Industry-Funded Dermatologic Research Within Academia in the United States: Fiscal and Ethical Considerations

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Biomedical research is expensive, requiring space, manpower, equipment, animals, indirect costs, and expensive supplies and biologic reagents. Within academia, biomedical research is seldom supported by hard money, i.e., unrestricted, long-term funding. Consequently, investigators are continously faced with the need to solicit funding to support their research. For most of the past three decades, the federal government (public sector) has been a major source of this funding in the United States. Federal funding has now plateaued or declined, however, even as the need for such support has increased with expanding research efforts and opportunities. Investigators are now turning increasingly to the private sector — industry, foundations, and the public at large — for funding.

Independent of the source of funding, the academic investigator is always faced with ethical issues such as conflicts of interest academic freedom, fraud, etc. Some of these issues have been prominantly aired in public view in recent years. Some are more likely to surface when research is industry funded.

This editorial has been prepared in the belief that further consideration of these and other factors, inherent in industry funding of dermatologic research within academia, may be of some help to investigators in academic departments in their pursuit of industry support. The practices discussed apply in the United States and will differ in other countries.

SOURCES OF PRIVATE-SECTOR FUNDING

Private-sector funding of biomedical research within academia may come from 1) industry; 2) private and public foundations; 3) professionals (dermatologists); and 4) the general public. Pharmaceutical companies and manufacturers of medical devices represent two industries that often fund biomedical research. In addition, dermatologic research may be funded by manufacturers of cosmetics and of soaps and detergents. These sources may be willing to fund basic and/or clinical research and product trials for drugs and cosmetics.

A survey [1] conducted by the Society for Investigative Dermatology in 1980 found that slightly over 10% of the research budgets of the Departments of Dermatology nationally came from industry. From a 1984 study, Blumenthal et al state that "16 to 24 percent of all funds for biotechnology R&D available to institutions of higher education" [2] come from industry.

Within the last few years, industry has been willing to fund dermatologic research through the Dermatology Foundation. In 1990, the cosmetic trade association and more than 30 pharmaceutical and cosmetic companies contributed approximately $1,000,000 to the Dermatology Foundation for the support of research.

Dermatologists, themselves, actively support the Foundation. More than 3,000 dermatologists are members paying annual dues; 230 have pledged annual contributions of $1,000 or more. The Dermatology Foundation does not solicit money directly from the public, as do the American Cancer Society and the American Heart Association.

FUNDING OF BASIC RESEARCH

What benefits may the pharmaceutical industry receive from the funding of basic research within academia? It is likely that much, if not all, of the industry-funded research conducted within academia could be performed intramurally by industry. It is possible that some types of basic research may be done less expensively within academia. Industry may value the talents of specific scientists within academic dermatology and may also seek contacts with representatives of other medical disciplines. Industry may react favorably to recommendations of academicians for research to help solve specific problems or to develop new products. I (not a clinician) have been successful in attracting partial support for basic research from industry since 1936, my first year at the Harvard Medical School. The records are somewhat vague but I may have received the first industrial fellowship accepted by the Medical School. My funding has almost always been in support of projects that I proposed.

If the sole purpose of a cosmetic were to present a surface with an appearance differing from that of the natural skin surface, e.g., the use of blush or eye shadow, there would be little need for dermatologic research on cosmetics. Only in fairly recent years has the cosmetic industry been actively concerned with the action of their products on the skin, recognizing that they may do more than simply alter the appearance of the skin, hair, and nails. More effective products may be developed if skin deficiencies are understood and products designed that correct these deficiencies, e.g., the development of moisturizers following a better understanding of the action of emollients on the skin. In recent years, significant advances have been made in a better understanding of the action of cosmetics on the skin both by academia and by industry. The relationship between dermatologists and the cosmetic industry is now congenial and productive; each group recognizes that it can learn from the other.

An outstanding example of a company within the cosmetic industry being willing to support basic research within academia is the 1989 agreement between the Shiseido Company of Japan and the Massachusetts General Hospital for the ten-year support of the MGH/Harvard Cutaneous Biology Research Center (CBRC) [3]. The CBRC is recruiting basic scientists who are willing to focus specifically on the skin. For the past 10 years, research at the MGH

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Dermatology Department has been strongly oriented towards photobiology of the skin. The CBRC will widen this orientation to include molecular and cellular biology, immunology, and other basic sciences. Currently there is a staff of 16 investigators with support personnel. It is expected that during the next 2 years seven to ten additional scientists will be recruited to work on specific topics that will include one or more of the following fields of study: 1) keratinocyte biology; 2) pigment cell biology; 3) physical properties of the skin; 4) physiology, pharmacology, and toxicology; and 5) photobiology.

The conditions under which this agreement was accepted by the Massachusetts General Hospital follow.

1) The overall research program and recruiting strategies of the Research Center will be determined by the Center's Director who is also the Chief of the Dermatology Service at the Massachusetts General Hospital, and Chairman of the Department of Dermatology of the Harvard Medical School. Each investigator is free to pose his/her own research questions and methodology. There is a Scientific Advisory Board of nine members, two from the Massachusetts General Hospital, two from the Harvard Medical School, two from the Shiseido Company, and three who have no connection with these organizations.

2) Research Center investigators may talk and collaborate with other scientists. Any collaboration is permitted but the Shiseido Company may restrict Research Center investigators from accepting financial support from industry if there is exchange of intellectual property.

3) Investigators may publish research results, having shown the proposed publications to Shiseido representatives prior to submission. Shiseido cannot delay publication but, to protect foreign rights, patent filing should have occurred in the United States before publication.

4) Any patents resulting from the research are the property of the Massachusetts General Hospital with Shiseido having rights of first refusal to exclusive, worldwide royalty-bearing licenses.

5) The agreement will fund a nucleus of established investigators. As is generally true in biomedical research laboratories, in addition to the funding by this agreement, most scientists within the CBRC will be expected to solicit additional funding from federal and/or non-federal sources other than industry.

It should be noted that these conditions are common to all research at the Massachusetts General Hospital that is supported by industry.

Research scientists from the Shiseido Company may receive training at the CBRC and participate in its activities.

FUNDING OF CLINICAL OR APPLIED RESEARCH

It is not always easy to classify research as basic or clinical, except perhaps drug trials. An investigator within academia who has developed new ideas within the laboratory will probably wish to apply these ideas to clinical situations himself/herself rather than ask industry to develop the idea clinically. Also he/she may be more familiar with the developmental phase of the project and be better qualified to carry out the applied research.

Clinical research and drug trials are usually conducted on human subjects, both normal and those with skin diseases, which are more easily available to academia (hospitals and medical schools) than to industry. Also in the academic environment such investigators are under the control of existing human studies committees. For these reasons, the pharmaceutical industry often solicits the help of academia in such research.

Drug Trials If basic research within academia or industry results in the development of a new drug or in the use of an old drug for a disease for which it has not previously been used, "official" drug trials will be required before the drug is marketed for such purposes. Pharmaceutical companies are eager to cooperate with academia and will fund drug trials. Such funding will pay the entire or partial salary of clinicians responsible for conducting the trials. There may be correlated research that the company may fund. Drug trials may be very instructive for residents.

Drug trials yield information about efficacy and side effects that the company may wish to use in obtaining FDA approval. Thus, most drug trials will follow strict FDA guidelines. These guidelines are delineated in Title 21 of the Code of Federal Regulations (CFR) pertaining to the Investigation of New Drugs, Antibiotics, and Biological Drug Products and can be obtained from the FDA (address: CDER Executive Secretariat Staff, HFD-008, FDA/Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857).

A pamphlet that includes "excerpts from Title 21 of the Code of Federal Regulations" and is entitled "Obligations and Responsibilities of Clinical Investigators" is available from Hoffmann-LaRoche, 340 Kingsland Street, Nutley, NJ 07110.

These guidelines outline the responsibilities of the "investigator" and the "sponsor." The "investigator" is usually a departmental staff member and the "sponsor" is usually a representative of the company funding the trial. The guidelines also detail the types of records to be kept and reports to be made. For the protection of human subjects, the project must be passed by an institutional internal review board, the composition and qualifications of which are specified. Patients will be required to sign informed consent forms. Depending upon the regulations of the specific institution in which the trials are to be conducted, a contract will probably be required by the institution's legal department.

If a clinical trial is to be run on a somewhat rare disease, the principal investigator of the trial may request colleagues to refer patients to him/her for the trial. At times, the colleague may be paid a "finder's fee" [4]. Such a transfer of money can raise ethical issues and it is important that there be a clear understanding among all parties and the institutions they represent.

Evaluation of Medical Devices The Wellman Laboratories of Photomedicine within the Department of Dermatology at the Massachusetts General Hospital have actively cooperated with industry to make new laser technology available to physicians. Clinical trials of new lasers are being initiated within academia by both industry and academia. These are essentially similar to sponsored clinical drug trials. For such trials, industry may donate laser devices to academia and may aid financially in sponsored research. Testing of medical devices, other than lasers, is not uncommon within academia and gifts of these devices can be categorized as funding of research by industry.

In support of academic research, industry may work through the NIH Small Business Innovative Research Grant (SBIR) program. Academia can play an important role in helping industry in submitting SBIR grant applications.

Cosmetic Evaluations Cosmetics and skin cleansers are evaluated on non-diseased skin. Consumers may be chosen for trials, whose skin, though not diseased, may be somewhat abnormal, e.g., drier or more wrinkled or more pigmented. Subjects for such evaluations are more readily available to industry than are patients for drug trials. Therefore, industry may carry out such trials without seeking any association with, or help from, academia.

Cosmetics and cleansers are usually evaluated for efficacy and consumer acceptance. Often it is the consumers' subjective reactions that are sought. Changes in appearance may be scored visually. With developing imaging techniques, however, there is an attempt to quantify changes in appearance.

The testing of safety of these cosmetics is time consuming. New products are first tested on animals but subsequent evaluation on humans is most desirable. Products are tested for irritation and/or allergic sensitization. Panels of consumers may serve as subjects for such tests or there can be a limited test marketing situation under close supervision. Industry may wish to request that a dermatologist supervise such tests.

ACADEMIA-INDUSTRY RELATIONSHIP

This editorial addresses the following ethical issues: exchange of information, publication, patent rights, conflicts of interest, and indirect costs. Some ethical issues are more likely to surface in industry-funded research than in research funded by the public sector. There has been a great deal written in recent literature on each of these subjects. A brief list for supplemental reading is presented. There is an ethics committee of the American Academy of Dermatology (Harry J. Hurley, Chairman) that is concerned primarily with ethical issues experienced by the clinician.

Exchange of Information The results of research within academia are in the public domain. Academicians relish their freedom of thought and communication; they are eager to explore their ideas with their colleagues, both within and outside their own institutions. When the research is supported financially by the investigators' institutions or by public funds, e.g., National Institutes of Health, few if any restrictions are imposed on verbal or written communication. The potential exists for some communication restrictions when the research is supported by industry.

In any exchange of information, academicians may be selective in choosing the part of their intellectual property that they wish to communicate to whom and when. Thus, in communicating with other members of academia or with industry representatives, even when there are no restrictions imposed on the academicians by their institutions (academic freedom), they may choose to withhold certain information temporarily. Within industry, the results of research and development are usually proprietary. Industry representatives are usually asked to be secretive in discussing new research results. After a relationship has been established between an academician and a representative of a company that is funding the academic research, a level of exchange of information is often established that is satisfying to both parties. Rules governing such communication are difficult if not impossible to formulate; situations are highly individualistic. In the unhampered pursuit of knowledge, open communication can be very useful.

Confidentiality often becomes more of a problem when an academician is employed by industry as a consultant. Industry may seek help from the consultant for the solution of a problem and in so doing must reveal confidential information. In accepting a consultantship, an academician usually must agree to hold proprietary information confidential. In a sense this is in conflict with academic freedom. An academician's institution usually asks to be informed of the existence of any consultantship. Again, once a relationship is well established, the exchange of information usually proceeds at a level satisfactory to both parties.

Even though investigators' institutions may place no restrictions on their communication, the institutions do have some responsibility for the accuracy and reliability of the data presented. Falsification of data must be avoided under all circumstances. Although instances of fraud within academia are uncommon, they should not occur at all.

Publication Academicians are eager to publish the results of their research; this is true also for the industry scientist but industry is more sensitive to the risk of divulging trade secrets. Academia and industry may wish to protect patentable information by delaying publication until after a patent is applied for. Further complications often arise when an academician wishes to publish the results of research funded by industry. The academician is usually required to submit all manuscripts to the funding company before they are submitted for publication. The company is expected to respond and to clearly state any objection to publication.

At the time of the funding agreement, it is common for rules regarding publication to be formulated. The company agrees to respond within a specific time period following the receipt of a manuscript. The agreement should state how a situation in which the company requests delay in publication or withholding publication should be handled. If industry representatives have had significant input to the research, they may be joint authors of the paper.

Patent Rights Before publication, it is important to consider whether research results are patentable. It is also necessary to know who will hold patent rights. Usually an employee of an academic institution is under an obligation to assign patent rights to the institution. If the employee's work is being funded not by the institution, but by an industrial company, the terms of agreement will define the company's rights. Under these conditions, the institution will continue to hold the patent, but the funding company may be granted a world-wide royalty-bearing license. Royalty payments by the company to the institution (and possibly the investigator) may be specified in the terms of agreement or may be negotiated.

A company that is funding a project will probably follow closely the progress of the project. The company will know the results considerably in advance of other companies and the scientific community. It can proceed with the application of these results and thus will have a significant lead-time over its competitors if there is to be no patent.

Conflicts of Interest and Commitment Among the major concerns in industry-funded biomedical research are conflicts of interests, real or potential. The American Federation for Clinical Research [5] has approved a set of guidelines that address the major areas of potential conflicts of interest.

Because an investigator has accepted funding for a specific project, he/she will feel obligated to devote a portion of his/her time to the project. If the academic institution is a hospital or a medical school, the investigator may have teaching, patient care, and administrative commitments. Academia may limit the percentage of a staff member's time that can be devoted to funded research.

Within the duration of a project, new interests may arise; a new and different avenue of approach may develop. Such changes in interests may not be conflicts. They may be explored by investigators and the funding company and/or by the investigators and their institutions. They need not lead to any decrease in productivity and may improve the project and result in greater productivity.

Funded research and/or drug trials may produce results that a company may wish to use in support of claims being made for a marketed or marketable product. Major conflicts may arise if it appears that an investigator is helping to "promote" a product by publicly presenting data obtained through research funded by the company marketing the product. The investigators may correctly feel that they are defending data quite independent of the source of funds used to obtain such data. Harvard feels that this situation is handled by its rule that faculty members must disclose to the public their financial interest in a subject that they discuss in a research publication, a formal presentation, or an expert commentary, and they must do so "simultaneously" as they speak or publish [6].

Conflicts of interest and patent issues often arise when medical devices are being developed. Frequently, academicians are encouraged by their institutions to file patents on the devices, which is one of the motivations for industry sponsorship. In general, it is to industry's advantage to be involved because new technology is being developed.

At Harvard, the filing of a patent on an invention that has resulted from industry-sponsored research is not considered to be a conflict of interest. The academic inventor, however, is not to have an equity or paid position or to accept stocks or other forms of incentive from the company involved. Although these principles discourage both large conflicts of interest and scientific bias, the broader principles of full disclosure and ethical review of each situation are key issues and cannot be replaced by "rules."

Indirect Costs Academia is justified in requesting indirect costs for industry-funded research. Indirect costs include such items as utilities, libraries, building maintenance (and, under some conditions, building construction), depreciation, and administration. For federal funding, the calculation of indirect costs is specified by the

Office of Management and Budget. For industry funding, there is no set rule for calculating indirect costs and they vary widely among different institutions, particularly between private and public institutions. Also, a single institution may accept various funding with different indirect costs. Indirect costs at times are firmly fixed by the granting agency. At times, an agency will make a grant of a total amount of money and permit the institution to allocate the direct and indirect costs. In recent years, indirect costs have skyrocketed at some institutions. There may, at times, be bureaucratic problems, but actually these increases usually accurately reflect the increased real cost of supporting research. Different institutions may include different expenses in indirect costs when negotiating industrial contracts. This whole area is in a state of flux [7]. Because high indirect costs increase the difficulty in obtaining funds, both the investigators and the institutions suffer.

SUMMARY AND CONCLUSIONS

Private-sector funding of biomedical research within academia may come from industry, foundations, the dermatologists themselves, and the public at large. Industry-funding is of benefit to both academia and industry. Industry may fund clinical and basic research and product testing. Industry is more willing to fund product testing and clinical research than basic research. Funds for dermatologic research may be obtained from manufacturers of drugs, medical devices, cosmetics, soaps, and detergents.

Questions of academic freedom arise when research is funded by industry. The results of academic research are in the public domain; the results of intramural industry research are often proprietary, i.e., "trade secrets." When there is industry funding within academia, any restraints on publication should be held to a minimum and be temporary. Publication should occur in a timely fashion, although recognizing the need for delayed publication if the results concern patentable material. When there is a consultantship, pre-arranged terms of agreement may restrict communication.

Patents usually are held by the investigator's institution. The funding company may be granted world-wide, royalty-bearing licenses.

Conflicts of interest may arise during any research endeavor; this warrants close attention when the research is industry funded. Stock ownership, speaker fees, blind contracts, etc., should be avoided. In any communication, funding agreements should be stated.

Indirect costs are a "necessary evil." There are non-research expenditures associated with all research projects for which the institution is justified in requesting compensation. Indirect costs must have definite connections to a project.

As industrial funding of research within academia increases, various facets of the academia-industry relationship are receiving increasing attention. Several aspects of conflicts of interest and indirect costs must yet be resolved. When faced openly and directly, all of these issues are manageable and need not reduce the benefits to both industry and academia that are inherent in this relationship.

Federal funding of academic research uses tax dollars; industry funding comes from private capital. Academia will benefit from the funding of academic biomedical research by industry. The ultimate beneficiary of the funding of academic research by industry, however, will be society at large as the medical advances derived from sound biomedical research and carefully controlled clinical trials aid patients. A solidly established academia-industry relationship is essential to the effective funding by industry of biomedical research within academia.

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