the private sectors
- A poor understanding of the nature of biomedical research (and of the drug development process specifically), leading to misperceptions and a lack of trust among all, including (most importantly) the public.

Few realize how interwoven this triple helix of industry, academia, and government has become.[2] A few striking examples from the University of California (UC) system highlight the interconnection[3]:

- One in three public biotech firms in the United States is located within 35 miles of a UC campus.
- One in three California biotech firms was founded by UC scientists, including three of the world's largest such firms (Amgen, Genentech, and Chiron).
- The University of California, San Diego, founded 113 biotech companies that were established in the San Diego area.
- The share of funding for clinical research in the UC system that is received from industry is about 10 times greater than the share received from the NIH.

High financial stakes

For academic institutions that take equity ownership in a start-up biotech company that has an initial public offering, academic equity has substantially outperformed licensing fees. In 2003 and 2004, 94% of academic equity value was captured by faculty members rather than by institutions, and half of these faculty members chose to remain in their academic positions rather than move to the private sector.[4]

With tens of millions of dollars at stake, it is not surprising that tensions are growing between faculty and university administrators, as well as between industry and academic institutions.

The financial stakes are also high from a societal perspective, as the development of new medicines continues to become more complex and more costly: public and private sector investment in biopharmaceutical research and development in 2005 consisted of $39 billion from the pharmaceutical industry, $28 billion from the NIH, and $18 billion from the biotech industry. As we heard from Dr. Norka Ruiz Bravo of the NIH earlier in today's conference, the funding mix increasingly includes public-private partnerships, a trend that is likely to intensify as the NIH continues to promote such partnerships.

WHERE THE PUBLIC STANDS

How have these developments affected public views toward biomedical research? In 2004, soon after the *Los Angeles Times* reported on conflicts of interest among scientists in the intramural NIH program, Research!America conducted a survey of the general public on views toward health-related research.[5] The results showed a general lack of knowledge about how drug development takes place:

- Only 41% of those surveyed knew that most

drug development in the United States is conducted by pharmaceutical companies.
- Only 25% thought that institutions conducting medical research in this country, such as government, universities, and the pharmaceutical industry, work collaboratively rather than competitively.

At the same time, the results showed a good deal of openness to industry-academia-government collaboration in drug development:
- 91% thought that institutions *should* work together to develop new treatments and cures.
- 88% believed that it is a good idea for pharmaceutical companies to fund research in universities, hospitals, and other institutions.
- 69% believed that scientists should be allowed to profit financially from their discoveries.

ESTABLISHING BOUNDARIES

Given that industry-academia-government partnerships are not likely to diminish—and actually should be encouraged to enhance the synergy that leads to public benefit—our shared goal should be to identify and manage conflicts of interest so as to preserve core scientific values and the benefits of innovation for all of society.[6]

The following measures should be undertaken at individual and institutional levels to maintain public trust:

Encourage personal integrity of individual investigators through good laboratory practices, good clinical practices, and codes of ethics.

Encourage personal accountability for following guidelines that govern the individual components of the triple helix as well as those that govern interactions among its three component sectors.

Educate the scientific community, policymakers, and the public about the complexity of developing new medicines and the critical need for collaboration among the public and private sectors.

Provide appropriate oversight and enforce boundaries at all levels.

Punish appropriately those who break the rules.

Many boundaries between the public and private sectors have already been established by professional associations, institutions, and legislation, resulting in codes of conduct and guiding principles. Of the three components of the triple helix, the pharmaceutical industry is the most heavily regulated and monitored. In fact, the pharmaceutical industry is among the most heavily regulated industries in the world:
- The US Food and Drug Administration, the Office of the Inspector General, and the

Overview of 'boundaries' at Eli Lilly and Company

Principles of medical research

At Lilly, the conduct of research, payments to health care providers, and the communication of research results are governed by Lilly's "Principles of Medical Research." These principles, which were refined in 2004, were designed to minimize bias and conflicts of interest with academia and health care providers and to increase transparency, accuracy, objectivity, and balance in communicating the results of medical research.

Data access

Access to clinical data has been an important issue in the pharmaceutical industry. Any investigator conducting studies sponsored by Lilly is free to access and publish data generated at his or her site. For studies conducted at multiple clinical sites, the investigators who will serve as study authors have access to all study data relevant to the publication.

Publication

Lilly publicly discloses all medical research that is relevant to patients, health care providers, or payers, whether the results are favorable or not, in an accurate, objective, and balanced manner. Lilly complies with the authorship requirements of the International Committee of Medical Journal Editors, which were updated in October 2004.[7] No payment is given for intellectual contribution or time spent authoring, and no ghostwriters or guest authors are allowed.

Lilly will not suppress research or veto any investigator's publication. Lilly reserves the right to review manuscripts, offer scientific comment, and delay publication for a short while only as necessary to take action to protect the company's intellectual property (eg, to submit a patent).

Funding of clinical research, continuing medical education

The medical division within Lilly is responsible for the design, conduct, analysis, and reporting of all clinical and outcomes research. Investigator-initiated grants are reviewed and evaluated by medical and scientific personnel, who also make the funding decisions.

The Lilly grants office reviews US requests for support from continuing medical education providers and makes funding decisions.

Funding of external research and continuing medical education is not contingent on the purchase or promotion of Lilly products.

Department of Justice all provide government oversight of the industry.
- The industry's trade associations (eg, Pharmaceutical Research and Manufacturers of America, International Federation of Pharmaceutical Manufacturers Associations) provide codes of ethics.
- Most scientists and physicians working in the industry are members of professional societies that have have established guidelines and codes that govern interactions, including the Federation of American Societies for Experimental Biology and the American Medical Association.
- Individual pharmaceutical companies set codes of conduct, principles, and policies that must be followed by their scientists and physicians (see sidebar on previous page for an overview of some of Lilly's boundaries).

Failure to comply with these boundaries may result in a range of appropriate consequences, depending on the transgression.

CONCLUSION

Industry, academia, and government have developed highly interwoven relationships in the pursuit of biomedical research. While these relationships have been a powerful force for innovation, they give rise to a host of potential conflicts of interest. To manage these conflicts, all components of this triple helix need to have appropriate values-driven boundaries in place to preserve scientific integrity and the collaboration that advances patient care, and these boundaries must be well communicated and enforced.

Opinions vary on the details of how to avoid conflicts of interest, but three commonsense notions stand out:

- First, there needs to be a high level of *clarity* in internal conflict-of-interest rules to eliminate the gray areas in which accidental or willful abuses most frequently arise.
- Second, *accountability* must be relentless, which means that education and enforcement of conflict-of-interest rules are always job requirements within the triple helix.
- Finally, organizations need to promote *transparency*—the fullest possible disclosure of relationships, funding sources, and research findings—so that oversight can work.

Clear, rigorously enforced standards will assure the integrity of biomedical research while preserving the professional satisfaction of scientists and clinicians, the financial incentives for investors, and the breakthroughs for patients on which the triple helix depends.

REFERENCES

1. Innovation's golden goose [editorial]. The Economist; December 12, 2002.
2. **Campbell EG, Koski G, Blumenthal D.** The triple helix: university, government and industry relationships in the life sciences. Working policy paper of the AEI–Brookings Joint Center on Regulatory Studies; May 27, 2004. Available at: www.kauffman.org/pdf/triple_helix_061104.pdf.
3. **Yarkin C, Murray A.** Assessing the role of the University of California in the state's biotechnology economy: heightened impact over time. Working paper of the Industry-University Cooperative Research Program, University of California; March 24, 2003. Available at: http://ucdiscoverygrant.org/pdf/UC_Role_in_CA_Biotech_Economy_March2003.pdf.
4. **Edwards M, Murray B, Yu R.** Gold in the ivory tower: equity rewards of outlicensing. Nat Biotechnol 2006; 24:509–515.
5. **Research!America.** America Speaks: Poll Data Summary. Volume 6; December 2004. Available at: http://researchamerica.org/publications/AmericaSpeaks/AmericaSpeaksV6.pdf.
6. **Business-Higher Education Forum.** Working Together, Creating Knowledge: The University-Industry Research Collaboration Initiative; 2001.
7. **International Committee of Medical Journal Editors.** Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication; 2004. Available at: www.icmje.org.

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