

# RESEARCH MANAGEMENT REVIEW

The Journal of the  
National Council of University Research Administrators

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## EDITOR'S PREFACE

This second issue of "Research Management Review" is predominantly a "special topics" number, featuring the Keynote Addresses and papers derived from presentations at the national conference sponsored by NCURA for universities and industry on "Strengthening the Cooperative Effort in Biomedical Research." The conference was held September 2-5, 1986, in San Francisco, California. Within that two and one-half day conference, a variety of problems and concerns common to universities and the pharmaceutical and life science-related industries were identified and analyzed in critical detail. Disseminating the knowledge and experience of some of the most significant conference contributions is a worthy and useful function for the journal. With the assistance of a skilled Editorial Advisory Board, the principal issues of the conference have been distilled into a collection that merits the attention of all research administrators, particularly those involved with the management of research and development in biomedical and life sciences.

NCURA Past President Ed MacCordy's "Introduction to Issues in the University-Industry Partnership" presents a good overview of the developing relationship, notably the important technology transfer aspects. His insight about the inefficiencies of the partnership and the variable technology "push-pull" options is most helpful.

Two Keynote Addresses from the conference are printed as delivered, with minor editorial revisions. Louis Lasagna and James Knill gave their personal comments on "The Biological Revolution: Commercialization of the Molecule." Lasagna clearly delineates the forces working for and against industry and university cooperation, describing the "big picture" that leads into many of the other papers. Knill's presentation includes a very educational description of the drug development process within the pharmaceutical industry.

While the remaining articles, with one exception (the Rosenzweig piece), have their genesis in presentations at the conference, they have been recast as papers to more fully and formally cover the topics. Gary Goldberg and co-authors have captured the essential points of their panel discussion addressing the competition for pharmaceutical industry funds incorporating some useful points about planning issues for university research managers, supported with examples from Goldberg's own experience. For anyone who is interested in pursuing drug company

funding, some intriguing ideas are reviewed from the perspective of a coherent plan of action.

Katherine Ku's manuscript points out the primary issues that must be resolved when universities contract with drug companies. This article is especially beneficial for the more inexperienced because it defines in a clearly written style, the primary issues they are likely to encounter, giving some guidance by reference to what Stanford University does in these instances.

David Seligman's article retraces some of the points raised by Ku, identifying potentially thorny issues in clinical trial agreements and contracts with drug companies in general, and does so from the drug company perspective. Following his article is an appendix of examples of clauses for each of the topics covered from actual industry-university agreements: these should be an aid for those looking for compromise language that has proven mutually acceptable to other university-industry interests.

These presentations and articles, in summary, represent a synthesis of timely analysis and comment on an important and growing subset of the university-industrial partnership. Comments from readers about the organization of a "special topics" issue would be particularly welcome.

In June, 1987, NCURA sponsored a conference on the "Management of Risks in Research." In a future RMR issue, we hope to present papers based on presentations from the meeting. However, Robert Rosenzweig's address on the changing environment and perception of responsibility for risk management within the university community is a thoughtful and opportune piece. It fits in well with many of the research risks and concerns already covered in this issue. Considering the amount of discussion it prompted at the meeting, delaying its publication until next spring did not seem to be in the best interests of RMR readers.

Obviously, this issue represented a major publishing effort for the journal. The resulting copy may be lengthier than we might have planned, but we had no desire to trade or compromise on substantive content and the benefit of bringing all but one of these complementary topics together in one issue. Two additional papers addressing specific human subject issues in biomedical research have been held for the Spring, 1988 issue of the journal.

Mary Ellen Sheridan  
Editor  
October, 1987

# INTRODUCTION ISSUES IN THE UNIVERSITY- INDUSTRY PARTNERSHIP

Edward L. MacCordy

In September, 1986, NCURA sponsored a national conference to consider a rapidly changing, imperfect, and underdeveloped partnership, that between industry and the nation's research universities including their affiliate hospitals. The partnership has been created by mutual agreement to pursue new scientific knowledge and new technology, an alliance in which each party makes unique contributions. Partnership activities are varied and consist primarily of research sponsored by companies, development and transfer of new technology from the universities and clinical evaluation of prospective company products. Thus, it is a relationship based on technology in which industry has a commercial interest.

In previous years focus was exclusively on new technology protected by patents, and considering the major investment required to bring new drugs to market, patented products are still the primary interest of the pharmaceutical industry. But today we find our institutions dealing in a broader arena, that of intellectual property which may take the form of patentable inventions, copyrightable software, or proprietary materials and know-how.

Recently we have seen growing interest in a new outlet for university technology, that of creating new start-up companies, and this interest probably is a reflection of the fact that all new and commercially attractive technology that comes out of research universities these days is not necessarily attractive to well established corporations. Large corporations have their own agendas. They have a finite capability to absorb new technology. They have criteria of profitability that are not satisfied by all the technology coming out of universities. Furthermore, they must constantly choose among alternative investments, new products being but one set of alternatives. Thus, universities are increasingly exploring an alternative outlet for their new technology,

new small companies that can exploit attractive market niches. Such new start-up companies also allow the universities to actively participate in regional economic development programs. Directly related to this effort we see such things as university based incubators, technology development centers, and research parks.

Although there are significant changes taking place in the university community, technology based relations with established companies continue to dominate. Besides research and technology licensing, there are clinical trials of industry technology utilizing the research and clinical resources of the universities. In addition, one facet of the relationship that has been going on for many decades cannot be overlooked, that of personal consulting with industry by academic scientists.

In this broad general partnership each party brings activities of value to the table. Universities are completely dependent on industry for assessment of whether university technology can satisfy societal needs as represented by market opportunities. From industry revenue streams come the financial resources to support a very expensive and risky process of research, product development, and commercialization of new technology conceived in the university. Industry provides capabilities beyond those of the universities, the capabilities of product development, production, distribution to consumers, and product safety and efficacy assurance whether demanded by government regulation or not.

Universities bring to the partnership mainly a creative contribution. Nationwide university research resources constitute a massive capability operating at the level of \$8 billion a year in expenditures for a research program conducted by in excess of 30,000 doctoral level research scientists. These university research resources are dedicated to the development of new knowledge and pushing out the frontiers of science, with the largest component being in medical science. The new knowledge being developed which may seem remote today represents the foundation for the development of new and better health care products for tomorrow.

This partnership between industry and universities works by an essential but rather inefficient matching of the interests and capabilities of individual participants. This inefficiency stems from two factors. The first is that industry and university use different language to describe their technological interest, the former being in terms of product and process objectives, and the latter in terms of scientific knowledge objectives. The second factor is the formidable problem each university and each company faces in attempting an orderly and comprehensive search of the other sector for matching technological interests. The

matching is dependent on the science and technology base from which each individual company develops its products and processes and the science and technology research capabilities of each individual university. Each interaction must serve a common, current technology interest of both parties. Though this matching of the parties' interests has proven to be productive there are continuing, unresolved problems most of which do not have easy solutions. One is the labor intensive, repetitive process by which agreements on the terms and conditions of individual projects are negotiated. By now it would seem that some approximation of a set of standard agreements for research and for clinical trials would have been developed rather than have each agreement a unique exercise in original draftsmanship and extended negotiation. Then, another problem to be addressed is the pricing of services, the university's insistence on receiving a segregated charge for its indirect costs being the main point of contention.

For this technology based partnership to be most productive the constraints imposed by the bare-bones cost reimbursement financing of university operations needs to be considered. In contrast to industry, universities do not have stable revenue streams to finance technology development opportunities which emerge from their research. Unless industry is receptive to financing such early stage developmental research much potentially valuable technology will die in lab notebooks of university scientists. Thus, a problem area which is presently limiting productivity of the university-industry partnership is characterized by an inefficient process for the matching of the university and industry interests plus a severely limited willingness by most companies to become significantly involved in research funding that will increase the "technology pull" on universities. A university has two basic options for transfer of its new technology: technology "push" and technology "pull". The former is typified by the classical patent-license program which seek buyers for university inventions, a process which must frequently contend with the "not invented here," syndrome in companies. Alternatively, technology "pull" contemplates direct involvement of a company in university research, as sponsor and often collaborator, whereby the company encourages technology development and stands ready to energetically commercial its product.

Another problem with a potential for major, adverse impact on the partnership is rooted partially in the austere financing of universities and partially in the legal system, notably in product liability law. As universities become more involved in technology development with and transfer to companies, large and small, they risk being considered by the courts as active participants in the "stream of commerce."

Simultaneously the courts seem to be allowing claimants to reach farther back in the product development process in their search for “deep pockets” able to pay monstrous damage awards. As court decisions establish new precedents universities become acutely aware that they do not have the product revenue streams of industry to build reserves for major litigation and damage awards. Increased bankruptcy filings, even by giants such as Manville, A. H. Robins and Texaco, and excessively high priced liability insurance has universities concerned that should their financial risk continue to increase it may reach the point where they are compelled for self preservation to cease all technology transfer activities.

Finally, one of the things that we most lack in the university community is an understanding of industry. As we know that universities are quite different, one from another, companies also have these differences. Our ability to interact with companies and to know their interests is quite dependent on acquiring a much better understanding of the industrial sector. For example, too often we in universities oversimplify the problems of our partnership with industry by attributing them to two causes, i.e., industry’s reluctance to accept outside ideas (the “not invented here” syndrome) and industry’s short term attitude toward investing in new technology opportunities. Obviously this is a simplistic view of industry which ignores the fact that each company has limited resources, few companies have mastered finding their way through the maze of 100 or so research universities, and several other relevant problem areas.

This is a brief overview of the issues which are addressed in this issue, hopefully to the benefit of readers from the private sector as well as universities.

# The Biological Revolution: Commercialization of the Molecule

Louis Lasagna, M.D.

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The biological health of the nation affects everyone directly and indirectly, no less than does the economic health of the nation. Universities and the pharmaceutical industry have, as acknowledged by virtually everyone, very special contributions to make to the public health. While the world has made enormous progress in treating the sick during the last half century, much remains to be done. There is hardly any disease for which we could not use either better or safer drugs and for some serious ailments our therapeutic cupboard is essentially empty. Many experts subscribe to the notion that the easy problems in this area have been solved - that what remain are the tough ones. Nevertheless, the basic science research data base has never been so impressive nor scientists so numerous and so talented. Despite the progress and despite the unmet needs, the buzz phrase of the day is "cost-containment." One must hear that phrase one hundred times for every reference to quality of health care. We hear and we read that our society cannot afford to increase the percent of gross national product now being spent on health. We are feverishly trimming the fat off the health care corpus. Drug costs, by the way, seem to be going down. Such efforts have not thus far, in my opinion, been attended by significant compromises in the quality of health care, but the future is quite another matter. New drugs, new surgical procedures, new medical devices, new vaccines, new diagnostic techniques - all of these tend, at least in the short term, to increase medical costs. So, the question is how can we, faced with an increasing elderly population and hence an increasing illness-afflicted society, keep health care costs down and still provide optimal care. Is it necessary to ration such care, despite the obvious lack of scarcity in society's apparatus for providing it? Who shall decide what percent of the GNP is appropriate for health care?

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The public, the politicians, the government bureaucrats, third party payers, rate fixing commissions - who and how? I would submit for your consideration the possibility that the public has been relatively neglected in making these decisions until now. I hope that will change in the future. These brief introductory remarks are intended simply to suggest that this is an especially interesting moment in history to consider ways in which cooperation between academia and industry can be helpful not only to the two sectors, but to society at large. There are some factors that serve to unite academic and industrial forces in this endeavor, but there are also factors which clearly oppose maximal cooperation. It may be useful to discuss these sequentially. Let's start with the unifying forces.

1. Both academia and industry want and need better drugs. The so-called "me-too" drugs which often used to be marketed despite the fact that on many occasions they seemed to resemble clones of older drugs are losing their economic and medical attractiveness. To compete for selection by health professionals and hospitals and for reimbursement on the overseas market, and increasingly even in the U.S. market, a drug has to be superior in some sense to drugs already on the market. I would point out to those of you who are perhaps not that close to the pharmaceutical industry's marketing problems that in most parts of the world, the important decision with regard to a drug's economic status is not approval for marketing but the decision to reimburse consumers for expenditures with regard to that drug. Thus real breakthroughs are more important than ever both medically and as a source of income to innovative firms. In search for such breakthroughs - which have always been rare and always will be rare - society cannot afford to waste valuable human resources, as we have in the past. Academia, in which I've spent a good many decades now, has not previously participated fully in this process, and its really awesome potential needs to be harnessed. We know that the road between basic and applied biomedical research is a two-way street. Basic science research can lead to therapeutic progress, and new drugs, even when serendipitously discovered, can lead to fundamental advances in basic science. Let me give an example. Chlorpromazine was discovered to be an antipsychotic drug, a discovery that was a serendipitous one, but it was not originally developed for that purpose. The drug not only made important contributions to the management of the mentally ill, but provided some insights into what might be going on in schizophrenia. An enormous amount of research has been spawned by the discovery that this drug had something to do with dopamine receptors. While I would not pretend that schizophrenia is simply a

disease, obviously dopamine has something to do with not only the disease but with some of the unpleasant side effects of these drugs. An enormous amount of fascinating research came about as a result of therapeutic progress. In other words, therapeutic progress led back to the basic laboratory.

2. Academia and industry both play a role in educating the laity as well as health professionals about disease, health, medicines, etc.

3. Academia and industry both have an interest in the economic aspects of drug development, including such matters as the rising cost of new drug discovery, the decrease in the effective patent life of new drugs as the drug improvement process lengthens, and the impact of drug-related litigation. Let me give two examples. First, the litigation aspects of pediatric vaccines. The damages that have been awarded in the past, for vaccine-related injury, real or spurious, and the inability to quantify future risks in this area quite clearly knocked out of the market most American manufacturers of vaccines, with unfortunate implications for the public health. Another example is the deleterious impact on post-approval research that comes about as a result of the erosion of effective patent life. Many of the most important aspects of a drug's utility are discovered only after the drug is marketed for the original indication. To get a drug approved for the subsequent indications costs money, it takes time, it consumes human resources, and, not unreasonably, innovators tend to be discouraged about plowing millions of dollars into the search for new indications for a drug when, in fact, generic competitors who have not spent those millions of dollars will be able to profit from such research investment.

4. The decline in NIH and NSF support for basic research has a deleterious impact not only on academia but on industry. In a sense, government-supported research can be looked on as an indirect subsidy to industry, since the building blocks for future drugs on many occasions come out of such research. Large cuts in federal support cannot possibly be made up by private foundations or by industry. The public needs to know this and to be aware that the gradual dismantling of our national research apparatus is a disaster. On the other hand, these pressures are forcing us to consider ways in which industrial research dollars can be spent profitably in academic laboratories, not as philanthropy, but as tough-minded business investment.

5. The biotechnology revolution has provided a new dimension to pharmaceutical development. Research in this field differs significantly from more traditional pharmaceutical development: the basic research is closer in form to the ultimate applied product, much of the expertise has until very recently been based in academia, the biotechnology

industry is a more volatile one than the traditional pharmaceutical venue, the economic advantages of basic research and the value of trade secrets provide pressures for delay in scientific publication that are at least quantitatively different from the case of most academic research, and the quality control aspects of biotechnology products pose challenges that make the usual problems with pharmaceuticals seem trivial by comparison. At a recent meeting of the American Association for the Advancement of Sciences, e.g., one was struck by the repeated references to the evolving and difficult technology in isolation, purification, and characterization in this field. One looked at the abstracts and read such phrases as “new complex analytical problems” and concern over the loss of potency due to “irreversible alterations of the dimensional conformation of proteins” two to three orders of magnitude larger than conventional drug molecules. One reads in these abstracts that sensitive and specific methods were relatively variable and that cell culture impurities could pose an immunogenic threat even when present at very low levels. We are not dealing in this area with a scientific literature of the magnitude and helpfulness of that available for small organic molecules. So, there are serious technical challenges. Finally, the evolving biotechnology industry needs not only capital but the well-developed skills and expertise of the older pharmaceutical industry to address effectively the various toxicological, regulatory, and marketing issues that emerge as new biotechnology products approach regulatory approval.

6. Academic research in the health professions and industry face some common hostile forces. There are the anti-vivisection activists who would like to end all animal research. There are the anti-research Luddites who believe that most researchers are evil Dr. Franksteins and that the occasional ethical problems that surface in the media are typical rather than atypical of the research apparatus. Scientists have enemies who thrive on the well-publicized (even if numerically infrequent) examples of fraudulent research in the industry or academia. Finally, we have the many criticisms leveled at both the pharmaceutical industry and health professionals by the third world and its advocates as a result of the interest of third world countries in making available to their peoples, cheaply and effectively, those products that already exist as opposed to worrying about getting new drugs on the market that are needed for the disease that we can't treat well at the moment. It is not an unreasonable attitude for them to take. If you are a developing country and worried about having your population live long enough to get chronic diseases, it's hard to be excessively preoccupied with the need for solving health problems that don't yet exist when

there are solutions available to the problems that do exist and which could be met by proper handling of the pharmaceutical provision aspects of the national health care scheme.

7. Academia and industry must understand each other's needs and problems. Academics are not all unrealistic fuzzy heads any more than all the people in industry are greedy capitalistic pigs. Cliches along these lines don't help very much, yet to the extent that we can understand each other's problems, and at least talk about them, that is a force pulling the two sectors together. There is a need to understand the rapidly changing nature of both academia and industry. The days when an industrial CEO could be either crooked or stupid or both and still make money for his company are gone forever - thank God! The old "Robin Hood days" of medical care as practiced in hospitals are also gone forever. When I was a medical student, the wealthy patients were charged \$19.00 for a chest x-ray, which was a lot of money in those days, so that the poor patients attending the clinic at that hospital could get their chest x-rays essentially free of charge. Those days are gone. We've developed new ways of trying to deal with those economic problems.

8. Academia and industry can at times help one another in public forums. It's helpful to have industry testify in Congress that private resources cannot make up for big cuts in NIH budgets. It's helpful to industry for academia to testify about a drug export bill that looks like a step in the right direction or the need for tax benefits to encourage the development of orphan drugs.

9. Industry and academia both need to concern themselves with a continued flow of new and high quality professors, nurses, physicians, veterinarians, dentists, and pharmacists. Industry will never be able to train these people by itself, and we need to avoid wild swings of the pendulum between attempts to beef up the output of universities to make up for putative deficiencies in numbers and then a swing to the other extreme, where we decide that we have too many doctors, nurses and Ph.Ds and therefore must cut down on that supply. We need to worry about the disincentives increasingly derived from malpractice litigation. We need to worry about the increasing amount of paper-pushing that health professionals have to engage in, because to the extent that the fun and the satisfaction are going out of the providing of medical care there is a problem for society and for industry as a part of that society. Finally, industry can help academia by providing satisfying employment opportunities for the Ph.D and the other trained human products of academia.

So much for the centripetal forces. What about the centrifugal

forces, the things that pose obstacles to the accomplishment of the maximal good? First of all, industry still has a negative image to overcome in the halls of academe. Many still look on pharmaceutical development as a zero-sum game where some people profit only at the expense of others. In fact, medicine and pharmaceutical development are not zero-sum games. When they are practiced properly, everybody gains.

Most people don't want to be research subjects but want the benefits of research. Most people resent health care costs because they are involuntary - not like the decision to buy a television set or a cable television contract or a new car. Most people don't want their Blue Cross/Blue Shield premiums to increase, but when they are sick they want the best quality care. Most people find it painful to ride the media roller coaster as they read what the newspapers and magazines and television have to say about the benefits and hazards of medical progress. One day one reads about Interleuken-II as a cure for previously resistant cancers, and the next day one reads about still another failure of an artificial heart or the withdrawal of a drug from the market because of excessive toxicity.

Academics who understand the drug industry reasonably well appreciate the need for long-term planning. The pharmaceutical industry is in many ways like the petroleum and natural gas industry. There's a big lag between investing and getting a return on that investment and there will always be. These academics are therefore troubled when they see companies living by the quarterly shareholders' reports or the annual shareholders' meetings. Even when we appreciate that there are good business reasons for such focusing, it is still troubling, because in the pharmaceutical industry you're in the game for the long haul or you shouldn't be in the game at all.

Universities have had a difficult time, in my experience, in being realistic about such things as patents and royalties. It is clear that the potential for university gain in this area is considerable. One figure I have seen suggests that less than five percent of federally held patents, for example, lead to usable products and since the doors opened to academic use of such information by the patent and trademark amendments of 1980, there is a lure there for universities, but the drafts that I've seen of institutional rules for academia dealing with industry with regard to patents and royalties have usually betrayed a naivete as well as greed on the part of the university administrators. At one institution, for example, in the first draft of their patent policy I was struck by the fact that the university seemed to believe that industry should supply all of the resources and get nothing in return, with no sharing of patents or royalties, and essentially all rights remaining to

the investigator, the university, or both. With the passage of time, more sensible heads prevailed and the current rules at that university can be lived with by both academia and industry. There is a tendency in academia to act as if there can never be one moment of publication delay, even when such delay of public disclosure may be crucial to the sponsoring firm in regard to a patent position. There are also problems engendered by traditional academic norms. It has been traditional for academics to follow their noses in research and to be led by independent, self-coordinated initiatives. There's the unfettered freedom to publish to which I've already alluded. There's the fact that academics are evaluated for promotion and tenure by colleagues who use such criteria as the kinds of research they have done, where they've done it, how freely they have published, and what is the research publication record. Academics tend to be solo researchers more often than not, rather than members of a team, whereas in industry, being a research team player is crucial. For years I told what was then an imaginary story but which now has turned out to be fact. I used to say that if a university had a faculty member who received a Nobel prize, even if that institution were doing a bad job of delivering its product, namely education, the alumni and the trustees would be deliriously happy. But if an industrial firm employs a scientist who gets the Nobel prize, and that person is a research director who is not leading the company successfully to its product, namely marketable drug entities, there is unhappiness for the board of directors and shareholders. Such a person might well be fired, a fate that would never befall the academic Nobelist.

(I have talked about these as if they are accepted academic norms, but in fact students of this situation like Polanyi or Merton [see editor's note] have pointed out that academics have always been ambivalent about these norms, even before any question of relations with industry came up. Academics certainly have at times been motivated by less noble principles than the ones traditionally listed.)

There's an academic need to maintain aloofness from the industry in order to have credibility as public critics of industry. Some years ago the city of Cambridge in Massachusetts was having hearings on some biotechnology problems. Scientists who were identified as consultants to industry were ruled out as witnesses able to provide credible testimony.

There's also a need to keep the academic flame burning. We need to keep worrying about where the next generation of professors is coming from. We cannot simply turn over our best and brightest products to industry. We have to maintain good faculties because there are problems that will continue to have to be met in academia by such faculties.

Finally, education is not the same as brainwashing or the promotion of drugs. Academics worry a lot about relations with industry in regard to educational efforts and the possibility that the result will be promotional rather than educational.

What principles should guide industrial-academic collaboration in the future? The answer is simple, in my view. There's a need for mutual respect which, to paraphrase the Smith Barney ads, should be gotten the old-fashioned way, i.e., people should earn respect. Academics have to remember that applied research is important, difficult, and no less worthy than a very focused pedantic interest in some abstruse molecular biological problem. There's a real danger in the wonders of molecular biology in that we may be so preoccupied with them that we'll forget that there are old-fashioned and important things like organ physiology, organ pharmacology, "whole animal" pharmacology, and "whole human" pharmacology. Second, we need clear rules to avoid misunderstanding about the terms of agreement. The relationship has to be based on mutual benefit, because if only one of the partners is benefitting, it will not be a happy relationship. It will not live for very long, nor will it deserve to live for very long. Finally, we need flexibility. At times industry will have to engage in what amount to "intellectual commando raids" on academia, darting in and out, looking for ideas, supporting them temporarily, and then cutting bait when it looks as if the research is not productive. At other times, there will have to be long-term agreements because the problems will only yield to long-term approaches. There is no reason why we can't have consultation relationships for some academics and investigator relationships for other academics.

In conclusion, you may remember that Charles Dickens, whom I consider to have been the greatest novelist that ever lived, opens the *Tale of Two Cities* with these words: "It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair..." That's about the way I feel concerning our present era. There are big threats, but also big opportunities. I can foresee a fantastic multiplier function for pharmaceutical development and for public health if industry and academia are imaginative and resourceful in pooling their talents. It can be done. It *is* being done, to a certain extent. The question is: Do we have the will to do this to the best of our abilities?

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*(Editor's Note: Two possibly relevant publications are: Michael Polanyi's "Scientific Thought and Social Reality: Essays," international Universities Press, 1974, and Robert King Merton's "The Sociology of Science: Theoretical and Empirical Investigation, University of Chicago Press, 1973).*

# The Biological Revolution: View from Pharmaceutical Industry

James R. Knill, M.D.

A book' describing the first sixty years of the American Society for Pharmacology and Experimental Therapeutics (1908-1969) edited by K.K. Chen describes the original Constitution of ASPET as barring from membership pharmacologists in the employ of the pharmaceutical industry. The alleged reason was that the founders and charter members were probably afraid that industrial pharmacologists might be engaged for unethical practices. Time and experience proved this restriction was not justified, and a Corporate Associates Program was initiated in 1958. "The pharmaceutical industry finds it necessary to have the services of basic or clinical pharmacologists as investigators, directors or officers. They are just as indispensable as chemists. The close interplay between these scientists has been a vast source of medical progress."<sup>2</sup>

The concerns in this bit of nostalgia continue to influence the relationship between universities and industry. Science conceived and practiced in the purity of the university is perceived by some to have a greater likelihood of validity than that emanating from the convex and cooperative environment of the industrial laboratory. From the perspective of an industrial scientist, selection of an industrial setting causes academic colleagues to believe that science is relegated to a second place.

Such supposition has no basis in fact. In my own organization, the development of Captopril was recognized as a landmark achievement in medicinal chemistry by the American Chemical Society (Alfred Burger Award), by the R&D Council of New Jersey (Thomas Alva Edison Award), by Medicine Practicienne (Prix Galien), and by the Ciba Award for Hypertension Research. This drug is but one member of a spectrum of medicinals identified in recent years by industrial scientists. Beta blockers, H<sub>2</sub> receptor blockers and calcium channel blockers have markedly influenced patient management. For the most part these agents were made possible through the recognition of therapeutic potential in the basic information provided by academic scientific discovery. Therefore the record of scientific achievement in the biomedical research area already has been a cooperative endeavor, although admittedly informal. Scientific members of both academia

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and industry can share a high level of mutual respect.

This background may explain in part the general impatience and disenchantment that seemed to echo from conversation as preparations were made for this paper. I perceived an understanding of the concerns of the academic partners but impatience in acknowledging or dealing with these special concerns. To enjoy a successful relationship neither party should attempt to change the culture of the other; in fact, the biological revolution and strengthening of future collaboration will be directly proportional to the ability of the parties to recognize and to oblige themselves to maintain these culture differences. A trending of the two cultures toward the mean leaves no differences, no need for agreement, nothing to strengthen, just competition. Negotiators of agreements should bear this in mind. The best method to introduce impedance in the scientific process would be to allow commercial interests to dictate the scientific agenda. It is also, I might add, the best way to end a revolution. Interestingly, the suggestion that cultural purity may be changing as a result of crossbreeding is contained in a recent review by Blumenthal et al.<sup>3</sup> This study, based on a survey of 1200 university faculty members from 40 major universities in 1985 suggests a difference in the method of operation between academic scientific staff supported by industry agreements compared to those who are not. Those with industrial support publish at higher rates, patent more frequently, participate in more administrative and professional activities and earn more than colleagues without such support. Also "...faculty with industry funds are much more likely than other, biotechnology faculty to report that their research has resulted in trade secrets and that commercial considerations have influenced their choice of research projects."<sup>4</sup> Conceivably a trend toward the mean may be in progress. Any attempt to strengthen the cooperative effort must incorporate safeguards to preserve the cultural individuality of the university and industrial partners in biomedical research. Otherwise, essential basic research unadorned by commercial glamor will be relegated to a poor second, if it gets done at all, and applied research will lose its foundation.

Representatives of research, research administration, licensing and legal, all of whom are associated with cooperative agreements within my organization were asked to respond independently to the following request: "Please identify the three primary issues that you believe must be addressed if we are to strengthen the cooperative effort in biomedical research between industry and the universities!"

During this process I was asked by participants; "What will you do if we all provide identical answers?" My reply was I would have three strong issues to bring before this conference. As it turned out, the

individuality of the participants shone brightly as did the impact of their respective disciplines. Opinions were obtained from four (4) senior scientists and two senior members from each of the Licensing, Legal and Research Administration areas. For descriptive purposes I have categorized responses with a representative framework.

Scientific opinion tended to focus on the perception of science in the university as compared to industry. One response: "The mission of the university is to expand knowledge and not to discover drugs," struck me as too strict; however, as the information developed it became evident that industrial scientists perceived the discoveries of basic scientific investigation within the university to be the foundation for drug discovery and development. The role of scientists in the two organizations were interdependent but unique. Their missions differed. University scientists were felt to lack the disciplined focus essential to drug discovery and development. Indeed academic scientists were perceived as having minimal interest in drug discovery, preferring instead the excitement of basic scientific exploration; however, I was advised that university scientists loved to get their hands on drugs that permitted chemical dissection of complex biological processes. When such a mutual interest exists, cooperation is not only beneficial and productive but can be down right exciting. Finally, industry scientists would view positively the development within academia of a spirit of collaboration between disciplines such as Chemistry/Pharmacology, Molecular Biology/Neurobiology and Pharmacology/Pathology.

Enhanced understanding and respect between the scientific communities of the university and industry, while maintaining the critical differences between their missions, has immense positive value and contributes to the biological revolution through successful cooperative biomedical research. Acceptance by academic researchers of the principle of goal-oriented research, as opposed to research solely for the sake of knowledge, along with proper appreciation by industry scientists of the principles of academic freedom and the absolute right of academic scientists to earn recognition for their discoveries are two elements that must be understood. Clearly, the process would be facilitated by identification of mutual scientific interests between their organizations.

Licensing is in need of better understanding. The economic risk in commercialization of any molecule can be taken only if it provides a commercial opportunity for payback and a proper fit with product, research and operating interests of the company. Too often in contractual discussions there is incomplete understanding of the commercial realities by university representatives. An attempt to understand the industry

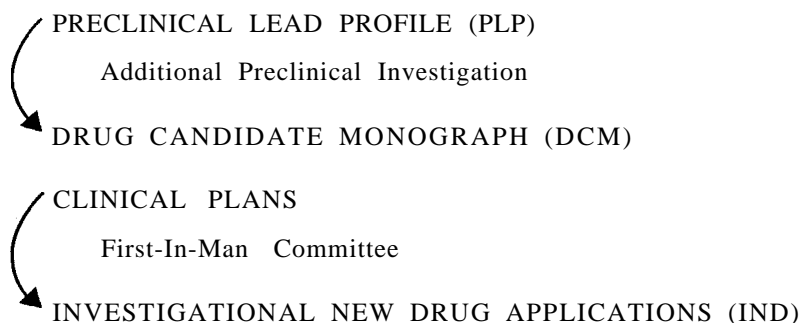
position would be viewed as a positive contribution to biomedical research cooperation. Risks to the molecule are encountered throughout the developmental programs; however, the commitment to a given therapy that draws continuing investments to this process in the face of these risks appear to be unappreciated by members of the university team.

What are they? A molecule once selected for development must survive preclinical pharmacological and toxicological screening, passing such hurdles as mutagenicity and carcinogenicity testing and be demonstrated to have a therapeutic index (activity/toxicity) that permits adequate therapeutic dosage. Such testing precedes human clinical testing by two to three years and costs approximately three million dollars.

This process as practiced in my organization is outlined in Table 1.

Table 1

**Division of Medical Affairs  
Medical Research Process**



A preclinical lead profile describes the preliminary chemistry, pharmacology and acute toxicity of a new lead drug candidate. Review with research management yields authorization to proceed with more extensive evaluation in each of these areas (including subacute toxicity evaluation in three or four species) as well as intensive formulations development work by Pharmaceutical Research and Development (R&D) and assay development by Analytical R&D. Identification of appropriate formulations for clinical evaluation and appropriate methodology to enable the identification of drug substance in biological fluids and tissues are needed to proceed with investigation in humans. Information from these programs provides the basis for a Drug Candidate Monograph that, in turn, is used to develop appropriate

plans for human testing.

At this juncture a formal critical review by a multidisciplinary scientific “First-In-Man” Committee to determine the appropriateness of proceeding into human clinical testing. The endorsement of this Committee is necessary before the filing of Investigational New Drug applications (IND) with regulatory authorities. The Food and Drug Administration after a 30-day review period either permits the initiation of human clinical programs or may raise questions requiring responses before the research proper can proceed. The FDA review at this stage is a model of efficiency and precision, and the requirements for background preclinical support data are well conceived.

Complete clinical evaluation requires approximately 4 years and longer if extended long-term human exposure is needed to support intended chronic use. Table 2 outlines the phases of the clinical research process, their magnitude and an estimate of these requirements. By design, limitation of human exposure in Phase I and Phase II is intended as a safeguard until reasonable assurance of an acceptable therapeu-

Table 2

**Division of Medical Affairs  
Medical Research Process**

|                            |  |
|----------------------------|--|
| PHASE I                    | Metabolism, Bioavailability, Clinical Toxicology, Pilot Efficacy<br><br>(~100 volunteers and/or patients)<br><br>9-12 months |
| PHASE II                   | Dose Response Efficacy and Safety<br><br>( ~300 patients)<br><br>12 months   |
| PHASE III                  | Efficacy and Safety Vs. Placebo and Positive Control<br><br>( ~2000 patients)<br><br>12-24 months                            |
| New Drug Application (NDA) |  |

tic index has been obtained. Only then are the more extensive proof of efficacy and safety studies begun in Phase III. As patients are exposed to the new drug, those who benefit remain on the drug (with their consent) providing up to 24 months of long-term treatment experience over the course of the clinical program. The latter experience documents the safety of those agents intended for long-term use. The New Drug Application (NDA) incorporates these data along with preclinical, technical, process and manufacturing data (see below) to enable regulatory review. Regulatory approvals permit the sponsoring organization to market the drug. Combined fixed costs and out-of-pocket grant costs for the clinical programs amount to 20-30 million dollars.

At any time during this process unacceptable toxicity or inadequate efficacy can interrupt the development process. On occasion this may not be encountered until humans have been exposed to the molecule for six months or more. Although responsible development programs define the safety profile of a potential new drug in a population of several thousand patients and support labeling contained in a new drug application, unacceptable events occurring with a low incidence (1 in 10,000 or less) may not be encountered until a drug has been marketed. M.J.S. Langman<sup>5</sup> recently discussed this issue noting "If modern drugs are perceived as powerful but relatively safe-they will be widely used, and in these circumstances toxic reactions of low frequency will become increasingly important." The unavoidable reality is that if prescription numbers are in millions but reactions occur once every 10,000 treatments then reactions will occur in hundreds. Paradoxically, however, the individual general practitioner who prescribes may not expect to meet such a reaction even once in 10 years. Several instances of this have caused the removal of apparently useful drugs from commerce. Thus full understanding is impossible (theoretically) until marketing of the drug broadens human exposure. Such secrets are uncovered through efforts to accomplish post-marketing surveillance studies and through spontaneous adverse reaction reports.

During the clinical development phase additional significant expenditures continue to occur in support of chronic (1-2 year) animal toxicological studies, pharmaceutical development of appropriate dosage forms and biological or chemical process development. The latter methodology is designed to produce commercial quantities of high quality bulk drug substance within acceptance standards. It is estimated that the total developmental effort can consume approximately 7 years and 50 to 100 million dollars. At least 10 years will have passed before a financial break-even point will be realized, given diligence in regulatory review and approval and in the marketing effort. Because the magni-

tude of time/money commitment of industry is extreme, it becomes understandable why licensing also considers patent coverage and exclusivity as key issues. A period of exclusivity is key to achieving the financial break-even point. These commercial realities dictate that material benefits to the university can come only if the industrial partner is protected against avoidable competition in the commercial sphere. Success depends upon practicing the maximum degree of secrecy consistent with the rights of the academic partner. This will involve some sacrifice on both sides. Any potential delay in achieving commercial goals through competitive dilution of economic return or for any other reason decreases the enthusiasm of industry for any cooperative research endeavor.

From the legal standpoint, patent coverage and exclusivity also were mentioned as issues. However, in addition, publication/disclosure was a key primary issue. Legal representatives were aware of the need for open and prompt publication of research results by university scientists. This need was contrasted, obviously, with the need of industry to avoid the public domain until appropriate patent protection has been sought. Although there is no intent to influence or prevent publication, a right of review of 30 to 60 days would permit attorneys and scientists in industry to identify potentially patentable information that conceivably might have been overlooked or ignored because of lack of interest by university faculty.

If liaison is close between the scientific and legal communities of the university and sponsoring industry throughout the full term of any agreement, such occurrences should be limited in number since patentable information should, with good communication, be recognized during the course of any research program. Sensitive handling of this issue should preserve academic scientific rights while avoiding any compromises of mutual commercial objectives.

Administration identified publication/disclosure as a key issue along with the need for exclusivity; however, a good mutual understanding of the nature of the research to be conducted under an agreement oftentimes was a potential issue. It was my judgment that this concern may have been based on the real possibility that although the respective scientific communities may be aware of the nature of the research other disciplines were not. This potential lack of understanding may arise out of a lack of recognition of the need by the scientific communities to communicate with their associates. Alternatively it could represent an inability of administrators to understand certain of the nuances. Whatever the reason, any disagreement between the scientific collaborators becomes difficult to resolve administratively or legally when

understanding is incomplete. Therefore, at the outset the time and trouble associated with educating legal and administrative colleagues and ensuring that they remain fully informed has real value in conceptualizing any agreement and ensures its maturation.

Finally administrators concern themselves with economics in another way. They recognize the need to provide a critical mass of funding and assure its availability for a defined period (usually 5 years). The duration of funding must provide adequate time to meet defined research objectives. A review process will permit evaluation of research achievement and provides the basis for extension of the agreement. Obviously, an agreement with provision for renewal financial support can be motivating and beneficial to members of both organizations.

Strengthening the cooperative effort in biomedical research will contribute positively to the biological revolution providing key issues associated with the process of product commercialization are considered. From both the industry and university vantage points, responsible agreements will recognize and acknowledge the need for:

- 1) Maintenance of and mutual respect for scientific cultural integrity.
- 2) Clear identification of mutual scientific interests and objectives.
- 3) Recognition of economic risks as well as benefits.
- 4) Development of guidelines for publication or disclosure of research findings.
- 5) Provision for patent protection and exclusivity.
- 6) Arrangements for adequate and stable funding with both review and renewal provisions.

Within these guidelines, in my judgment, will be forged the elements of a successful and continuing revolution.

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# Competing for Pharmaceutical Industry Funds: Planning Issues for University Research Managers

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Abstract. A university or department or division within a university which is seeking pharmaceutical industry funds in support of its research programs is, by definition, participating in a competitive process. The authors present their point of view which is based on the management premise that success in this kind of competition is a planned phenomenon and that university research managers can take the lead role in such strategic planning statements, i.e., documents which detail an academic unit's basic policy towards competition for pharmaceutical industry funds (usually discussed in terms of focus versus diversity) together with the operating systems and structures it will build up in order to activate its policy. As they relate to the development of capability statements, specific planning issues concerning research personnel and management support services are examined, and, in conclusion, examples of how university research managers can use capability statements for marketing as well as planning purposes.

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In their role as strategic planners, it is useful for university and industry research managers alike to recognize that in certain fundamental ways there is little difference today between what goes on in an academic research institution and what goes on in a pharmaceutical company. Both kinds of organizations want and need to do basic research and seek to recruit and retain the most productive professional, technical, and support talent available to achieve this end. Also, both want to generate sound basic scientific data to guide and give direction to their future activities and to translate that basic research into some meaningful or gainful end. In either setting research is not undertaken unless it can be justified or shown to be significant in terms of some broader, longer-range objectives. Thus, it seems reasonable that a profit-making organization would often want to help fund the research of an academic group and to make use of the data which it produces. From this perspective, a university research manager might ask, "What are the specific ways this kind of partnership can be activated? What models for approaching industry sponsors are most effective"?

All university research managers are concerned today about the relatively steady, and in some cases decreasing, amount of external funds which are available to support an increasing number of academic scientists and laboratories. Along with the emergence of contract research firms, this creates increased competition, and the competition today is talented and deep. Frequently, quality academic research goes unfunded or is supported at reduced levels with intramural funds. Some university research managers seek to redress this situation by working, primarily through political and legislative means, for increased extramural funding. We recommend a complementary approach - one which focuses on helping a university to find and develop different ways it can compete successfully for limited funds. Our approach is based on the management premise that successful competition is a *planned* phenomenon.

In terms of planning to compete effectively for pharmaceutical industry funding, a university or a department or division within a university should begin by considering two fundamental issues:

- 1) the kinds of commitments for competition which it wants to establish and;
- 2) the operating structures and systems which it will build in order to activate these commitments.

This does not imply a value judgement that an academic unit ought to have any one kind of commitment or structure for competition, although some can clearly be more effective than others in terms of obtaining grants; however, an academic unit must begin by specifying

the particular niche within which it wants to compete for pharmaceutical industry support. In this way, it will have a meaningful and useful foundation or point of reference to guide its subsequent research development and grantseeking activities. The unit should spell out its thinking and achievements with respect to its commitments and structures for competition in a brief written document which we will be referring to as a capability statement,

### **CAPABILITY STATEMENTS**

An annual report or a project listing may outline areas of faculty research interest and what research an academic unit is doing or has recently accomplished. A capability statement expands upon this information but is a distinctly different kind of document which details the professional and technical skills, resources and support services the unit is offering in specific areas of research performance. An effective capability statement should begin with a description of the unit's basic policy for planning and developing its competitive niche. Basic policy can be discussed in terms of focus versus diversity, as outlined below, and can then be followed with specific examples of what the unit is doing to implement its policy - particularly in critical operating areas such as research personnel and management support services.

Focus versus diversity. In order to create a plan for competition, a university or a department or division within a university must first decide on a basic policy - i.e., whether it wants to pursue a focused or a diverse approach in its interactions with the pharmaceutical industry. Focused activities can help an academic unit to establish leadership in a specific area of research activity. Based on its record of successful performance over time, for example, XYZ University may become synonymous with pharmaceutical dosage form work, or with pharmacokinetic studies of antibiotic compounds, or with Phase IV clinical trials of nonsteroidal anti-inflammatory agents in the treatment of osteoarthritis. Focus represents a depth or density of research personnel, research resources, and professional-interest networks with pharmaceutical industry scientists for the purposes of peer review and grantseeking which have been established within a unit. It may be in one research area or in several distinct pockets. In a focused mode, individual projects complement and potentiate each other, and findings from one study naturally form the basis for new studies which may be proposed to pharmaceutical industry sponsors.

On the other hand, diversity implies less depth or density and projects which are not interrelated and do not necessarily develop into subsequent work. That is, successful performance on a project in one

area may not help the institution to secure work in different areas or even additional (“spin-off”) work in the same area. A pharmaceutical sponsor, for example, may be pleased with the performance of the oncologists in a department of internal medicine with whom it has been placing its Phase III and IV clinical trials of anticancer chemotherapeutic agents - primarily because they deliver the patient panel and the number of usable case report forms called for in the study protocol. On this account, the sponsor may want to begin funding the department to perform Phase II toxicity studies with health volunteers and/or additional bioavailability work based on tissues biopsied from subjects in the clinical trial studies. In either case, however, unless the department has the requisite depth (i.e., a willing and able Ph.D. laboratory scientist), it will not be in a position to undertake such projects.

Also, diversity with respect to research sponsored by the pharmaceutical industry can be risky in and of itself since help with technical, financial, project management or other problems inside an individual faculty-investigator’s capabilities may not be forthcoming in timely fashion from elsewhere within the university. By necessity or circumstance, academic units which are new to competition for pharmaceutical industry funding often begin with a diverse approach. Over time, however, diverse activity can be developed into pockets of focus. The discussion below of two principal operating areas crucial to establishing a focused approach, research personnel and management support services, gives suggestions for the academic unit which plans to accomplish this.

*Research personnel.* Once an academic unit has elected to pursue focus as its basic approach to competition for pharmaceutical industry funds, it can begin planning for what types of research personnel it will support, in which scientific areas, and in what ways it will help them to grow and develop professionally. In this regard, it may wish to consider the following personnel issues.

*Ph.D. faculty.* Will a clinical department in a medical school recruit and appoint Ph.D. scientists as faculty members to perform research in areas which complement the practice interests of the physicians in the department? This can be a particularly effective grantseeking strategy because it puts scarce resources which are valued by the pharmaceutical industry (i.e., patients and diagnostic and pathologic specimens) together in one setting with the laboratory scientists who can study them in meaningful and productive ways.

Ph.D. faculty can also serve as mentors for faculty physicians who are new to research but who wish to develop their practice experience

and insights into clinical applications which may be of interest to pharmaceutical industry sponsors. This can be accomplished by providing advice and guidance on the design and performance of pilot studies and the preliminary analyses of data which are required to bring forward a fundable proposal. One example of this kind of Ph.D.-physician interaction is a urologist at the University of Medicine and Dentistry of New Jersey who was concerned about reducing the incidence of infection he had observed with indwelling catheters. He first worked together with a Ph.D. colleague in the Department of Surgery on pilot studies of surfactant coverings for catheters to which a variety of antibiotics could be bound. Subsequently, they licensed this application to a pharmaceutical firm for further development.

*Physician faculty.* Will a clinical department in a medical school recruit and appoint physicians to full-time research faculty positions, and/or will it provide its physician-investigators with release time dedicated to research activity? Will the school or department pay for research training fellowships at outside institutions for young physician-investigators who are committed to research careers in academic medicine? These are all exciting faculty development strategies because they help physicians to build up the skills, experience, and record of performance required of independent investigators. They can all be effective grantseeking strategies, too, because they directly address two primary concerns of pharmaceutical industry sponsors - (a) Is the pressure on a physician-investigator to produce clinical practice income balanced by his or her commitment to produce clinical research? and (b) Does a physician-investigator have the real time to become and remain involved in the research work which he or she agrees to do?

A university can further emphasize its commitment to research faculty through its policy for the return of salary and indirect cost recoveries to faculty-investigators whose grants include these kinds of funds. With regard to salary recoveries, for example, in accord with our AAUP contract at the University of Medicine and Dentistry of New Jersey, bonus payments are made directly to any faculty member who is awarded a grant (including a pharmaceutical industry grant) which supports a portion of his/her salary. Such payments are equal to one-third of the grant support for a faculty member's salary up to a maximum of \$5,000 per fiscal year. Any remaining salary recoveries are placed in a departmental account for the investigator to use (with administrative overview by the department chairman) in further support of his or her research programs.

Indirect cost recoveries are a percentage of direct costs and are negotiated individually with each sponsor. At the School of Osteo-

pathic Medicine of the University of Medicine and Dentistry of New Jersey, approximately 15% of indirect cost recoveries from a grant are placed in a departmental account for the investigator to use (with administrative overview by the department chairman) in further support of his or her research programs. The remaining indirect cost recoveries are distributed at the state, university, medical school, and department levels; in some cases, department chairmen have passed their share back to the investigator's account.

Research nurses. Will a clinical department in a medical school provide the seed funds to hire a research nurse (initially, perhaps, on a part-time basis) to help its faculty-investigators in the performance of clinical trial protocols? Additional funding for research nurses can be obtained through the budgets for clinical trial studies which the department's faculty-investigators negotiate with each sponsor. Most clinical trial sponsors want to pay for the time of a research nurse to help the principal investigator with various administrative aspects of the study. This might include, for example, preparing the documents needed for Institutional Review Board approval before the study can begin, screening office patients and informing them about the study and the opportunity for them to participate in it, and completing individual case report forms and scheduling subjects for study visits according to protocol throughout the course of the study. Over time, a department's successful record of clinical trials performance, which its research nurse can in large part help to produce, will usually result in the placement of larger and longer-term studies with that department.

A related approach to pharmaceutical industry funding for the services of a research nurse was recently taken by a rheumatologist at the School of Osteopathic Medicine of the University of Medicine and Dentistry of New Jersey. Together with a Ph.D. colleague in the Department of Medicine, he is being sponsored by a pharmaceutical manufacturer to study, in-vitro, the effects of recombinant human interleukin-1 on human articular cartilage and chondrocytes in osteoarthritis and the pharmacological modulation of such responses. He has arranged, through the Department of Surgery, for the human articular cartilage samples necessary for this study (i.e., cartilage which is normally discarded during joint replacement surgery). Accordingly, the sponsor has agreed to pay for his research nurse to monitor the surgery schedule, to harvest sterile samples from the orthopedic surgeon in the operating room, and to document the clinical histories of patients from whom samples are taken.

Management *support services*. Pharmaceutical industry researchers are concerned not only with producing sound and meaningful scien-

tific data but with producing it in timely and cost-effective fashion as well. To achieve this, they may call on the professional advice and guidance of line supervisors, team leaders, project managers, and support personnel in areas such as budget accounting, purchasing, and equipment maintenance. University researchers, whether or not they have this kind of support, are expected to perform similarly when dealing with the pharmaceutical industry. There is no compelling business reason for the pharmaceutical industry to be sympathetic to a university's internal productivity problems.

In this context, a university which is planning to compete for pharmaceutical industry funds must decide how it will help its faculty-investigators to manage and support their research programs. It must decide in what operating and management areas and in what ways it will help. Is it ready, for example, to waive or partially support vivarium per diem costs to help faculty-investigators set up their animal colonies and maintain them in periods between grants? Or, does it plan to provide an inspection service and maintenance contracts and to store spare parts for shared laboratory instruments to help prevent unnecessary delays due to down-time? And, at the most basic level of planning, how will the university organize its research division or office or research administration to help faculty-investigators manage resources, anticipate problems, otherwise prevent crisis management - and thereby permit them to hone in more and more on the science they have agreed to produce?

## **CONCLUSION**

Within this kind of framework, capability statements can serve as planning documents for research managers in universities or other academic units which want to compete for pharmaceutical industry funds. They discipline the unit in spelling out its basic policy for establishing a competitive niche, usually discussed in terms of focus versus diversity, and over time can also serve as guides and models for setting up the unit's first and/or subsequent pockets of focus.

A capability statement can be of help to university research managers in at least three other ways, as follows:

1. As a pre-marketing statement which represents the unit's prior discussions/negotiations with its own faculty-investigators and what they have agreed to do in terms of research sponsored by the pharmaceutical industry. Prior discussions are the most effective method for preventing lose-lose situations like those in which a faculty member makes a commitment, on the basis of expressed interest, for a scope of work which either his/her own

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or the unit's capabilities cannot support. This might include, for example, a physician who agrees to participate in a multi-center clinical trial but whose practice is not yet sufficiently organized to deliver the number of study subjects and usable case report forms required by the protocol.

2. As a marketing tool for honing in, together with pharmaceutical industry researchers and research managers, on areas of mutual (or complementary) professional interest.
3. As a negotiating document which outlines in upfront and straightforward language the academic and intellectual wants and needs of faculty-investigators in areas such as patent, licensing, and publication rights. In this way, a faculty member's professional concerns can be incorporated early on as building blocks in the development of projects with pharmaceutical industry sponsors - rather than as stumbling blocks to them later on.

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# Agreements at the Pharmaceutical/University Interface

Katherine Ku

Abstract. Specific agreements which arise at the interface between universities and pharmaceutical companies include sponsored research agreements, license agreements, clinical study agreements, material transfer agreements, and patient consent forms with respect to commercialization rights. The article points out particular issues pertinent to these agreements about which research administrators should be aware. Because the interface is fundamentally a good one, based on mutual respect and complementary interests, the issues should be thoughtfully resolved.

## I. INTRODUCTION

**T**he fundamental interface between pharmaceutical companies and universities is a very good one (actually, one of the best among the industry-university relationships) for many reasons:

1. Pharmaceutical companies understand the need for and the value of research. Because they internally spend much money, time, and effort on research, they themselves have an appreciation of university-based research.
2. Pharmaceutical companies are willing to take risks. They know that they may have to screen hundreds of compounds in order to find the one that is going to prove effective and marketable. And so, although university technology is usually at an early state of development and thus very risky, pharmaceuticals are more willing to take the risk by collaborating with universities and willing to recognize the university's contribution by sharing with us some of their rewards, if any.

3. The pharmaceutical industry believes in and respects patents. They often license technologies to each other so they've been very supportive of university licensing programs, in general.  
The origins of biotechnology came out of university research. Cohen-Boyer gene splicing and Kohler-Milstein hybridoma technology gave rise to a new industry and form the basis of the newest innovations in the pharmaceutical industry. Thus, when we examine the biotechnology revolution, we can also find reasons why the pharmaceutical-university interface is fundamentally strong.
4. The pharmaceuticals have generally recognized their need for a "window" into university research. Biotechnology is very fast moving. Because university researchers have been at the forefront of this biotechnology, companies have sponsored research programs at various universities, e.g., the Hoechst/Massachusetts General Hospital and Monsanto/Washington University agreements.
5. The exchange of biological material between industry and university scientists has become very important. Several years ago, the flow was from universities to industry, i.e., university researchers biological materials such as vectors or fusion partners to use in their industrial research. Now university researchers are interested in receiving materials such as IL-2 or alpha-interferon for their research. This exchange is providing an interface that is important both for university research and for industrial development.
6. Pharmaceuticals have been willing to recognize and acknowledge university contributions to the biotech industry by being licensees and paying royalties. For example, Stanford's Cohen-Boyer program has eighty-one (81) licensees including the major pharmaceutical companies who are investing in recombinant DNA. For example, Lilly is paying royalties on human insulin and Genetech is paying royalties on human growth hormone.
7. Lastly, with the new biotechnology products coming on the market such as interferon and IL-2, clinical trials at universities and hospitals are essential. These products are new. Generally, they have not previously been available, and they need to be tested in patients. Who has the patients? We do - the hospitals and universities.

## **II. SPECIFIC AGREEMENTS WHICH OCCUR AT THE PHARMACEUTICAL INDUSTRY- UNIVERSITY INTERFACE**

The agreements of pharmaceutical industry-university interface include sponsored research, license agreements, clinical studies, material transfer agreements, and patient consent forms. Each type of agreement and specific interesting issues are briefly discussed below.

### **A. Sponsored Research Agreements**

At many universities, the indirect cost rate for industry-funded research is higher than for government-funded research. Industry, understandably, always negotiates to pay the lowest indirect cost they can. It seems that most pharmaceutical companies now are reasonably accepting of universities' indirect cost structures. Publication review used to be a problem and is much less so now. Most universities will and should allow only a limited delay on publication, if any, because of our faculty's need to publish. Industry is beginning to understand university priorities better, and so we are not finding too much resistance on that front.

Many industrial sponsors want to include a confidentiality clause in research agreements, requiring the university to keep the sponsor's proprietary information confidential. As you all know, it is a major challenge, if not impossible, for a university to maintain confidentiality. Each university must decide its own "confidentiality" policies and what kind of terms are acceptable. Industry must understand that the strength and advantage of the university environment is its openness, the freedom to exchange ideas and the chance for cross-fertilization.

With few exceptions, industry sponsors are agreeable to universities retaining title. And so "title" is not usually an issue; however, issues arise in the "option to a license" clause. Many times a sponsor will want an exclusive, royalty-free license, which is essentially the same as "title." Each university needs to decide whether it is willing to give in on those kinds of terms or whether it is going to forego the funding (and we all know our faculty want that funding very badly). Thus, there is funding pressure to give in to certain demands from industry. The pharmaceutical industry generally understands that they are expected to pay patent expenses and a royalty for inventions arising out of the research if they have an option to a license.

For many universities, a royalty-free license to a research sponsor involves a policy decision because the university will be foregoing the ability to influence technology transfer and a share

of potential royalties, if any.

The indemnity clause in a sponsored research agreement is a potential problem. Although typically, in Stanford's agreements, we ask a sponsor to indemnify Stanford, some sponsors are not willing to do so for their own reasons. This is an area which deserves further attention.

**B . *License Agreements***

License agreements are another interface. Recently passed, PL 98-620 gives universities a flexibility in licensing large companies, such as the established pharmaceutical companies. You may recall that PL 96-517 placed a restriction on the length of the term of exclusive licenses to large companies: five years from the first commercial sale or eight years from the date of the agreement, whichever came first. Now, with PL 98-620 removing the restriction on exclusive license terms, universities will likely have more pressure to grant life-of-the-patent exclusive licenses. At Stanford, our practice is to grant exclusive licenses for a period long enough for the licensee to recoup its investment and to make a reasonable profit. Admittedly, these can be vague standards, but we believe that 17 years of exclusivity is often too long. Industry, however, believes otherwise and will undoubtedly wish to negotiate the longest term of exclusivity possible.

One issue facing industry and universities is royalty layering. The Licensing Executive Society (LES) Biotechnology Committee has addressed this increasingly complex issue. Universities are eagerly filing patent applications and aggressively negotiating licenses, and all inventors think their invention is especially significant. In most cases, the reality is that we have only a piece of the pie. Even if each university negotiates only a half a percent (0.5%) earned royalty, pretty soon the total royalty per product can stack up. As royalty layering becomes a growing concern for companies, universities will likely find more resistance by companies to paying even a small royalty.

Universities should understand what is being licensed and what part it plays within the realm of the technology. Many bio-materials and technologies are not unique. Generally, if an area of research is hot, there are many players at many universities doing similar research. Some inventions may be just one piece of a larger pie; while the invention may be important, it is but a small contribution to the overall product, e.g., there may be three other inventors in various other institutions that may have similar inventions. Many times, our technologies are not unique. Researchers may have

developed a cell line which is licensable but another university may have something that is quite similar. There may be other cell lines that produce substantially the same material. Even if the licensable material is not unique, one can make allowances for "substantial functional equivalents" in the marketplace. One way to handle this situation is to agree that if there is a substantial functional equivalent marketed by the competitor above a certain level - such as 25% or 50% of the market - then the royalty rate will be lowered.

C. *Derivatives and Equivalents*

"Who owns derivatives" is an interesting issue. Those knowledgeable about biotech know that cells proliferate on their own and they often mutate spontaneously or through the intervention of man. Who owns these derivatives, whether they change spontaneously or whether they are man made? The results of a survey by the Biotechnology Transfer Committee of the Licensing Executives Society reveal that there is little agreement on what is or is not a derivative: Scientists define derivatives one way and lawyers define derivatives another way. There is no easy answer. If covering biological materials, the agreement should define derivatives and specify who owns derivatives.

The insurance clause, if required, may be an issue. Are university licensors going to be held responsible if a product that is developed by the licensee turns out to have some problem? To date, straight patent licensors have *not* been liable but the current litigious climate means that the university licensor may be in the chain of those being sued. Stanford is now requiring insurance clauses for "risky" technologies, such as therapeutic licenses which involve biological materials which will be used to develop a drug. Even though we have an indemnity clause, we also require an insurance clause because the indemnity provision is terminated if the license agreement is terminated. The insurance covers activities "during the agreement and thereafter resulting from the agreement!" For risky technologies, we generally ask the company to provide \$50 million coverage per occurrence. Most small companies are not able to buy insurance at those levels. Although the large pharmaceutical companies have been agreeing to such levels, in general, these large companies are not the ones about which we worry. We are not concerned about Hoffmann-La Roche going out of business; we *are* concerned about the small biotech company going out of business. And these small companies are the ones who are having trouble getting the insurance.

Try to be flexible. For small companies, we have agreed that they will have \$1-\$5 million worth of insurance per occurrence during Phase I and Phase II clinical trials. The rationale is that Phase I and Phase II include a limited number of patients and involve a controlled situation, so we feel that the risk is reasonably assessable and containable. We do, however, then require the sponsor or the licensee not to proceed to Phase III clinical trials or general marketing until we have mutually agreed upon the appropriate insurance levels.

The insurance industry is basically in an upheaval right now. We hope that in the next few years biotechnology companies will be able to obtain affordable insurance coverage. On one hand, we are not sure if \$50 million per occurrence is enough insurance in these days of big judgements, but, on the other hand, if there is legislation, \$50 million may be unnecessary. The insurance situation is unpredictable for now, both for university licensers and for biotechnology and pharmaceutical industries. We need to work together for a reasonable solution,

D. *Clinical Studies*

Clinical Studies are a very active interface currently. As Stanford, the indirect cost rate is lower for clinical studies than for sponsored research because clinical studies are performed in patient care areas where some of the costs are met by patient rates. Clinical studies are not considered “research” because a specific protocol, like a recipe, is required and must be followed. Thus, we do not see the necessity for patent/licensing provisions in the clinical study agreement. In addition, if a company is funding a clinical study, presumably they have patent protection on the substance being studied so additional patents are generally not necessary.

The concern about confidentiality was mentioned earlier. Recall, it is very difficult for universities to keep data or company information confidential. Thus, we encourage companies to make private agreements with the faculty whereby the faculty agrees to keep information confidential. As an institution, we make reasonable efforts to keep confidential those materials that are clearly marked, but, in general, industry needs to recognize that confidentiality poses a very practical implementation or enforcement problem for universities.

The “access to data” clause in our clinical study agreement apparently has raised questions. We generally agree to give the sponsor reasonable access to records as required by the FDA regulations. But some sponsors want more access. The university or

hospital then must balance the patient's need for confidentiality against the PI's need to publish research results.

Indemnity with respect to clinical studies has been a problem. For example, a company gives the faculty doctor materials to test in patients, but the company claims that it cannot control the doctor's activities or know whether or not the doctor will administer the drug properly, etc. With this rationale, a company does not feel compelled to indemnify the university. On the other hand, the university believes that the faculty doctor is receiving essentially unknown material from the company. The doctor often does not know whether the drug is safe or effective in humans, how pure it is or whether or not it might cause some side effects. The university position is that the company ought to indemnify the university. I think there is some validity to both perspectives; it is an issue that needs to be resolved reasonably. The university may have to decide if the clinical research funding is worth the risk of not having an indemnity or insurance clause.

E. Material Transfer *Agent*

Another interface which has been active lately is the material transfer agreement. In the early days, the flow of biological material was from university researchers to company scientists. Now with the companies producing novel biomaterials, our faculty are eager to use these materials in their research. Should there be patent and licensing provisions in material transfer agreements, either from industry or universities?

Our basic position is that we would like to encourage the uninhibited free exchange of biological materials among researchers without concern about proprietary positions. But, we are also realistic. Many companies are very protective of their material and will not exchange biological material without some assurances. We are seeing three kinds of agreements. Company A asks that: (1) the PI not transfer the material without company's consent; (2) the PI not do any other research other than the studies that are specifically described; (3) the PI provide a written report; and (4) the university hold Company A harmless. Such an agreement is short and not unreasonable.

Company B requires (1) that the PI use the material for research purposes only with no further transfer without Company B's consent; and (2) an option to a royalty-bearing nonexclusive license with the right to negotiate an exclusive license. Although the nonexclusive license may not be the best means to encourage technology transfer, this is not an unreasonable agreement.

Company C requires that the PI not transfer the material and that the material be used in *in vitro* research only. In addition, the agreement requires that the material not be used in research which is subject to other consulting or licensing obligations. From the company's point of view, they do not want to give the PI valuable material and have the PI use it for research which would benefit the company's competitor. From the university perspective, most of us have licensing obligations to the government so universities need to be careful about wording. The university and PI need to make sure they can comply with this provision. The company wants the PI to submit a manuscript for review but does not imply that the company could require the PI to withhold publication. Finally, the company wants a first option to an exclusive license or a nonexclusive license. A "first option" is different from Example 2 wherein Company B wants the right to negotiate an exclusive license. From Company C's perspective, they have proprietary rights in the material and many researchers want the material. If an invention arises out of university research, the company would like to have a first opportunity to a license. Each university must decide whether or not it will give a company a license or an option to a license without any funding money changing hands. Our general policy would be to not give rights. Since this is a research material transfer only, no indirect costs are involved and no Company C dollars are coming to the university. Someone else is paying for the research.

F. *Patient Consent Form*

Patient consent forms raise two potentially important issues:

1. Who owns a patient's cells? A well constructed patient consent form can help to resolve the issue. One proposal is to give a patient a consent form with three choices: (1) the patient's biological material cannot be used for research purposes; or (2) the patient's biological material can be used for research purposes only; and (3) if the material can be used for research purposes, the patient chooses either to waive any right to any royalties or the patient wants a share of the royalties. An alternative is to give patients a choice to allow or not allow researchers to use the patient's biological material for research and possible development. If the patient does not want his/her cells to be used, they are automatically discarded. Because almost all the pharmaceutical products that are coming out of biotech are based on human biological material and the genes must come from

somebody, it is an issue that is very pertinent.

2. How informed is informed consent? A company wants to do tissue plasminogen activator (TPA) clinical trials. A patient in a heart attack situation is given a consent form to sign; e.g., do you (patient) want the experimental drug TPA or do you want the traditional drug urokinase (or streptokinase)? Even without a consent form, this would be a difficult decision. In situations, where there has been no cure (such as AIDS or cancer), perhaps it is not such a difficult choice. But in this heart attack scenario where one has the choice of a new drug that has not yet been approved by the FDA versus an old drug that has been approved by the FDA, what is the meaning of consent?

In summary, the relationship between pharmaceutical companies and the universities is an excellent one. There are and will always be issues that we need to work out, but as long as we understand each side's perspective, remain flexible, and recognize the mutual benefit of working together, we can resolve any situation.

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Editor's Note: All of the above publications with the exception of "Ownership of Human Tissues and Cells" are available upon request at the NCURA National Office.

# Problems in Clinical Trial Agreements

David A. Seligman

Abstract. These comments mainly concern clinical trial agreements. Points to be covered include the need to specify what is actually being paid for in the way of research activities and reports; the need for and purpose of confidentiality provisions; publication review provisions; patent arrangements; the need for indemnity provisions and what these provisions should provide; and certain points concerning informed consent requirements and termination provisions.

These comments reflect the author's concepts with respect to this type of agreement and do not necessarily **represent** the policies or practices of the Hoffman-La Roche company.

## **OBJECTIVES AND PAYMENT FOR THE STUDY**

It is important to determine the objectives of a study in order to properly define what is being funded by the sponsor and how the financial arrangements for the study are to be formalized.

The item which a company finds most useful is what might be termed a completed evaluable case report. This is a report on a subject who has complied with all of the conditions of the protocol; who has taken the drug, placebo or control; who has completed all of the tests required by the protocol and who has completed all of the requirements of the study. After this we have case reports on subjects who might have completed the study but for one reason or another are not evaluable with respect to a determination of the effectiveness of the drug. This might be because they were not in sufficient compliance with the requirements of the protocol, missed one or more doses of the drug, or some other reason.

Then we have case reports on subjects who entered the study but who dropped out part way along in the study. These reports might be useful, depending upon the type of study, for certain efficacy para-

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meters, even though they did not complete the study, or they might be useful for a number of safety parameters. We then have subjects who might have started the study but then soon dropped out of the study, most often due to side effects. There are also subjects who are screened for entry into the study but are never administered test drugs. In certain protocols, due to the tests involved, the screening of these subjects is quite an expensive activity.

When the protocol and the arrangements for the study are initially designed, it is important to determine how much will be paid to each subject who completes each aspect of the study, and for the company to reach an initial determination in setting budgets for any study, the approximate number of subjects who will fall into each category. Payments may be made based upon various measurements: 1) the number of subjects in each category for whom all reports are received; 2) the various number of procedures and physician visits or hospital days involved in the study with or without regard to completed evaluable reports; and 3) a calculated sum based upon what the anticipated costs of the study will be, or some other basis. The important point is for all parties to understand the basis upon which the amount for the study is being determined so that there are no subsequent surprises or disagreements.

## **CONFIDENTIALITY**

Confidentiality provisions are usually designed to protect information provided by the company to the university from being disclosed to third parties. Clauses on publication are designed to prevent premature disclosure of results of the study. At times, the way these provisions are worded, a gap is left with respect to disclosure of data developed from the study. This point should be covered in one or the other provision.

Many people might downplay the value of information concerning a clinical study; however, even the fact that a company is conducting research in a particular field or is working on a specific drug, and especially the advantages and disadvantages of that drug as compared to other drugs that are presently on the market or involved in the research process, may be a very valuable piece of information.

Disclosure of this information may serve to stimulate research on a competitive drug that it can get to the market place first or may save a competitor a significant amount of money by helping it avoid putting dollars into research on a drug that would be a poor second choice.

A confidentiality provision should of course not be too broadly worded. It should not prevent disclosure of any information previously

considered confidential once that information has been otherwise disclosed or independently developed by a third party. Additionally, it is suggested that any provision on confidentiality provide that all proprietary information be returned to a sponsor upon completion of the study to avoid any question of subsequent disclosure. The university might possibly wish to retain a single copy of the material under seal so it can demonstrate, in any future disagreement, that the material disclosed was or was not actually included in the confidential materials provided to it. Also, the contract should specify what is confidential and information considered confidential should be so marked.

There may be a problem in actually enforcing the confidentiality provision in a contract unless the contract is signed not only by the primary investigator but also by the university and by other parties who may have access to the information. Often the contract is only signed by the primary investigator or the university, or both, but not by those additional parties. Unless these additional persons are restricted by separate agreements with the university, a sponsor of a study may find that confidential information has been disclosed by a party against whom it has no ability to take any action.

## **PUBLICATIONS**

Many companies believe it is very useful to have the results of clinical research published prior to the time a drug is marketed. If the results are unsatisfactory and this finding is duplicated in other studies, it is unlikely that the drug would be marketed. If the finding is positive a publication by investigators at a recognized institution can be one of the most effective marketing tools. Publications of this nature can create a positive awareness of the drug and a receptive market for it; however, a company often wishes to have prior review or to delay publications for a number of reasons. The most important of these reasons is to make certain that the disclosure of the information is not premature and does not comprise any potential patent position which the company may be developing. Thus, clauses on publication often provide for a right of the company to review a manuscript prior to publication and to delete portions dealing with unprotected information to insure that they remain confidential. These agreements often provide that the sponsor must complete its review within a certain specified period of time, normally thirty to sixty working days, after receiving the manuscript.

An interesting situation can occur when a study involves more than just one center. If a half dozen universities and investigators are involved in a multi-clinic study of a drug, conflict may develop over who has

the right to publish the results of the entire study or even one part of the study unless the contract carefully covers the point. If an individual part of a multi-clinic study is published, this may affect the value to the other investigators of publication of their parts of the study. Additionally, the usual reason for a multi-clinic study is that the number of patients involved in any one center will not yield sufficient data to obtain statistically significant results of the effectiveness of the drug. Hence it is necessary to combine the results of studies from a number of centers. Thus publication of results from one center may make it appear that the drug is not effective when in reality the drug may be quite effective. Therefore, multi-clinic studies should be covered by agreements which specify how publication of the results of the study is to be handled between the various centers.

Another reason to review publications is that, if the company uses the results of the publication in promotion, it is subject to certain FDA rules concerning advertising and labeling. If the publication contains information beyond the scope of the package insert that is eventually approved by the Food and Drug Administration, it may mean that the publication will be very limited in its potential use. Therefore, the company might wish to have the paper focus, if possible, on the use of the drug in the study that is within the anticipated scope of the package insert.

A company may also want to review publications to make certain there are no errors or for product liability reasons. There are often many ways to express a thought. Some may be damaging while the same information expressed another way may not be a problem.

## **PATENT RIGHTS**

With clinical research agreements for late phase II or phase III research many people believe that a specific provision covering patent rights is probably not even necessary. By the time a compound enters late phase II or phase III studies, the purposes of a study should be very well defined, and the intent of the study should be either to prove or disprove a specific use of the drug. At this point, all patent applications and patent data should be completed. There really should be no new discoveries. Theoretically, at this point, the only way for a drug to be subject to a new discovery would be for the drug to be used outside of the protocol. This should, of course, not be done by the investigator and should also be specifically prohibited by the contract.

The two previous paragraphs used the words “probably” and “should!” Apart from being excellent words for lawyers to use, serendipitous findings still have a way of occurring in drug studies. Thus,

although an argument may be made that a patent provision is not necessary for late stage clinical research contracts, at times a new use does arise from a clinical study. Thus, even in these agreements, it is better to include a provision providing for ownership of any patentable invention. On studies involving basic research projects or phase I or early phase II clinical work, patent clauses are of primary importance.

Negotiating patent provisions in contracts of this nature often provide some of the most interesting discussions. Companies, of course, would like to obtain all rights to any invention arising out of such research. Many universities either cannot, or will not, agree to a complete assignment of inventions to a company, requiring instead that the invention be assigned to the university. If the university insists upon ownership of any invention, the company's next position is to obtain an exclusive license for any invention. After this, it is a matter of negotiation.

In order to avoid another potential problem in this area, it is also necessary to determine whether any government funding may have been involved in the invention. Whatever the final contractual provision may provide, its intent should be clear and there should be no sense of disagreement about where the rights to any invention lie. Also, any obligations of the inventors in obtaining the specified rights should be included.

## **LIABILITY AND INDEMNIFICATION PROVISIONS**

With the recent trend of escalating insurance premiums, the inability to obtain insurance and the problems both of the insured and the insurance industry, it is not surprising that indemnification agreements covering clinical studies have become more of an area of interest. Most provisions have the indemnification flowing from the sponsor to the university. However, there are now a number of instances where companies are requesting indemnification agreements from the investigator or the university.

Generally most large companies have no problem in providing for indemnification of the clinician and institution. This indemnification is usually subject to: (a) the investigator following the protocol for the study; (b) the providing of prompt notice to the company of any actual or threatened litigation; (c) the investigator and other pertinent parties cooperating in the defense of any litigation; (d) the company being allowed to select defense counsel; and (e) the investigator not being otherwise negligent with respect to the causation of the injury.

## **INFORMED CONSENT**

In the very recent past most clinical study agreements provided that the investigator was to obtain informed consent from patients involved in the study, or from their guardians, in accord with federal regulations. The specific form of the informed consent was left up to the investigator and the institutional review board.

An interesting situation occurred when a company tried to draft certain consent forms in particular investigational studies. There was disagreement with certain investigators who felt that the consent forms were too restrictive or frightening and that they would not be able to obtain any patients for the study with the wording of the consent form. The investigators preferred to reword the forms into phrasing they thought would be more acceptable to their particular patients. Also, it was believed that these consent forms included many potential adverse affects which were not relevant to the particular study.

Even with the potential difficulties in agreeing on wording in consent forms, many companies now appear to find it more efficient and believe it provides greater assurance of proper consent in drafting informed consent forms for use in studies rather than leaving it up to the investigator; however, the author is not aware of any company which has encountered any significant problem in allowing knowledgeable investigators and institutional review boards to draft consent forms for use in their studies based upon information on the drug provided to them by the company. In either situation the objective is to obtain a suitable consent form.

## **TERMINATION PROVISIONS**

This section should probably be titled “when you don’t get what you paid for,” or, from the point of view of the university or hospital, “when you don’t get paid for what you do!” The primary problem encountered under which a termination provision might be utilized is when the study either does not produce the number of patients or type of patient desired within the time period specified in the agreement. Termination of a study should also be provided in the event of failure to maintain or allow proper access to records, failure to follow regulatory requirements or consistent failure to comply with the protocol. The provision should provide for termination upon receipt of written notice to avoid any disagreement about the termination notice actually being received. The provision should specify return receipt mail to avoid any disagreement about the exact date of termination. A termination provision should cover very specifically what payment will be due to the university or hospital, or what refunds may be due to the company at the point of

termination, and what data are to be delivered to the company. The contract should include reference to any continuing obligations of the parties either after termination of the contract or completion of the work.

Problems with termination provisions arise when the contract does not cover the circumstances under which either party may end the agreement prior to the time of its contemplated completion.

The last and most important comment is to reiterate a prior point: any agreement for clinical research should clearly set forth all pertinent points concerning the work. It is far better to discuss before than to argue after.

Samples of various clauses referred to above are included as an appendix for further information and possible use.

APPENDIX  
T o  
PROBLEMS IN CLINICAL TRIAL  
AGREEMENTS

Within the specific topical area, a variety of sample clauses taken from university/industry agreements are included.

**OBJECTIVES AND PAYMENTS**

University agrees to complete and provide to Company 40 evaluable patient case reports. (For purposes of this Agreement an evaluable patient is defined as that patient who has been entered\* and maintained in the study by the investigator in full compliance with Protocol requirements, who has completed the full course in the study, and whose data is included in the safety and efficacy analyses for the drug).

Company agrees to pay University the sum of \$\_\_\_\_\_per evaluable patient case report received and approved by the company. Company will also pay this sum to University for each case report received and approved by Company for patients who, although not evaluable, are otherwise acceptable (For purposes of this agreement, an “acceptable” patient is that patient entered in the study who has followed all Protocol requirements and who 1) has been terminated from the study for reasons of treatment failure or adverse effects serious enough to cause cessation of drug therapy or 2) has died during participation in the study or 3) has experienced an intercurrent illness during participation of the study).

For purposes of this Agreement, an “entered patient” is one who meets the full entrance criteria as required by the Protocol, and who has actually been provided placebo or test drug.

\* \* \*

Company will provide you with study drugs, clinical report forms, and other materials required for the study. In addition, Company will provide financial support for your study. The attached budget indicates the total support due for your designated number of fully-qualified patients who are entered in the study within a maximum of ( ) months of start and who complete all visits. However, full payments will be made for each actual visit of patients treated in full compliance with the protocol and this agreement even if, for reasons beyond your control, they do not complete the protocol. Company will compensate for work done in the following manner:

Payments will be made to your institution (e.g., Medical School, Hospital, or Academic Department). If another payee is requested a letter must be provided from a responsible official of your institution (e.g., department chairman) which: authorizes payment to a payee other than your institution, states that such payments can be made in concert with the rules and policies of your institution, and certifies that such payment will not violate applicable laws (e.g., state, local, etc.). If you are an independent investigator (e.g., you do not receive remuneration from the institution in which the study will be performed, or the study will not be conducted in an institution), you must provide in writing to Company acknowledgement of this fact and provide instructions regarding to what entity the payment of the study grant should be made.

• • •

Research Management Review

Company has contracts with the U.S. Veterans Administration. If Veterans Administration facilities, employees (full or part-time), or patients are to be utilized in this study, please provide written confirmation from the director of the Veterans Administration facility involved that:

- 9) the research to be conducted is authorized under Veterans Administration policies;
- ii) the amount and manner of payment is appropriate; and
- iii) the designated payee \_\_\_\_\_ (insert name of payee) is appropriate under Veterans Administration requirements.

If the foregoing paragraphs are applicable to this grant, please obtain the written approval of your V.A. facility director, as provided above, and furnish a copy to Company along with the executed copy of this agreement.

It is understood that the approved reimbursement rate for the study is \_\_\_\_\_ (\$ \_\_\_\_\_) per "completed" patient (as defined herein, below) with an approved maximum contract of \_\_\_\_\_ \$ \_\_\_\_\_ for "completed patients.

It is further understood that as a part of this maximum contract, \_\_\_\_\_ (\$ \_\_\_\_\_) represents advance payment for the first \_\_\_\_\_ ( ) "completed patients. This amount shall be payable at the time the contract is signed. The entire maximum contracted sum of \_\_\_\_\_ (\$ \_\_\_\_\_) represents professional and administrative fees which shall be apportioned, on a patient by patient basis, to actual work performed and disbursed according to the provisions *on* Schedule B attached hereto and made a part hereof.

A patient shall be considered "Completed" for the purposes of this agreement when all of the following criteria are met.

- a. Receipt by Company of legible (either handwritten in black ballpoint pen or typed) case records representing all forms provided to the investigator by Company for completion of each patient.
- b. Completion of and appropriate recording on case report forms of all the tests and assessments contained in the protocol (Schedule A).
- c. Compliance with all other aspects of the clinical protocol.

Sponsor will supply the Institution with samples of the compound known as \_\_\_\_\_ (the "Compound"). Institution agrees to perform certain tests with the Compound that are described in Exhibit A (the "Protocol"), which is attached hereto and incorporated into this Agreement by reference. The work to be performed by Institution under this Agreement is sometimes referred to below as the "Study"! The Study shall be performed in accordance with applicable law.

### **CONFIDENTIALITY PROVISIONS**

University agrees that all information received from Company and all information developed by the investigators hereunder with respect to the test drug is and shall be considered throughout the term of this Agreement and subsequently thereto as confidential information and the sole and exclusive property of Company. University agrees to hold such confidential information in strict confidence and disclose confidential information only to its investigators and other employees and on a need-to-know basis. All such employees and investigators shall be bound by and obligated by similar provisions of confidentiality. University agrees that it shall not disclose to any third person any of the confidential information which is disclosed to it by Company or the investigators or which is generated in the course of this agreement until such time as such information becomes part of the public domain through no fault of University, or University is authorized in writing by Company to make such disclosures.

University agrees that it will execute a confidentiality agreement with each investigator and all other employees in the study in keeping with the form agreement, which is attached hereto and made a part hereof (Exhibit IV). This agreement will also include a provision to the effect that the investigator will refrain from engaging in any other study of a drug intended for use in subjects with the same medical condition as the subjects which are the subject of the study under this agreement.

\* \* \*

You will keep in confidence all information provided to you by Company until Company gives you written permission to disclose it, except for information required by federal, state, or local laws or regulation to be disclosed to the IRB, the patient, or the FDA. All data emanating from your study shall be transmitted promptly to Company and, where appropriate, to your IRB. Also, Company will inform you of adverse experiences or other information it believes should be reported to your patients and to your IRB. Company shall keep your data confidential with the following exceptions:

1. All data may be reported by Company to the FDA and other federal, state, and local governmental authorities and agencies, domestic or foreign;
2. When disclosure is required by or in accordance with any applicable federal, state, or local laws or regulations, domestic or foreign;
3. Descriptions of adverse experiences from your study may be shared with all investigators conducting studies with the same products; and
4. Joint summaries of data pooled from several investigators may be distributed and made publicly available by Company.

\* \* \*

- (A) It is understood that in the course of carrying out this Agreement, Sponsor may wish to provide Institution with proprietary or confidential information of Sponsor ("Proprietary Information"). Institution agrees not to disclose Proprietary Information to any third person or any Institution personnel not working on the Study without the prior written consent of Sponsor.
- (B) The obligation described in subsection (A) above shall not apply to any Proprietary Information which: (a) is or becomes publicly known through no wrongful or negligent act on the part of Institution or any third party; (b) can be shown to have been known to Institution at the time of Sponsor's disclosure; or (c) is generally disclosed to third parties by the Sponsor without similar restrictions on such third parties. The obligations of Institution under this section 4 shall continue indefinitely, regardless of any failure to renew or termination of this Agreement.
- (C) Except as otherwise specified by law, all Proprietary Information shall be delivered to Sponsor upon completion of the study.

\* \* \*

During the term of this Agreement and thereafter, University agrees to treat as confidential and make no further use or disclosure of information or data (i) arising from work performed under this Agreement, or (ii) disclosed to it by Company, or (iii) obtained by its representatives while visiting Company facilities. This restriction shall not apply to information or data which is public knowledge (through no fault of University), or which is made available to University by an independent third party, or which is already in University's possession at the time of receipt from Company (and such prior possession can be properly demonstrated by it), or which is required by law to be disclosed.

\* \* \*

The investigator will hold all information disclosed to him by Company or

developed by him with regard to Investigational Drug which information is not already in the public domain, in the strictest of confidence and will not disclose the same to any third party without the express permission of Company. Nothing herein shall be construed as preventing the investigator from publishing the clinical data generated from this study.

\* \* \*

### **Confidential Information**

- A. University acknowledges that it may be necessary for Sponsor to disclose information which Sponsor considers confidential (“Confidential Information”) in order to accomplish the work of this Agreement.
- B. In addition, it is agreed that Sponsor shall disclose only information necessary to the work. If any such information is considered confidential, it shall be clearly marked “Confidential Information” and sent by Sponsor in writing only to the Principal Investigator or orally disclosed to the Principal Investigator and reduced to writing by Sponsor within thirty (30) days of disclosure. The Principal Investigator agrees that Confidential Information shall remain the property of Sponsor and, for a period of ten (10) years from the end of the Agreement, Confidential Information shall not be used or disclosed to others except in furtherance of this agreement; provided, however, that the foregoing obligation of non-use and non-disclosure shall not apply to any portion of the Confidential Information which: (i) is or shall have been known to the Principal Investigator before receipt thereof and such prior knowledge can be demonstrated; (ii) is disclosed to the Principal Investigator by an independent third party, provided such information was not obtained by said third party directly or indirectly from Sponsor; or (iii) is or shall have become known to the public through no fault of the Principal Investigator.
- C. University agrees to promptly deliver to Sponsor, upon its request, all Confidential Information and proprietary data and/or information obtained from Sponsor, provided such request is sent within 120 days of termination of the study to be conducted under this Agreement.
- D. To permit Sponsor an opportunity to intervene, University shall immediately notify Sponsor if it is requested by a court order, a governmental agency, or any other entity to disclose Sponsor’s Confidential Information.

\* \* \*

### **PUBLICATIONS**

Company shall retain ownership of all data which result from the study. Notwithstanding, however, the College shall be free to publish papers consistent with the protection of any patent rights dealing with results of research under this Agreement. All proposed publications based on the study must be reviewed and approved by Company prior to submission, said review (1) to ascertain if any data proprietary to Company are set forth therein, and, if so, to have it removed before publication, and (2) to ascertain if any patentable inventions are set for therein, and, if so, to delay publication until a U.S. Patent Application is filed in the U.S. Patent and Trademark Office, but in no case longer than six months after receipt by Company.

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Company shall retain ownership of all case records which result from this study, however, the Investigator may have publication privileges provided such manuscript is submitted to Company for review at least 60 days prior to submission for publica-

tion. Should the Investigator decide not to publish such study, which decision shall be evidenced by the failure to provide Company with a final manuscript within six months of study completion, Company shall have the right to publish the results.

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### **Publication of Results**

Institution shall be free to publish the results of the Study, provided that any such manuscript is first reviewed by Sponsor. Sponsor shall complete its review within thirty working days after receipt of the manuscript from Institution. In its review, Sponsor shall be free to remove any of its Proprietary Information appearing in the manuscript, but shall not make other editorial changes without the author's consent. Any raw data or other information resulting from the Study that is not published as provided above shall be deemed Proprietary Information unless otherwise specified by Sponsor.

\* \* \*

University agrees that, in order to protect the patent priorities of the parties, prior to submission for publication, any paper written by its employees pertaining to work performed under this Agreement must first be approved by Company scientific and legal departments; such approval will not be unreasonably withheld.

\* \* \*

Any proposed publication by one or on behalf of its employees, assistants, or associates, involving work hereunder shall be submitted to \_\_\_\_\_ for review and publication or presentation. At the end of ninety (90) days after said submission to \_\_\_\_\_, \_\_\_\_\_ shall be free to proceed with publication, provided however, that if either \_\_\_\_\_ or \_\_\_\_\_ believes patentable subject matter to be a part of or to have arisen out of the work performed and/or services provided by \_\_\_\_\_ pursuant to this Agreement, such party shall identify such subject matter to the other and \_\_\_\_\_ thereupon agrees for itself and its employees, students, assistants or associates, to withhold any publication or presentation of or involving such subject matter until such time as a patent application covering such subject matter is filed with the United States Patent and Trademark Office or through the Patent Contract Treaty. In no event shall publication be withheld more than one (1) year from the date of initial submission of the proposed publication to \_\_\_\_\_.

\* \* \*

### **PATENT RIGHTS**

(a) Any and all inventions conceived by any personnel of University, including its students, assistants or associates, or in accordance with directions given by Company personnel (whether patentable or not and whether made solely by them or jointly with others who are not Company employees) and resulting from any services which University provides under this Agreement are the sole property of University.

b. University agrees to promptly disclose to Company any invention covered by the provisions of Paragraph a. and notify Company as to each country in which it elects to file a patent application on such invention. University hereby agrees to timely effect all such elected filings.

c. If University elects not to file a patent application on said invention in any country or fails to file an application on said invention in an elected country, Company shall have the right to file, on University's behalf, but at Company's expense, patent applications on such invention in such countries.

d. With respect to any patent that issues on a patent application filed under

## Research Management Review

paragraphs b. or c., University hereby grants Company and its affiliates a royalty-bearing exclusive license on the following terms:

(i) The term of the exclusive license for each such patented invention shall be the earlier of five (5) years measured from the date Company or its affiliate commercializes a product which embodies or employs the invention claimed in the patent, or eight (8) years measured from the date of this Agreement, with respect to the invention or discovery covered by the patent, excepting the time before regulatory agencies to obtain premarket clearance.

(ii) During the period of any exclusive license hereunder, Company agrees to use reasonable efforts to commercialize the invention(s) licensed to it under this Agreement. If Company does not or decides that it will not undertake and maintain reasonable efforts at commercialization, University shall notify Company in writing, and Company shall thereafter have sixty (60) days in which to demonstrate the undertaking of and maintenance of reasonable efforts to commercialize the invention(s). If Company fails at the expiration of that period to demonstrate such efforts, Company's license or licensing hereunder as to such invention(s) shall immediately terminate.

(iii) University shall be free to use any invention or discovery, whether or not patented or patentable, and know-how conceived by it in performance of this Agreement for its educational and research purposes only.

(iv) Company shall pay to University for such exclusive licence a royalty, said royalty to be negotiated in good faith between the parties and based on a reasonable balancing of various factors, including but not limited, to the relative contributions (financial and non-financial) of University and Company to the product, to the invention(s) involved, etc., to be determined no later than the date of first commercial sale of any product or process embodying the invention.

(v) Company shall have an option to extend the term of the exclusive license as set forth in Paragraph d.(i) to the maximum period grantable by University, said option being exercisable no earlier than sixty (60) days prior to expiration of the initial term.

e. University shall give Company all reasonable assistance in connection with the preparation and prosecution of any patent application filed by Company on University's behalf and shall cause to be executed all instruments and documents as may be necessary or appropriate to carry out the intent of Paragraph c. University shall timely provide Company with copies of all patent applications filed by University hereunder and prosecution documents associated thereof, and Company shall have the right to comment thereon and to make suggestions in connection therewith.

f. The exclusive license rights granted to Company and its affiliates hereunder shall survive termination of this Agreement.

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University agrees (i) to notify Company in writing promptly of any discoveries, improvements, and inventions arising directly from services performed under this Agreement, and (ii) that all such discoveries, improvements, or inventions, whether patentable or not, and all technical information and data resulting from services performed under this Agreement shall be Company property, and (iii) that at the request of Company and without further consideration, University will execute any documents necessary to vest in Company (or its designee) the entire right, title and interest in, to and under any such discoveries, improvements, inventions and technical information and data. With respect to patentable inventions, University further agrees to execute any patent applications in order to obtain for Company complete patent protection for any such discoveries, improvements, or inventions in the United States and foreign countries. Company shall assume all financial expenditures necessary to prepare and maintain patent applications.

The College agrees to assign to Company, at Company's request, the sole and exclusive ownership of any inventions, whether patentable or not, made in the performance of the research contemplated by this Agreement and to execute such instruments prepared by Company, as is deemed necessary to vest in Company the aforesaid sole and exclusive ownership. The College agrees to require its employees to render to Company reasonable assistance necessary for the perfection of Company's patent rights on such inventions. All reasonable expenses incurred as a result of this assistance will be paid by Company.

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All inventions, suggestions, ideas, innovations or reports made by investigators employed by University which arise or relate directly to the clinical studies which are the subject of this Agreement will be promptly disclosed to Company. Any such invention, suggestion, idea, innovation or report, shall be the sole and exclusive property of Company. University and investigators will cooperate with Company in obtaining patents on any such invention and shall execute any documents tendered by Company to convey or perfect ownership in such inventions. The obligations of this paragraph shall survive expiration or termination of this Agreement.

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**6) Patent Rights**

(A) The work to be performed under this Agreement is the testing of the Compound supplied by Sponsor as specified in the Protocol. Institution may not use the Compound in any way other than as specified in the Protocol.

(B) If in the course of the Study a new use for the Compound is discovered, Sponsor shall have the sole right to obtain patent protection for such new use for itself. However, if Institution has contributed to the discovery of such new use, Sponsor agrees to pay to Institution an amount to be agreed upon by the parties negotiating in good faith and taking into consideration the Institution's relative contribution to the discovery and the commercial value of the discovery. Institution will assist Sponsor in gaining patent protection for the new use and Sponsor will reimburse Institution for all reasonable expenses incurred thereby. Any patent application shall be filed and prosecuted by Sponsor.

(C) Institution shall promptly disclose only to Sponsor any discovery arising under this Agreement and Sponsor shall advise Institution in writing within ninety days of such disclosure to Sponsor whether or not it wishes to secure a patent as provided above. Any publication of the Data or of the results of the Study shall be withheld until all patent rights have been secured.

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**Inventions and Discoveries**

A. All rights to any invention conceived or conceived and reduced to practice in the direct performance of the work conducted under this Agreement in accordance with the detailed clinical testing Protocol provided by Sponsor to University shall belong to Sponsor. University agrees to assign to Sponsor, at the request of Sponsor, the sole and exclusive ownership thereto, upon the payment of costs by Sponsor, if any, incurred by University in the filing, prosecution, or maintenance of any patent application or patent issuing thereon. Such ap

- plication, if any, shall be filed and prosecuted by Sponsor.
- B. All rights to inventions and discoveries arising from research conducted under this Agreement, other than as provided for above, shall belong to University and shall be disposed of in accordance with University policy. To the extent that sponsor pays all direct and indirect costs of the research project, including an amount equivalent to a pro rata share of the Principal Investigator's salary, Sponsor shall be given a right of first refusal to obtain an exclusive, royalty-bearing license to any patentable inventions or discoveries conceived and first actually reduced to practice during the course of the research project. Said license shall contain reasonable terms and royalties and shall require diligent customary performance by Sponsor for the commercial development and early marketing of such inventions or discoveries. In the event an invention is conceived but not actually reduced to practice during the course of this project, said license agreement shall further include a provision for actual reduction within a reasonable time by either Sponsor or by the University under funding provided by Sponsor.
- C. University shall promptly disclose to Sponsor on a confidential basis any invention or discovery arising under this Agreement, and Sponsor shall advise University in writing within ninety (90) days of disclosure to Sponsor whether or not it wishes to secure a commercial license to such invention or discovery. If Sponsor elects not to secure such license, rights to such invention or discovery shall be disposed of in accordance with University policies, with no further obligation to Sponsor.

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## **INDEMNIFICATION**

In consideration of Investigator conducting an investigation of the effectiveness and safety of Investigational Compound, and submitting a complete report of the results of such investigation, it is hereby understood and agreed as between Company and Investigator that Company covenants and agrees to Indemnify and Save Harmless Investigator, the agents, servants and employees of Investigator from and against loss, damage, cost and expense of claims and suits seeking damages alleged to have been caused by or attributed to Investigator in testing and/or reporting the results of testing of Investigational Compound, including the cost and expense of handling said claims and defending said suits, provided, however, that (1) Investigator, the agents, servants and employees of Investigator are shown to have adhered to and complied with all dosage and other specifications, directions and recommendation furnished in writing by Company for the use and administration of Investigational Compound, and (2) provided further that Company is promptly notified of any such claim or suit and, (3) provided further that Investigator agrees and covenants to fully cooperate in the handling of any such claim and in the event of suit to attend hearings and trials and assist in securing and giving evidence, and obtaining the attendance of necessary and proper witnesses.

Company will reimburse Investigator for all reasonable expenses incurred at its request in connection with item (3) above. Company at its own expense will carry out sole management and defense of such claims or suits, and will provide attorneys of its sole choosing to defend against any such claims or suits. Said agreement by Company to Indemnify and Save Harmless shall not cover loss, damage and expense arising from negligence of Investigator.

It is, however, understood and agreed as between Company and Investigator that the above agreement to indemnify is not intended as or for a substitute for full and

complete malpractice and other forms of liability insurance and that Investigator shall obtain any insurance coverage necessary and proper for the regular conduct of activities as an investigator.

. 4 .

Company undertakes to indemnify and hold harmless Investigator and University, their trustees, officers, agents and employees from any and all liability, loss or damage they may suffer as the result of claims, demands, costs or judgements against them arising out of the activities to be carried out pursuant to the clinical research protocol designated as [name of study, study number]; provided, however, that any such liability, loss or damage resulting from

- (i) a failure to adhere to the terms of the protocol or Company's written instructions relative to use of the investigational drug,
- (ii) failure to comply with any applicable FDA or other governmental requirements, or,
- (iii) negligence or willful malfeasance by Investigator or University, their trustees, officers, agents and employees

is excluded from this agreement to indemnify and hold harmless.

Investigator and University agree to notify Company as soon as they become aware of a claim or action and to cooperate with and to authorize Company to carry out the sole management and defense of such claim or action. Company agrees, at its own expense, to provide attorneys to defend against any actions brought or filed against Investigator, University, their trustees, officers, agents and employees with respect to the subject of indemnity contained herein, whether such claims or actions are rightfully brought or filed.

Neither Investigator, University nor their trustees, officers, agents or employees shall compromise or settle any claim or action without the prior written approval of Company.

\* \* \*

## Termination

1. The study may be terminated by written notice from Company to the investigator for any of the following reasons:
  - a. Notification to Company from Federal or State Regulatory Authorities to terminate said study.
  - b. Determination by Company that the investigator after a reasonable opportunity, is not performing, or is unable to perform, the study as required in the protocol.
  - c. Failure of the investigator and/or institution to provide access by Company representatives to any and all original medical records necessary to verify entries on study case report forms.
  - d. Failure of the primary investigator, associates or any other person engaged in this study, excluding patients, to be available upon reasonable notice by Company, to meet with Company monitors during the course of this investigation as necessary to discuss information relevant to the study.
  - e. Case report forms provided to the principal investigator by Company for use in this study, are not legibly completed and forwarded to Company or its designated representative, as appropriate, within 30 days of each patient visit date.
  - f. Failure of the investigator to comply with all regulatory requirements as delineated in Form FD 1573 (or 1572) signed by investigator and attached hereto. (Schedule C).
2. In the event that Company wishes to exercise its right to terminate this study based on any of the enumerated grounds above, written notice of its decision

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to exercise such right shall be given by registered mail delivered fifteen days before said termination.

3. Immediately upon receipt of a notice of termination, the principal investigator shall stop entering patients into the study and shall cease conducting procedures, to the extent medically permissible, on patients already entered into the investigational protocol.
4. In the event of termination, the sum payable under this agreement shall be limited to pro-rated fees based on actual work performed pursuant to the protocol. Any unexpended funds not due \_\_\_\_\_ under this calculation but already paid \_\_\_\_\_ shall be returned to the Company.
5. Notwithstanding any of the above, if during the life of this agreement \_\_\_\_\_ is approved by the Food and Drug Administration or information becomes available to Company which places the safety or efficacy of the product in doubt, the parties agree to negotiate in good faith with an objective being the modification of this contract to reduce the number of patients to be studied and/or similarly modify any other relevant requirement.

\* \* \*

1. Either party may terminate this Agreement by giving sixty (60) days written notice when they determine that just cause for termination exists, or that termination is in the best interest of either party and not arbitrary. Upon termination, Hospital shall return to Company any monies received but not encumbered as of the date of termination. Company shall reimburse Hospital for all expenses encumbered in its performance of the investigation through the date of termination. Upon termination, Hospital shall return any unused investigational materials to Company.
2. Any notice, statement, or report required by this Agreement shall be considered given if sent postage prepaid, return receipt mail, and addressed as follows:

. . .

### ***Term and Termination***

- (A) This Agreement shall become effective as of the date written above and, unless earlier terminated as provided in subsection (B) below, shall continue in force for the period through \_\_\_\_\_ except with respect to the obligations under sections 4 and 6 above, which shall continue beyond the term of this Agreement. Institution shall complete the Study \_\_\_\_\_
- (B) Either party may terminate this Agreement at any time upon sixty (60) days prior written notice to the other party. Upon the termination of this Agreement by Institution before the end of the term, the total amount payable by Sponsor under this Agreement shall be \$ \_\_\_\_\_ per completed evaluable case report received by Sponsor in accordance with the Protocol. Upon the termination of this Agreement before the end of the term other than upon Institution's initiative, the total payable by sponsor under this Agreement shall be an amount equal to the non-cancellable expenses incurred by Institution in the performance of this Agreement until either the termination date or the receipt of notice of termination, whichever is earlier.

## **Termination**

Company retains the right to terminate the clinical study at any time by giving written notice to University. Upon University's receipt of such notice, there will be no further acquisition, screening or entry of patients. University will have thirty (30) days from the date of its receipt of such notice for wind-up of the study. Upon such notice of termination University will take all steps necessary to terminate the study at the earliest possible date and to reduce or eliminate further costs. Company will pay to University the sum of \_\_\_\_\_ per evaluable patient case report received by Company prior to the date of termination and approved by Company. Company will also pay this sum to University for each case report received by Company prior to the date of termination and approved by Company for patients who, although not evaluable, are otherwise acceptable. Reimbursement to University for patients entered into the study but who have not yet completed the study to enable University to submit either "evaluable" or "acceptable" case reports will be made in accord with paragraph 6.

In the event this Agreement is terminated for whatever cause, University shall promptly deliver all completed or partial case report forms, all unsued drug supplies, all data and any and all other documentation relating in any way to the study.

# Universities Move Toward New Responsibilities in a More Complex Environment

Robert M. Rosenzweig

(Editor's note: This paper was presented as the Luncheon Address at the Conference "Management of Risks in Research" sponsored by NCURA in cooperation with the University Risk Management & Insurance Association, Washington, D.C. June 7, 1987.)

Most subjects benefit from a bit of context, so let me start by placing the subject of this meeting, "Management of Risks in Research," on a time line that begins at the end of the Second World War. At that time, nearly forty years ago, the subject of this meeting would have been inconceivable, in the literal sense of that word: No one could have or would have thought of it as a topic to be discussed. The war was over, and science and technology had been a key to victory. The task was to harness what was seen as the unlimited power of science to the nation's pent-up economic energies in order to make America prosperous and to rebuild the world. There was no room on that agenda for doubts and doubters, even if any had existed.

Twenty years later, in the mid-Sixties, the nation was in quite a different state. The environmental movement had been born, the treatment of human subjects in research had become a concern, the recent debate over a test ban treaty had made radioactive fallout a matter of fresh concern, and suspicion of the motives and practices of all important social institutions was fashionable. However, a meeting to talk about how to manage research risks, had one been held, might have been attended by some Ralph Nader acolytes, but surely not by the respectable establishment represented here today.

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Ten years ago, the university community, like much of the rest of the country, was beginning to react to what was increasingly seen as a bad case of government overregulation. You will recall, I have no doubt, the stream of stories about what were described as arbitrary, petty, and costly rules adopted by OSHA and the even more rigid and damaging administration of them. And there were others. Affirmative action programs were a burden, the government insisted that the handicapped not be faced with barriers to college attendance, and the requirement of equity for women imposed new financial and administrative obligations.

It was commonplace during that time to find articulate and forceful indictments of the government from the academic world for all of those developments and more. Indeed, to the extent that a public impatience with the growth of regulation contributed to the election of Ronald Reagan, we in the universities may be said to have played our part in producing that result.

In retrospect, though, it is hard to escape the conclusion that the rhetoric of antiregulation actually served to inhibit thought about what was really happening. There were certainly major battles over human subjects regulations, proposals to regulate recombinant DNA research, nuclear power, and a number of other specific processes and technologies. But each of them was fought as if it were unrelated to the others and as if it could be won or lost on its own merits. More to the point, there was a sense among many that a change in Washington administrations would make some fundamental difference. The Republicans, of course, did what they could to encourage that belief, and in response the Democrats acted as if they too were committed to slaying the alien force that had imposed all of this red tape on us. As a consequence, I don't remember many efforts like this one, in which the concept of risk could be viewed as a single, organizing idea with many specific manifestations, an idea, moreover, that needed to be dealt with historically, philosophically, politically, managerially, administratively, and financially.

To bring the time line to the present, it is probably accurate to say that we are now busy dealing with the consequences of the developments I have described that we hardly have time to wonder why it took us so long to figure out what was really happening. If I am right about that, it would truly be a pity. It should now be clear that the growth in regulation of the processes and products of research was not a political aberration curable by electing a conservative Republican rather than a liberal Democratic President. There are powerful social forces at work that will have their way in the political

system regardless of who sits in the White House, and we had better understand what they are or we will constantly be in the position of being caught off guard by their latest manifestation.

That being so, I want to spend my time with you today giving you one view of why we got to the point at which a meeting such as this one is not only necessary but overdue, and where I think we are heading. And in the interest of simplicity, I will focus primarily on issues of health and safety, though I recognize that your agenda-and mine-has other important matters on it.

To start with the obvious, let me observe that universities have changed over the last forty years. Some of the important changes are evident, some less so, but those of us who live in the university world are familiar with most of them. Compared to forty years ago, today's universities are larger, more complex, more competitive for money and people, have more capital needs, are more dependent on government, particularly but not exclusively in the area of research, and more involved in politics-not the partisan kind, but the kind that has to do with policymaking. All of that, together with other changes I have not enumerated, add up to institutions that are not different simply in degree from their earlier form but that are, in some real sense, different in kind. That difference is perhaps best captured by the term "research university," a term which has only recently come into the vocabulary of higher education. It expresses the heavy concentration on organized and sponsored research that now characterizes more than one hundred American universities, a number that would have been thought astounding and unrealistic not much more than a generation ago.

But something else has been happening during that time, too, and just as we earthlings are unaware of the motion of the earth through space because gravity holds us to the surface, so those of us in the university world may be led by the force of our daily responsibilities to lose sight of the fact that our changing enterprise is part of a world that is also changing and that the pace and direction of change for the two, while not always identical in the short run, are intimately related in the long run.

For all of the period since the end of World War II, science and technology have grown in scale and sophistication on university campuses, and for most of that period they grew in an atmosphere that was substantially protected from some profoundly important social changes taking place in the world outside. The country was growing richer, indeed, the whole of the western world was growing richer. Life expectancy was growing, and along with a change in expectations about how long life could reasonably be expected to last, came changes in

expectations about what its quality should be. As people have come to expect more, they have quite naturally, it seems to me, been less inclined to risk losing what they have. As life grows in length and quality, it becomes more valuable, not less. Threats to public well-being that would hardly have been noticed among the routinely expected calamities of earlier times loom larger in importance as the background against which they are seen becomes calmer.

A report issued in 1982 by the National Academy of Sciences, called "Risk and Decision Making: Perspectives and Research," provides vivid supporting evidence. "Life expectancy at birth has increased in the United States from 47 years in 1900 to 74 years in 1979. The age adjusted death rate has fallen by two-thirds. . . The probability of 'early' death-death before age 65-has declined from over 60 percent at 1900 mortality rates to under 25 percent at 1979 rates. . . Similar improvements have occurred in other countries as well, including dramatic ones in the less well developed countries considered as a group."

It is startling to lay those figures alongside evidence of the public's perception of the risks to which they are subject. Louis Harris reported in 1980 that 78 percent of the people asked agreed that "people are subject to more risk today than they were twenty years ago." Only 6 percent thought there was less risk. Moreover, more than half expected the risks produced by advances in science and technology to increase in the next twenty years.

I don't want to trivialize what has been an excruciatingly difficult issue of policy, but surely the contemporary metaphor for what I am describing is the odyssey of the *Islip*, New York, garbage scow. Here we have a truly modern marriage of affluence and effluents. An affluent society trying to protect itself from the health hazards of its own effluents finds that no one else in the hemisphere is willing to assume that risk for them. The comment about it that made the point best for me was the cartoon showing two rats on that scow, surrounded by steaming garbage, gazing out to sea, and one says to the other "Did you ever think back there in New York that we would be taking a Caribbean cruise?"

What has happened is that society's view of what constitutes an acceptable degree of risk to the public health and safety has been changing as the work of the university has been changing. Not surprisingly, since a good part of newly perceived risk derives from developments that began on university campuses, the work of the university and the changing tolerance for risk have been on a collision course.

One other development has exacerbated the problem, especially

in the United States. It is, as you are well aware, the extent to which our legal system, that is to say our collective secular conception of what is right and what is wrong, has come to emphasize the right of individuals to be recompensed not for injury they suffer at the hands of other individuals, but for injury caused by products or processes, whether or not the injury is the result of malice or negligence. Thus, we have collectively expressed our growing aversion to risk through regulation and through tort law in an effort to make it clear that risk reduction is a necessary part of doing business. When it is inadequately done, or simply fails to work, money damages will be exacted for the injury caused.

Let me now return to the university campus and the subject of research risks. My main conclusion from the foregoing is that those of you who are engaged in university programs of risk management are not likely to suffer from early unemployment caused by sudden relief from regulation. Six years of an administration as committed by ideology to that goal as any we are likely to see has hardly made a start in that direction, and if I am correct in my understanding of the way our political system works, concern about danger to the public health and safety will grow and will be translated into governmental action.

That conclusion needs a little explanation. The National Academy study reported that between 1965 and 1980 the Congress had passed more than 30 major laws "aimed at coping with occupational, consumer product, environmental, transportation, and other sources of risks." In addition, at least a dozen regulatory agencies were either created or significantly strengthened during that time. And to complete the picture, the number of interest groups concerned with issues of health, safety, and the environment mushroomed. We have here the classic "iron triangle:" familiar to us all from the literature of public administration. Congressional committees, interest groups, and bureaucrats all stand to gain by doing more of what they have been doing, and they stand together in opposition to efforts by mere Presidents to have them do less.

A President, as this one has done, may push back the boundaries a bit, but in the area of risk management everything else is working in the opposite direction. As television brings us vivid pictures of enormous man-made disasters such as the one at Bhopal and Chernobyl, there are profound reverberations for the public perception of the dangers of toxic chemicals and nuclear power. And as the evidence accumulates that the disasters were the product of human error, the pressure for closer regulation of the behavior of those who work in those areas grows. The forces on the other side, while frequently

powerful as a consequence of their economic resources, are unlikely to prevail for long against skillfully organized public concerns and against the certainty that the capacity for human error-not to mention negligence and greed-is far from exhausted.

It would be nice, but it would be wrong, to think that universities are any more trusted to exercise care for the public health and safety than is business. If that was once the case, it surely no longer is. Furthermore, there is no reason on the merits to ask that universities be held to a lower standard of care or responsibility for similar risks. I make this point, even though it may seem self-evident, because I think we may in the past have held such an expectation. I have sensed, indeed, I have even been a party to, resistance to some kinds of regulation that now seem to me to have been quite justified, at least in their purpose if not always in the exact form in which they were proposed. Too often, it seems to me, our response has been “You can’t do that to us,” rather than, “Let’s see if we can find a better way to do what we know needs to be done.”

The plain fact is that universities will not be held harmless from efforts to increase the public’s margin of safety from the hazards of modern life. Nor, as I have argued, can we expect those hazards to diminish. Both the reality of risk and the nature of politics suggest otherwise. As you well know, however, there is a tendency among faculty to resist regulation of any kind as it affects their own laboratory, no matter how necessary they may believe it to be for others. There is, too, a tendency among academic administrators to resist demands for money that divert funds from academic pursuits. Who, then, will argue on campus for the interests of health and safety, not from the perspective of the regulatory interests and agencies, but from the enlightened and knowledgeable interests of the university? And who will help save institutions from a reflexive, defensive response to the assertion of newly-discovered sources of risk, a kind of response that is the political equivalent of self-mutilation? As I see it, you and I are the ones on the spot. No one on campus is in as good a position as you to bring to your faculty and administration an informed and objective assessment of your university’s responsibilities in law and in good sense and to its vulnerability in the political and social climate that now prevails. Moreover, if there is any justification other than the simple pursuit of self-interest for the existence of organizations like the AAU, it must be that we can help to shape and articulate policy positions for the entire sector we represent that are difficult for individual members to pursue alone. It is not our job to be the conscience of our members, but it is our job to collect and distill the good sense and high ethical

standards that reside among them and bring those qualities to bear on policy.

Thus, we have a shared duty, one that has been imposed on us by paradox: Life for most of us is longer and healthier than for our forebears, but we see it as more threatening, in part because of the very science and technology that has produced the gains. It is a paradox rich with ethical and moral ambiguity and full of political risk. There is hardly a more demanding or important set of issues on our agenda, and I take your presence here today as a sign that you agree.

## Instructions to Authors

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