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Entrepreneurship

Published online: 25 August 2003, doi:10.1038/bioent760

Navigating US conflict-of-interest rules when commercializing research

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Biomedical researchers and institutions looking to commercialize their inventions are faced with an array of policies and regulations for managing potential conflicts of interest.

US biomedical researchers face a raft of policies and restrictions on their financial activity that can begin when they are students and can continue throughout their tenure at a research institution. In part, these rules are intended to preserve the objectivity of science, and in part to safeguard the well-being of human subjects participating in research. In some cases, these policies are mutually contradictory, and at times they appear to serve the interest of the institutions over those of researchers. While the basic principles in this area are codified by federal laws and regulations, most academic institutions have their own set of regulations, which in some cases are more restrictive than those adopted by the US government.

Negotiating these complex, interlocking and mutually contradictory policies can be a rigorous undertaking in itself. This article outlines the significance of the federal Bayh-Dole Act of 1980 for universities and researchers, and describes various conflict-of-interest regulations and policies for researchers who are involved in university research, the licensing of technology to a company, the conduction of clinical work on inventions and the referral of certain services and goods to Medicare or other public beneficiaries.

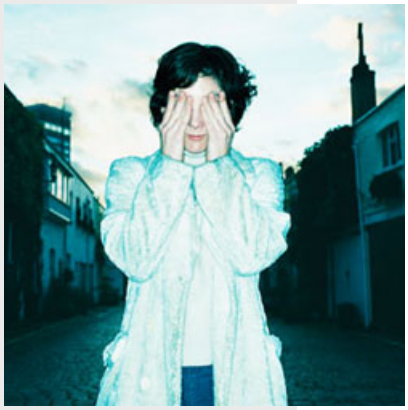
Preclinical issues

Under the US Bayh-Dole Act of 1980, patents on medical inventions or discoveries can be vested with the research institution that employs the scientist who makes the discovery. Most institutions claim ownership of any research conducted by their employees, whether on- or off-site, even if funded by a private company. In exchange for giving universities a patent interest in federally funded research, the Bayh-Dole Act then obliges institutions to attempt to get the technology to market. Many academic research institutions have reaped large windfalls for their parent universities under the Bayh-Dole Act, but they have also made large investments in technology transfer offices and legal staffs in order to get technology into production.

During the early stages of biomedical research, the financial interests of inventors and the licensing corporations are governed by contracts with the patent-holding institution. The financial remuneration allowed to researchers varies among institutions, as do the kinds of confidentiality standards the institutions' contracts with scientists may entail. Some merely restrict the researcher from publishing results until a patent can be filed (sometimes overnight), whereas others may forbid the use of patented biological material for other research purposes. A further complication arises when graduate students work on research that might be commercialized, as their careers could be hindered if they are prohibited from publishing their work.

Universities also vary on the role they allow inventors to play in the licensing to private companies of technologies they have patented. Some institutions are reluctant to allow scientists to serve as CEOs, whereas others demand that all compensation in excess of their salary be turned over. Many will not even allow the researcher to know the details of the licensing agreements, or to participate in licensing negotiations. Although institutions sometimes attempt to justify these restrictions by claiming that they avoid government-proscribed financial conflicts of interest—such as the Food and Drug Administration (FDA; Rockville, MD, USA) rules or the rules of government-funding agencies described below—the universities may actually be protecting their own financial interests by keeping their faculty from engaging directly in the negotiations.

Researchers seeking guidance in these areas could consult with their institution's technology transfer officers or patent attorneys. However, their loyalties, by definition, belong to the institution and hence, they might not be of much help to the individual researcher.



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Clinical studies

Potential conflicts of interest for clinical trial research funded by any US government agency (such as the Public Health Service (Washington, DC, USA), National Institutes of Health (Bethesda, MD, USA), Centers for Disease Control (Atlanta, GA, USA) and the FDA) are regulated by a set of rules referred to as the Common Rule. These can be found under the headings for each agency; for example, the Public Health Service version of the Common Rule is found at 42 CFR 50.605[1] (see Table 1). These rules were adopted to protect human subjects, but in addition, they have provisions for managing possible financial conflicts of interest. This enables the federal agencies to evaluate the conclusions of the researchers in the context of the financial relationships. It should be noted, however, that additional FDA regulations[2] (212 CFE54) pertain to research that involves an investigational agent. Therefore, it is possible for at least two sets of federal regulations to govern the same biomedical clinical research.

Under the Common Rule, institutions doing federally funded research are required to gather data on financial relationships annually, to disclose the data, and to manage or eliminate the conflicts, for example, by requiring recusal of conflicted individuals, or in some cases by appointing an independent data safety monitoring board, among other methods. Under the Public Health Service (PHS) definition of a conflict of interest, holdings worth more than $10,000 represent a potential conflict (see Table 2).

The FDA's Rule 54 (ref. 2) requires disclosure when an investigator conducting a clinical trial holds $50,000 or more in equity in a research sponsor, when the sponsor is a publicly-traded corporation or goes public within a year of the study. Significant payments of other sorts (including those involving consulting or other relationships with privately held companies) of $25,000 or more (not including the costs of research) must also be disclosed.

It should be noted, however, that the FDA's Rule 54 is currently in flux. The agency is soliciting comments on a proposed guidance which encourages institutions to adopt a variety of prophylactic measures, including disclosing an investigator's financial relationship to human participants, submitting financial relationships to an independent body for decision-making, and analyzing an institution's stake in the research. Although the trend does not seem to approach the rigor of the PHS rules, it does seem to be exploring new avenues for the increased regulation of financial involvement by researchers.

Finally, the Association of American Medical Colleges (AAMC; Washington, DC, USA), a voluntary body representing the consensus among American medical colleges, released its policy on individual financial interests in 2001 (ref. 3). It calls for member institutions to disqualify individual researchers with certain threshold financial interests (using the same limits as set by the PHS) from engaging in clinical trials in the area, subject to certain exceptions, for example, if the individual is uniquely talented.

In October of last year, the AAMC released a second policy dealing with an institution's financial interests[4]. This policy says that institutions and individuals with a financial stake in the outcome of clinical trials ought to be prohibited from being involved in them. This seems to directly contradict the Bayh-Dole Act, which encourages institutions doing patentable research to have a financial stake in it. While the AAMC is not a regulatory group, such guidelines could most likely be admitted as evidence in tort litigation. Many biomedical inventors circumvent these policies by allowing another academic institution or a contract research organization, which is not subject to the disqualifying conflict of interest, to test the discovery out in clinical trials.

The American Society for Clinical Oncology (ASCO; Alexandria, VA, USA) has adopted even more stringent guidelines. Its policy on clinical trials requires disclosure of more than $1,000 in interest by investigators to eliminate any researcher with such an interest from a position of chief investigator[5]. Keep in mind that rules of professional societies are at the midpoint between laws and norms. Although not binding, they operate as a gauge of public, professional and regulatory consensus, and may serve as a proving ground for or predict binding policies of the future. While these organizations do not have the resources to police their members, ASCO, for example, enforces its rule by denying the opportunity to publish or present research at its annual meetings unless members disclose their financial relationships

Marketed products

Finally, physician bioentrepreneurs have an additional hurdle to overcome once they have succeeded in bringing their agent or device into the US marketplace. For physicians who prescribe FDA-approved drugs, agents or devices to patients, US federal law comes into play once again. When the physician prescribes a product in which he has a financial interest to a beneficiary of Medicare or a state payer program, the compensation must satisfy any of a number of complex requirements. Otherwise, the physician could face civil or even criminal sanctions, or denial of reimbursement.

The detailed requirements are found in two statutes, the Anti-kickback Statute (elements of which have been around since the Depression, but the most important amendments to it date from 1987)[6] and the Physician Self-referral Prohibition of 1991 (42 USC 1395)[7]. While these laws have become notorious in the medical community for their complexity, they do provide certain exemptions to physicians who have financial stakes in the products that they prescribe, for example, services provided in a doctor's office and through academic institutions (see Box 1). Although many clinical researchers who bring a new drug or device to market will not make a living principally by prescribing their inventions, for those who see patients, these exceptions are worth looking into, especially considering the unique expertise many researchers will develop regarding their products (see Box 2).

The Anti-kickback Statute makes it a crime for anyone to pay money or anything of value with the intention of inducing the referral of Medicare business. This rule presents difficulties because some applications of the rule view employment by a medical college or a research institution as such an inducement.

The physician self-referral law, on the other hand, prohibits physicians from referring Medicare or Medicaid business to an entity with which they (or any family member) have a financial relationship, unless certain requirements are met. The exceptions to both laws are complicated and detailed. The group practice exception, for example, requires a centralized office structure, and the statute even discusses whether it is permissible to build a footbridge from a hospital to physicians' offices.

Whereas the Anti-kickback Statute provides for criminal penalties, the self-referral law only states that services provided in violation of it will not be reimbursed. The Anti-kickback Statute also requires proof of what the referring physician intended to do, and proof of something so intangible is often difficult to produce.

Conclusion

Biomedical entrepreneurs, throughout their careers, have to deal with a confusing maze of restrictions in the form of confidentiality requirements, conflicts-of-interest policies and contractual limitations set by various federal agencies and by their institutions, which themselves have conflict-of-interest issues. While the Bayh-Dole act may have started research institutes down the path of commercializing their patented technologies, the most recent set of policies, which effectively prohibits institutions from testing their own inventions, seems to be questioning the wisdom of this policy.

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Table 1: Agencies adopting the Common Rule

Rule	Agency
7 CFR Part 1c	Department of Agriculture
10 CFR Part 745	Department of Energy
14 CFR Part 1230	National Aeronautics and Space Administration
15 CFR Part 27	Department of Commerce
16 CFR Part 1028	Consumer Product Safety Commission
22 CFR Part 225	International Development Cooperation Agency for International Development
24 CFR Part 60	Department of Housing and Urban Development
28 CFR Part 46	Department of Justice
32 CFR Part 219	Department of Defense
34 CFR Part 97	Department of Education
38 CFR Part 16	Department of Veterans Affairs
40 CFR Part 26	Environmental Protection Agency
45 CFR Part 690	National Science Foundation
49 CFR Part 11	Department of Transportation

Table 2: Selected regulations and policies on conflict of interest

Regulation	Application	Rule
FDA-21 CFR 54[a] Financial disclosure by clinical investigator	After research is conducted	$50,000 in equity $25,000 in income for one year following trial
PHS (NIH/NSF) 42CFR50[b] Objectivity in research	Before research is conducted	Salary, royalties or other payments exceeding $10,000/year
Policy		
AAMC[c] Oversight of individual financial Interest	Before and while research is conducted	Any financial interest that would reasonably expect to affect research
ASCO[d] Oversight of clinical trials	Participants in clinical trials Authors submitting abstracts or manuscripts	$1,000 in publicly traded companies
NEJM[e] Financial associations of authors	Authors submitting manuscripts	NIH rule
ASGT[f] Financial conflict of interest in clinical research	Those involved with patient selection or clinical management of trials	No financial involvement with sponsor

Sources: [a]FDA, http://www.access.gpo.gov/nara/cfr/waisidx_99/21cfr54_99.html
[b]Public Health Service, Department of Health and Human Services, http://grants2.nih.gov/grants/compliance/42_CFR_50_Subpart_F.htm
[c]American Association of Medical Colleges, http://www.aamc.org/members/coitf/firstreport.pdf
[d]American Society for Clinical Oncology, http://www.jco.org/cgi/content/abstract/JCO.2003.04.026v1?ck=nck
[e]New England Journal of Medicine, http://content.nejm.org/cgi/content/full/346/24/1901
[f]American Society of Gene Therapy, http://www.asgt.org/policy/

Box 1: Exemptions to Anti-kickback and Physician Self-referral Statutes

Exceptions to the Anti-kickback Statute

1. Investment interests
2. Equipment and space rentals
3. Employees
4. Personal services and management contracts
5. Discounts
6. Referral services
7. Sale of a practice
8. Warranties
9. Group purchasing organizations
10. Waiver of coinsurance and deductibles
11. Ambulatory surgery centers
12. Underserved areas

Exceptions to Physician Self-referral Prohibition (the Stark law)

1. Qualified physician services
2. Qualified in-office ancillary services
3. Prepaid health plans
4. Clinical laboratory services furnished in an ambulatory surgical center or end-stage renal disease facility
5. Academic medical centers
6. Ambulatory surgical centers
7. Dialysis-related outpatient prescription drugs
8. Preventive screening tests, immunizations and vaccines
9. Eyeglasses and contact lenses following cataract surgery
10. Publicly traded securities
11. Mutual funds
12. Rural laboratory or Puerto Rico
13. Rental of office space or equipment
14. Bona fide employment arrangements
15. Personal services arrangements
16. Physician recruitment
17. Isolated transactions
18. Certain payments by a physician to a lab
19. De minimis compensation
20. Fair market value compensation
21. Risk sharing
22. Compliance training
23. Indirect compensation

Box 2: Unique talents yield exemptions

Most professional societies recognize that there must be some exceptions to any policy against allowing inventors to participate in research. A policy developed by the AAMC and ASCO allows participation when an inventor is uniquely talented. However, because such individuals often treat patients, the Medicare rules on self-referral sometimes come into play.

"There should be no inhibitions on people being compensated for their work or their good ideas, but there has to be oversight, which is what internal review boards are for," says Joseph Fetto, associate professor of orthopedics at New York University Medical Center (NYU; New York, NY, USA). Fetto's institution filed a patent on an invention for hip replacement in 1993, and the technology was licensed in 1996 to Encore Medical, (Austin, TX, USA). Having passed through the FDA process, the device is now in use in thousands of patients worldwide. When the technology was first licensed, it went to Zimmer (Warsaw, IN, USA). However, Zimmer was encumbered by 25 internal competitive designs for replacements. "Zimmer had already invested significant amounts in these other designs, so the product just sat on the shelf for a while," says Fetto. With Zimmer's cooperation, though, the product was eventually relicensed to Encore (Austin, TX, USA), which did not own any competing models.

It seems antithetical to the principles of Bayh-Dole for the university to license its patent to a company with a competing product, just to serve an anti-competitive purpose. However, that appears to be what happened initially in Fetto's case, and inventors ought to beware of such practices, especially if they are compensated on a royalty basis. According to NYU's faculty bylaws, the royalty resulting from the sales of the model is split evenly by Fetto and the institution. However, federal law prohibits physicians from referring Medicare patients to receive services if the referring physician has financial interests, unless certain complicated exceptions are met. In this case, as the inventor of the hip replacement, Fetto is uniquely qualified to install his device, and he has done so with some 400 patients. However, to avoid any conflict of interest, neither Fetto nor NYU receives royalties from devices installed at the university. It seems reasonable that the federal Medicare regulations should follow ASCO and the AAMC in allowing an exception for worldwide talent.