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Roundtable for the Development of Drugs & Vaccines Against Acquired Immune Deficiency Syndrome (AID$) Grant No. DAMD17-92-J-2022

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Fort Detrick
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Work Summary held on May 6, 1994 on "Government and Industry Collaboration in AIDS Drug Development"

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The purpose of the workshop was to examine the challenges and opportunities inherent in government and industry collaborations on HIV/AIDS research and therapeutic development. Many of the concerns and suggestions that surfaced during the workshop deliberations, however, have broad applications beyond the field of HIV/AIDS drug development. Workshop participants explored some of the current impediments to collaboration; the implications for progress toward the discovery of novel therapeutic candidates and their development into marketed products, particularly when barriers that discourage or prevent collaborative research may exist; and ways to overcome existing obstacles. A variety of perspectives on these issues was presented, including those of government researchers and administrators, the pharmaceutical industry, the biomedical and clinical research communities, congressional staff, and consumer advocates.

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INSTITUTE OF MEDICINE

Workshop Summary

Government and Industry Collaboration in AIDS Drug Development

1994

94-32584

Government and Industry Collaboration in AIDS Drug Development

Summary of a Workshop Held on May 6, 1994

Leslie M. Hardy, *Editor*

Roundtable for the Development of Drugs and Vaccines Against AIDS

Division of Health Promotion and Disease Prevention

INSTITUTE OF MEDICINE

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This workshop summary was prepared by the Institute of Medicine's Roundtable for the Development of Drugs and Vaccines Against AIDS, chaired by Barton F. Haynes and Paul A. Volberding and directed by Leslie M. Hardy. The document reports major themes of the workshop discussions; these themes, however, do not represent policy statements by the Institute of Medicine.

The report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemuseen in Berlin.

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Acronyms and Abbreviations

ACTG	AIDS Clinical Trials Group
AIDS	Acquired immune deficiency syndrome
AZT	Zidovudine
CRADA	Cooperative Research and Development Agreement
CTA	Clinical Trial Agreement
ddI	Didanosine
DHHS	U.S. Department of Health and Human Services
GAO	U.S. General Accounting Office
HEW	U.S. Department of Health, Education, and Welfare
HIV	Human immunodeficiency virus
ICC	Inter-Company Collaboration for AIDS Drug Development
IP	*Intellectual property*
IPA	Institutional Patent Agreement
NCI	National Cancer Institute
NIH	National Institutes of Health
PHS	U.S. Public Health Service

Preface

The Roundtable for the Development of Drugs and Vaccines Against AIDS was established in 1988 by the Institute of Medicine. Composed of leaders from government, the pharmaceutical industry, academia, and patient advocacy groups, its mission is to identify and help resolve impediments to the rapid availability of safe, effective drugs and vaccines for human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS). The Roundtable accomplishes its mission through regular meetings of its membership, during which urgent issues are identified and discussed, as well as through public conferences and workshops that explore scientific and policy matters central to the development of AIDS therapeutics. This report is a summary of a workshop held on May 6, 1994, in Washington, D.C.

The purpose of the workshop was to examine the challenges and opportunities inherent in government and industry collaborations on HIV/AIDS research and therapeutic development. Many of the concerns and suggestions that surfaced during the workshop deliberations, however, have broad applications beyond the field of HIV/AIDS drug development. Workshop participants explored some of the current impediments to collaboration; the implications for progress toward the discovery of novel therapeutic candidates and their development into marketed products, particularly when barriers that discourage or prevent collaborative research may exist; and ways to overcome existing obstacles. A variety of perspectives on these issues was presented, including those of government researchers and administrators, the pharmaceutical industry, the biomedical and clinical research communities, congressional staff, and consumer advocates.

This report is not a consensus document but rather a synthesis of selected scientific or public policy aspects of the workshop presentations and discussions. It contains no recommendations or conclusions, and the Roundtable has neither altered nor commented on the views and opinions expressed by the speakers except for purposes of clarity. The Roundtable and staff wish to thank our consultant, Tom Burroughs, for his able assistance in preparing this summary. We also thank, once again, the workshop speakers for their thoughtful presentations and all participants for the lively, provocative discussions throughout the workshop.

Contents

Government and Industry Collaboration in AIDS Drug Development

INTRODUCTION[1]

As the toll from the acquired immune deficiency syndrome (AIDS) and human immunodeficiency virus (HIV) disease continues to mount in the United States and around the world, accelerating the discovery and development of new, more effective drugs and vaccines is critical to the treatment and prevention of HIV infection. Simply spending more money on HIV/AIDS research, however, is not the sole answer; some scientists question whether additional funds could indeed be spent productively. They argue that a better strategy would be to enhance the effectiveness of current investments in therapeutic research and development efforts. Increasing collaborations among AIDS researchers in the public and private sectors hold considerable potential in this regard, because cross-fertilization among scientists interested in a common problem can accelerate the advancement of scientific knowledge and understanding.

HIV/AIDS therapeutic drug research and development is under way in three sectors: government (primarily through the intramural research program of the National Institutes of Health [NIH]), academia (supported in large part by NIH grants and contracts), and the pharmaceutical industry. Research collaborations between industry and academia and between NIH and academia are regarded as generally effective and productive. Indeed, numerous joint efforts have helped to provide a detailed understanding of the virus and its life cycle and to identify the first generation of antiretroviral agents that offer therapeutic value, albeit of limited duration. But, in recent years, researchers have frequently expressed dissatisfaction and skepticism about the effectiveness of current mechanisms for government and industry collaborations.

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[1]This section is based on material presented by Patrick Gage.

Increasing the importance of government and industry collaboration is the considerable investment that each sector makes in HIV/AIDS research. The federal government has spent more than $3 billion during recent years, and in fiscal year 1994 NIH will have spent approximately $1.3 billion on HIV/AIDS research. Although precise monetary estimates are not available for industry, survey data collected by the Pharmaceutical Research and Manufacturers of America (formerly Pharmaceutical Manufacturers Association) indicate that pharmaceutical and biotechnology companies are making a substantial—perhaps comparable—investment.[2] In 1993, for example, 74 companies had 103 HIV/AIDS-related products in development, and already 21 medicines for HIV disease and its associated conditions have been approved by the Food and Drug Administration. Promoting a fundamental collaboration between these two major research enterprises is expected to make both programs more effective, and in turn yield faster progress in HIV drug and vaccine development.

The recent blending of research goals, methods, and outcomes in public- and private-sector laboratories has been driven in large measure by advances in molecular genetics. The pharmaceutical industry today embraces a "rational drug discovery" strategy that depends inherently on state-of-the-art research and modern tools of biotechnology. In this approach, industry scientists strive to elucidate underlying disease mechanisms and then use novel targets (e.g., viral enzymes), identified through this fundamental research, for powerful drug design efforts. Basic research in government and university laboratories, while continuing to reveal new information, also increasingly yields product concepts or actual therapeutic candidates that immediately go into development, often in biotechnology companies. The separation between basic and applied research in the life sciences, including HIV/AIDS research, has thus become blurred, with important contributions in each area being made across the scientific community.

The time seems right, then, for enhancing collaboration between government and industry. Yet representatives from both sectors maintain that establishing collaborative relationships is increasingly difficult and complicated and thus hampers this type of research. Workshop participants identified a number of obstacles to greater research collaboration between government and the pharmaceutical industry. These obstacles concern such issues as the disposition of patent rights to cooperatively developed inventions; the government's role in establishing or restricting the price of drugs, particularly those developed with federal support; and companies' access to data from government-sponsored clinical trials. Carefully eliminating or lowering the barriers in these and other areas, workshop participants agreed, would allow the nation to tap more fully the potential of scientific interaction. Indeed, they felt that fostering government and

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[2]Pharmaceutical Manufacturers Association, *AIDS Medicines—Drugs and Vaccines in Development*, November 1993.

industry collaboration promises to benefit not only HIV AIDS research but also all drug discovery and development efforts.

The following sections examine the evolution of federal policies regarding the transfer of government technology to the private sector and, in particular, the rules governing the assignment of patent rights to federally supported pharmaceutical inventions. The sections also highlight several impediments to government and industry collaboration on HIV drug and vaccine development and present suggestions by workshop participants for ways to overcome these obstacles. It must be emphasized, however, that these proposals do not represent a consensus, nor do they necessarily reflect the views of the Roundtable or the Institute of Medicine. In addition, because of the nature of the workshop format, a comprehensive analysis or discussion of the relative merits and shortcomings of the proposed solutions is beyond the scope of this report.

HISTORICAL PERSPECTIVES ON GOVERNMENT TECHNOLOGY TRANSFER POLICY AND THE PHARMACEUTICAL INDUSTRY[1]

Ever since the federal government in the 1940s began to invest heavily in scientific research conducted in the private sector, there have been conflicting theories about the proper allocation of rights to inventions arising from research supported wholly or in part by public funds. Some observers argue that inventions supported by any amount of taxpayer money should be freely available to the public. Others contend that such inventions effectively reach the public only when they are commercialized by private companies with exclusive patent rights. Neither approach has ever entirely prevailed, and since 1955 government policy has taken a variety of positions regarding the issue of intellectual property rights deriving from federally sponsored research.

The federal government has generally claimed a property right in any invention developed (even in part) with federal funds. If the government decides to relinquish its property right, it always retains a nonexclusive right to use that invention anywhere in the world without paying royalties. Still in question, however, is whether the federal government will grant no rights, nonexclusive rights, or exclusive rights to an invention to private institutions or companies.

Prior to the 1950s, the federal government had no uniform policy concerning patent rights to inventions arising from federally funded private research, and the

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[1]This section is based on material presented by Peter Barton Hutt and Thomas Mays. It also draws heavily on a background paper, *A Brief and General History of Government Policy Concerning Patent Rights to Federally-Funded Pharmaceutical Inventions*, prepared for the Roundtable by Lewis A. Grossman and Peter Barton Hutt, Covington & Burling, April 18, 1994.

various agencies and departments followed their own patent guidelines or policies. In 1955, the U.S. Department of Health, Education, and Welfare (HEW) — the parent department of NIH — promulgated regulations spelling out its approach to patent rights. HEW (now the U.S. Department of Health and Human Services [DHHS][4]) took the position that inventions supported in any way by federal funds should generally be dedicated to public use or, if patented, be made available to the public on a nonexclusive and royalty-free basis. Accordingly, HEW freely published the results of most NIH-sponsored research and dedicated many inventions to public use.

HEW recognized, however, that it is sometimes necessary to use the patent process "to foster an adequate commercial development to make an invention widely available." Toward this end, HEW's 1955 regulations allowed the U.S. Surgeon General to enter into Institutional Patent Agreements (IPAs) with grantee institutions. These agreements permitted the institutions themselves to determine the ownership and disposition of patent rights, as long as the inventions were made available to the public without unreasonable restrictions or excessive royalties. Between 1953 and 1958, NIH entered into IPAs with 18 private institutions, primarily universities. HEW added more leeway in 1957, when it ruled that contracts with private industry for cancer chemotherapy research would not be subject to the presumption against privately owned patent rights.

The first effort to establish a uniform patent policy for the federal government came in 1963, when President Kennedy issued a memorandum[5] stating that the government should generally acquire the principal or exclusive rights to inventions derived from federally supported research. IPAs would be permitted only in exceptional situations, and although it was not stated specifically, the intent seemed to be that IPAs would not apply to research or inventions that affect the public's health or welfare. Although many agencies remained flexible in their interpretations of the Kennedy memorandum and continued to routinely assign patent rights to private contractors, HEW did otherwise. The Department declined to enter into IPAs with any of the 34 institutions that made requests during this period, and almost never assigned grantees or contractors the patent rights to inventions.

In 1968, the U.S. General Accounting Office (GAO) issued a report[6] stating that HEW's policy of retaining patent rights deterred industry from cooperating

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[4]The National Institutes of Health are part of the U.S. Public Health Service (PHS), which is part of DHHS.

[5]President John F. Kennedy, *Memorandum and Statement of Government Patent Policy*, October 10, 1963.

[6]U.S. General Accounting Office, *Problem Areas Affecting Usefulness of Results of Government-Sponsored Research in Medicinal Chemistry*, GAO Report B-164031(2), August 12, 1968.

in the development of potentially important new drugs. Without the certainty of obtaining exclusive patent rights, companies would be unwilling to undertake the investment needed to develop promising compounds into commercial products. Indeed, the report concluded that few, if any, drugs arising from NIH-supported research during this period had been successfully developed and marketed. In response, HEW agreed to reinstate the IPA program.

During the next 10 years, government patent policies were once again variable and often confusing. By the late 1970s, there were approximately 22 different administrative policies regarding patent rights to government-sponsored inventions. HEW appeared to have resurrected its earlier patent policies discouraging private ownership and had become increasingly reluctant to admit new participants to the IPA program. Industry participation in the development of new drugs supported by federal funds once again began to stagnate. In 1978, Senator Robert Dole's office compiled a list of 29 important medical discoveries whose development had been significantly delayed because of HEW's inability to readily determine whether it would retain or transfer patent rights.[1]

By the end of the decade, there was growing support for legislation to create a government-wide patent policy to encourage the commercialization and use of federal technology. As a first step, Congress enacted the Patent and Trademark Amendments of 1980, commonly known as the Bayh-Dole Act (P.L. 96-517). The law gives universities, nonprofit institutions, and small businesses a right to retain title to inventions developed in the performance of government grants and contracts. A 1987 Executive Order,[2] issued by President Reagan, extended similar rights to large businesses.

Because the presumption is that the private grantees and contractors covered by the Act will acquire title to patents, the burden rests on the federal government to justify title acquisition for itself. Yet the government still retains a nonexclusive right to use the invention anywhere in the world without paying royalties. The law also provides government with "march-in rights" to require a delinquent grantee or contractor to grant a license to a responsible applicant. The government may exercise such rights primarily in situations in which a grantee is not taking effective steps to achieve practical application of the invention or in which the action is necessary to address pressing public health or safety needs.

To further encourage private companies to commercialize federal inventions, Congress passed the Federal Technology Transfer Act of 1986 (P.L. 99-502). This statute authorizes federal laboratories to enter into cooperative research and development agreements (CRADAs) with nonprofit institutions and private companies, with preference given to small and domestic businesses. Through CRADAs, federal agencies can provide personnel, services, facilities, equipment,

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[1]U.S. Congress, *Congressional Record—Senate*, August 4, 1978, pp. 24423-24426.
[2]Executive Order 12591, 52 *Federal Register* 13414, April 22, 1987.

and other resources, but not funds, to nonfederal organizations for the conduct of specific research and development projects. These organizations can contribute similar resources as well as funds, and in return the government can agree in advance to grant them exclusive patent rights to inventions arising from the collaborative research, including inventions made by federal employees working under the agreement (who receive compensation through royalties and cash awards programs). The CRADA also offers government agencies an option to negotiate an exclusive commercialization license with industrial partners.[9] These statutes enhanced research collaborations among industry, government, and universities[10] and facilitated the discovery and development (and ultimate marketing) of many important new drugs—such as Taxol, didanosine (ddI), dideoxycytidine, trimetrexate, and fludarabine in the fields of cancer and AIDS treatment.

Some consumer and congressional representatives have criticized the private commercialization of government-sponsored inventions. They argue that, at a minimum, the government should exercise some control over the price of drugs whose development has been supported by federal funds. A turning point in the public debate occurred in 1987, when consumer advocates and some government representatives claimed that the introductory price ($10,000 per patient per year) for the AIDS drug zidovudine (AZT) was excessively high, and therefore would prevent the drug from reaching many individuals who needed it or would create a significant financial burden for government when paying for the drug under programs such as Medicaid. These concerns were addressed in a widely publicized March 1987 hearing of the House Subcommittee on Health and the Environment, chaired by Representative Henry Waxman.

Responding to this criticism about drug prices, NIH made an administrative decision in March 1989 to adopt a policy of inserting a "reasonable (or fair) pricing" clause into its CRADAs with private organizations. Although the clause includes no specific reference to "reasonable pricing," the adoption of this policy was clearly intended by this clause (Article 8.3 of the Model PHS CRADA), which states: "NIH has a concern that there be a reasonable relationship between

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[9]Article 8.1 of the Model Public Health Service CRADA states: "With respect to Government intellectual property (IP) rights to any Subject Invention not made solely by the Collaborator's employees for which a patent or other IP application is filed, NIH hereby grants to the Collaborator an option to negotiate, in good faith, the terms of an exclusive or nonexclusive commercialization license that fairly reflect the relative contributions of the Parties to the invention and the CRADA, the risks incurred by the Collaborator, and the costs of subsequent research and development needed to bring the invention to the marketplace."

[10]U.S. General Accounting Office, *Universities' Research Efforts Under Public Law 96-517*, GAO Report B-207939, April 4, 1986.

the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public. Accordingly, exclusive commercialization licenses granted for NIH intellectual property rights may require that this relationship be supported by reasonable evidence." Such pricing provisions also are included in NIH exclusive licensing agreements.[11] The clause is not contained in nonexclusive licenses, however, because of the expectation that market competition will act to restrain prices when there are multiple manufacturers.[12]

Drug pricing remains a hotly debated and politically controversial issue. Since the 1987 Waxman hearing, several members of Congress have called for more direct and restrictive participation by the federal government in the pricing of drugs, particularly those that are discovered or developed from government-supported research.

IMPEDIMENTS TO COLLABORATION IN HIV DRUG DEVELOPMENT[13]

Pharmaceutical research and development is an inherently risky, time-consuming, and costly venture. The process spans 13.5 years on average,[14] and only about 20 percent of all drugs that enter clinical testing ultimately reach the marketplace.[15] On average, the after-tax research and development cost per new

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[11]Article 5.04 of the Model PHS Exclusive Patent License Agreement states: "DHHS has responsibility for funding basic biomedical research, for funding medical treatment through programs such as Medicare and Medicaid, for providing direct medical care, and more generally, for protecting the health and safety of the public. Because of these responsibilities, and the public investment in the research that culminated in the Licensed Patent Rights, PHS may require LICENSEE to submit documentation in confidence showing a reasonable relationship between the pricing of a Licensed Product, the public investment in that product, and the health and safety needs of the public. This paragraph shall not restrict the right of LICENSEE to price a Licensed Product or Licensed Process so as to obtain a reasonable profit for its sale or use. This paragraph 5.04 does not permit PHS or any other government agency to set or dictate prices for Licensed Products or Licensed Processes."

[12]B. Artim, *Pricing of Pharmaceuticals and Other Therapies Developed in Part with NIH Funds*, Background Paper, Office of Technology Transfer, National Institutes of Health, 1994.

[13]This section is based on material presented by Patrick Gage, Thomas Mays, Bruce Chabner, Stephen Carter, Harold Edgar, and Martin Delaney.

[14]D. Dranove and D. Meltzer, "Do Important Drugs Reach the Market Sooner?," *RAND Journal of Economics*, 25(Autumn 1994):1-22.

[15]J. A. DiMasi, R. W. Hansen, H. G. Grabowski, and L. Lasagna, "Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics*, 10(1991):107-142.

drug approved for marketing is between $140 million and $194 million (in 1990 dollars).[11] Industry executives maintain that these features are compounded in HIV/AIDS drug development. The following are among the reasons cited: the ultimate market and commercial lifetime of a given drug may be limited and the research and development process is accelerated, which means that substantial resources must be invested in a compressed time frame. Pharmaceutical companies, then, are reluctant to enter into collaborations with government that they believe may hinder this already complex enterprise.

Government and industry representatives agree that although federal policies governing collaborative research were generally implemented with good intentions, these policies have sometimes led to contentious negotiations or inhibited research collaboration altogether. The single most significant obstacle cited by pharmaceutical executives is the role that government has assumed in setting prices for jointly developed products. A second major impediment is the possibility that government may assign rights to new intellectual property developed during the collaboration in ways that benefit a company's competitors or lead to uncertain licensing arrangements. Other obstacles include the federal government's operating policies for the management of clinical trials under the auspices of the AIDS Clinical Trials Group (ACTG) -- a network of academic clinical research centers under the control and funding of the National Institute of Allergy and Infectious Diseases -- and the burdensome, lengthy, and bureaucratic process of establishing cooperative research and development agreements.

Underlying these specific barriers there exists an environment of uncertainty and instability fueled by the periodic shifts in federal policies governing research collaborations. There is also what many observers regard as a mutual lack of trust between government and industry. Workshop participants agreed that collaborative relationships would be improved by measures that each party might adopt to become more trusting and reliable partners.

"Reasonable Pricing" Considerations

As described earlier, NIH adopted the "reasonable pricing" clause as a means of achieving a balance between its dual statutory missions to conduct and promote biomedical research and education for the benefit of public health and to foster the transfer of federal technology. It is one of several mechanisms that NIH uses to help protect the public investment in collaborative research and

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[11] U.S. Congress, Office of Technology Assessment, *Pharmaceutical R & D: Costs, Risks and Rewards*, Report OTA-H-522 (Washington, D.C.: U.S. Government Printing Office), February 1993.

ensure that the broadest spectrum of individuals has access to medical products arising from this research. NIH officials point to the successful commercialization of two drugs - the cancer drug Taxol and the AIDS drug ddI - both of which were jointly developed with the Bristol-Myers Squibb Company by using the CRADA mechanism and an exclusive licensing agreement, respectively. Both the CRADA and exclusive license carried "reasonable pricing" provisions requiring that the public's investment be considered along with the company's investment in setting market prices for the drugs.

Despite these successes, however, the pharmaceutical industry generally views "reasonable pricing" provisions as too broad and threatening to their proprietary interests in a highly competitive marketplace.[17] Companies maintain that they will not know for years whether the prices allowed under "reasonable pricing" will permit a fair return on their investments. Faced with this uncertainty and the consequent inability to predict expenses, pharmaceutical companies that can afford to pursue research and development independently of government collaboration appear increasingly likely to do so.

NIH also collaborates with industry through Clinical Trial Agreements (CTAs), in which a company's patented product is transferred to or shared with the federal government for further research or clinical testing -- for example, to assess the safety, efficacy, or method of use or administration of the candidate drug. Although this collaborative mechanism has generally been productive, an official of the National Cancer Institute (NCI) pointed out that some CTAs are not sufficient to assure industry that their agent, when jointly developed with government, will not be subject to pricing restrictions if the drug proves to be effective and subsequently marketed. Furthermore, a CTA offers no assurance that the company will receive future rights to any invention that results from the clinical collaboration. In NCI's experience over the past 2 years, most large U.S. firms have been reluctant to collaborate with the institute in clinical drug testing. Only the smallest companies, which need this support for their clinical trials, can accept the unpredictability of collaboration.

Much of industry's concern centers around the uncertainties associated with "reasonable pricing" provisions. Industry representatives contend that they must agree to the provisions without knowing how the government will attempt to implement their intent when it comes time to market a product.[18] In addition, there is no ready definition of what a "fair or reasonable price" should be, and experience has demonstrated that perceptions about drug prices -- within industry

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[17]U.S. Department of Health and Human Services, Office of the Inspector General, *Technology Transfer and the Public Interest: Cooperative Research and Development Agreements at NIH*, Report OEI-01-92-01100, November 1993.

[18]See note 17.

and government and among the public are highly subjective and can vary widely. Industry therefore considers it impossible to calculate the risk and make responsible financial projections. Offers from NIH to "negotiate" when problems occur are considered equally vague and unpredictable. Even the examples of Taxol and ddI cited by NIH are widely viewed in industry as evidence of the potentially heavy hand of government. A Bristol-Myers Squibb executive expressed general satisfaction with the collaboration, but noted the company's worry that government may alter its position under continued political or public pressure and exercise more burdensome requirements at indeterminate times in the future.

NIH administrators readily acknowledge that the institutes lack the appropriate expertise to undertake meaningful analyses of private-sector product pricing decisions.[16] Moreover, NIH recognizes that there is no statutory authority for government agencies to participate in the pricing of products developed under CRADAs or CTAs. Indeed, NIH is one of only two federal agencies (along with the Bureau of Mines, U.S. Department of the Interior) that bind collaborators to "reasonable pricing" provisions.

NIH officials express a willingness to consider the implications for industry of "reasonable pricing" policies, but stress political pressure and the overarching need to safeguard the public's interest and ensure broad access to new drugs. For their part, industry executives maintain that the government and public interests are best served by increasing the flow of innovative medicines and letting market forces, such as competition, exert their customary control of prices. They argue that rather than ensuring access and lowering costs, pricing provisions are in fact discouraging collaboration and thereby the accelerated development and marketing of important new drugs. Society, in turn, is denied the benefits of their broad utilization.

Intellectual Property Rights

Patents are critical to the pharmaceutical industry because they protect developers' rights to medical products and processes that allow for an eventual

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[16] See note 17.

[17] In its February 1993 report, the congressional Office of Technology Assessment noted: "At present, the PHS has no established mechanism or standards for reviewing the reasonableness of prices for products marketed under exclusive licenses and lacks the legal authority to enforce its policy in cases where prices would be deemed unreasonable" (U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks and Rewards*, Report OTA-H-522 (Washington, D.C.: U.S. Government Printing Office), February 1993, p. 37.

return on investment. In addition, patents on successful products help ensure a return on the company's investment capital that is adequate to cover the costs of research and development (which include the resources used to investigate and evaluate the many drugs that ultimately never obtain marketing approval). Only a small percentage of the drugs that are marketed eventually earn a rate of return sufficient to recover the costs of development.[2]

The federal government has an obligation to administer its patent rights in a responsible manner that benefits society. This means, for one thing, not privatizing patents covering "core research" technologies that are critical to the creation of a pool of common scientific knowledge on which everyone can draw equally. Although industry representatives recognize government's social obligations, they contend that the government guards its patents and licenses too closely and thus does not provide companies with the property-right assurances that they need to engage in collaborative research.

Industry generally regards CRADAs as a useful framework for collaborative research. Their major advantage, as noted earlier, is that government and industry can negotiate in advance exclusive patent rights to some or all of the inventions that may arise. Under CTAs, however, the government generally does not assign intellectual property rights in advance to the industrial collaborator. In fact, most federal agencies interpret the licensing regulations and statutes as not permitting them to assign rights to future inventions outside of the CRADA mechanism; however, several workshop participants disagreed with this interpretation. If the research leads to follow-on inventions—such as new formulations or dosing strengths of an existing compound, novel ways to administer a drug, or new or combination uses for a drug—the government is not obligated to transfer patent rights or licenses to the company, which puts the ownership of key patents on the drug at risk. The government can in fact grant such rights to competitors, and a company could thus find itself competing with other companies that offer similar products based on its own initial research and development.

Additionally, the increasing number of "use" patents, "compound" patents, and "process" patents makes it difficult to determine who has or who should have what level of rights in regard to intellectual property from research collaborations. Industry therefore would like to see an improved and clearer definition of the patent process itself. Of greatest concern is that the principles governing property rights in this area remain clear, consistent, and stable as political leadership changes.

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[2]H. Grabowski and J. Vernon, "A New Look at the Returns and Risks to Pharmaceutical R&D," *Management Science*, 36(1990):804–821; P. Joglekar and M. L. Paterson, "A Closer Look at the Returns and Risks of Pharmaceutical R&D," *Journal of Health Economics*, 5(1986):153–177.

ACTG Complexities

A number of pharmaceutical companies view the process of working through the ACTG as cumbersome, bureaucratic, and inflexible. This has led some companies to conclude that they can develop candidate drugs more quickly on their own than through government partnerships. Another particularly divisive issue for industry is the question of sponsor access to data in ongoing clinical trials. Some in industry argue that since NIH staff are allowed early access to data without apparently threatening the successful completion of studies, there should be a way to permit senior executives of pharmaceutical companies to have interim access to data as well. Although such preliminary or early examinations of data should not be permitted to affect the conduct of the clinical trials, some in industry consider it important for sponsors to be aware of these data for long-term operational and financial planning purposes.

CRADA Negotiations

Industry also considers the process of establishing CRADAs to be lengthy, complex, and inefficient. Negotiating the agreements and achieving final approval entails several layers of review and involves numerous government officials and technical or CRADA committees. The process typically takes about a year, which many investigators believe is far too long to advance innovative research. Indeed, many NIH and industry collaborators are frustrated by this unwieldy process and view it as a disincentive to continued participation in the NIH CRADA program.[22]

OVERCOMING OBSTACLES TO COLLABORATION AND PROMOTING HIV DRUG DEVELOPMENT[23]

Pharmaceutical executives and government officials are committed to improving collaborative research efforts. Both groups also believe that the relationships must be as clear, consistent, and stable as possible. Industry representatives stress that if collaborations are often subject to future revisions or added expectations from other parts of government or new political leadership, engaging in collaborative research will be seen as a poor business decision because of the many uncertainties involved.

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[22]See note 17.

[23]This section is based on material presented by Martin Delaney, David Barry, Anthony Fauci, Timothy Westmoreland, David Schulke, Patrick Gage, and Peter Barton Hutt.

Workshop participants offered a variety of proposals for eliminating or reducing the obstacles seen as thwarting collaborative HIV research. Foremost, they identified alternative approaches to NIH's "reasonable pricing" provisions and methods of assigning intellectual property rights, and they examined options that can be used to deal with several operational impediments. They also surveyed the political landscape of government and industry collaboration, focusing particularly on the issue of "reasonable pricing."

"Reasonable Pricing" Considerations

Pharmaceutical executives argue that NIH should simply remove the "reasonable pricing" clauses from all CRADAs. At a minimum, they say, NIH could eliminate the pricing provisions in HIV/AIDS research collaborations as a test case and monitor the number and products of collaborative research projects that result. Industry believes that a likely outcome of this approach would be an acceleration of HIV drug and vaccine development. Because the "reasonable pricing" clause was inserted into NIH agreements by administrative discretion, industry representatives maintain that the clause could be similarly deleted. Government officials state, however, that NIH can do this only if there is public and congressional support.

To address concerns about gaining access to promising new therapies that are developed through collaborations, NIH could require pharmaceutical companies to enter into contractual agreements stipulating that no patients who need important drugs would be denied access to them because of an inability to pay. Many companies already have special patient access programs through which needed drugs, once approved for marketing, are provided to individuals who are unable to afford them. The principal difference would be to make such agreements formal and required. Consumer representatives caution, however, that this approach may still exclude some people, for instance, those who are not sufficiently impoverished to meet the standard set for special access provisions but who are unable to pay for the drug on their own without incurring significant financial hardship.

Government also could increase the use and perhaps size of royalty payments. For example, in exchange for an exclusive license, the industry partner could pay the government a negotiated royalty on product sales, which would be determined in advance and thus would be predictable and could be factored into the company's financial planning calculations and marketing decisions. Several workshop participants expressed concern, however, that royalties might in fact increase the cost of a drug because they may be added to the market price. They also questioned how the royalty would ultimately be calculated.

To address pricing concerns and to achieve broad access to cooperatively developed drugs, some combination of these options may be required. Both

industry and government representatives expressed their readiness to negotiate agreeable and swift solutions. To this end, NIH recently assembled representatives from industry, academia, and the federal government at a July 1994 forum to advise the director of NIH on ways to improve the negotiation, execution, and implementation of CRADAs.

Intellectual Property Rights

Because patents are a keystone of the pharmaceutical industry, its representatives propose that both CRADAs and CTAs should automatically guarantee prospective property rights or licenses to industrial partners. Companies receiving patents would pay the government appropriate royalties agreed upon in advance. Some industry and government representatives suggest that this solution should be accomplished through legislation to insulate the policy mandate from being buffeted by the winds of political change. Others say that although legislation may be welcome, existing contract law may offer more immediate relief. If permitted administratively, NIH and companies entering into CTAs could contractually agree to the automatic flow of property rights to the industrial collaborator. Contracts also offer a solution in cases in which clinical trials involving drugs developed by industry are conducted through universities. The Bayh-Dole Act now requires the federal government to assign to universities the patent rights to most intellectual property arising from government-funded research. However, such follow-on inventions might be handled contractually by stipulating that the university, as a condition of engaging in the clinical trial, would agree to grant the industrial partner a license and would receive a specified royalty in return.

As a model of the potential value of using contract law to settle patent rights, industry representatives cited the success of the Intercompany Collaboration for AIDS Drug Development (ICC). Sixteen pharmaceutical companies, ordinarily competitors that closely guard their intellectual property, have joined together under a cooperative contract to conduct collaborative research on anti-HIV drugs. A representative from one of the participating companies stated that under the ICC agreement each company retains proprietary rights to its compound. The companies completed their contractual agreements in about 6 weeks, which industry contrasts to the lengthy negotiations typically required in government collaborations.

ACTG Reorganization and Management

Although industry's experience with the ACTG has often been frustratingly slow and cumbersome, most companies recognize that the ACTG can play an

important and otherwise neglected role in helping define standards for HIV-related care and the optimum ways for using approved drugs to treat HIV disease and its associated conditions. NIH officials involved with the ACTG report that the recent reorganization and reform of the group are intended to place a heavy emphasis on improved efficiency and management and thus should address many of industry's concerns about its responsiveness.

In addition, NIH and ACTG researchers want to address industry's interest in gaining early access to clinical trial data, comparable to the access available to NIH staff. Industry and NIH representatives identified several key components of a possible resolution to this concern. First, all participants need to clearly identify the types of study data to which access should be limited to protect study integrity and quality. Second, companies must make a clear and convincing argument for gaining access to specific data and develop ways to safeguard the integrity of a study if such access is granted. Finally, government in turn needs to recognize and accept the role that access to these data plays in the corporate planning process and find ways to either accommodate necessary access or develop and adhere to a more consistent policy that similarly limits access by NIH staff.

Streamlining the CRADA Process

NIH also recognizes the need to simplify, clarify, and accelerate the negotiation process involved in developing CRADAs, and officials reported that a streamlined review and approval process for NIH CRADAs should be in place shortly. One suggestion is that NIH should assign additional staff members or establish a centralized committee to monitor and coordinate negotiations. A centralized committee, it was proposed, could eliminate the need for multiple levels of review by providing a single site for negotiating and approving CRADAs. Streamlining the CRADA process will allow this type of collaborative research to better keep pace with a steadily changing commercial and scientific environment.

Political Overview

Congress seeks to reconcile the need to stimulate and support pharmaceutical research and development with the public's need for access to innovative drugs. Many congressional representatives believe they are protecting the public's interest in asserting the right to require "reasonable pricing" when a product is developed (at least partially) in collaboration with government at taxpayer expense.

Members of Congress have proposed, or are in the process of proposing, several legislative initiatives. Among them, Representative Ron Wyden has offered a twofold approach. One step would establish an enforcement mechanism for negotiating "reasonable prices" for products resulting from CRADAs or NIH grants to private research institutions and universities. A second measure, designed to create incentives for industry to collaborate with government in clinical research, would authorize NIH to enter into CTAs with companies and would stipulate up front that the institutes will not claim intellectual property rights or assert "reasonable pricing" provisions for products that result from the collaborations.

Although industry representatives supported the proposal to eliminate the possibility of pricing considerations in CTAs, they questioned the basis for attaching "reasonable pricing" clauses to all CRADAs. Workshop participants agreed that differentiation among the various types of CRADAs is important with respect to application of "reasonable pricing" considerations. Although some CRADAs include a critically important invention or intellectual contribution from government, others involve situations in which government acts more like a contractor than an inventor, providing little more than screening techniques or other testing procedures. Thus, industry maintains that it is critical to avoid regulations or requirements that would assume similar major government contributions and rights in all CRADAs. Instead, the rights of government should be commensurate with its actual contributions. For example, in collaborations in which government has had a minimal role in developing a pharmaceutical product (i.e., a company discovers and patents a drug, but then brings it to government for additional screening or clinical evaluation), "reasonable pricing" provisions are less defensible. Industry executives argued that a broad, generic assertion of government rights or involvement in pricing decisions is likely to discourage industry from entering into such research collaborations. Indeed, some companies have already cited pricing clauses as the reason for their refusal to participate in CRADAs.[24]

The message, then, is that NIH and industry must find ways to work together to resolve pricing concerns in ways that reduce industry's anxiety about achieving a sufficient return on investment and allow government to protect public interests. Congressional staff cautioned that continued failure to achieve practical and mutually agreeable solutions could lead to unilateral action by Congress. If the majority of pharmaceutical companies object to congressional solutions, some observers predict that research collaborations and, in particular, investments in HIV drug development will diminish. Because many companies view HIV drug research and development as an inherently risky venture, further erosion of an already fragile research enterprise could hamper efforts to develop more effective treatments for HIV infection and AIDS.

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[24]See note 17.

CONCLUSION

The federal government and the pharmaceutical industry are the nation's major investors in HIV AIDS research. Enhancing the collaboration between these vast research enterprises offers perhaps the best hope of accelerating the development of innovative HIV drugs and vaccines. Unfortunately, a number of events, both AIDS and non-AIDS related, in recent years have led to increasing tensions and the lack of trust in their relationship.

Workshop participants highlighted a number of barriers that hamper research collaborations. The two most important ones are the role that the federal government has assumed in regulating prices for jointly developed products and the federal government's disposition of rights to intellectual property developed during collaborative research. These impediments are compounded by industry's overall concern about unpredictable shifts or variability in government policy regarding collaborations.

Yet there is room for optimism. This is founded on the recognition that both NIH and the pharmaceutical industry are deeply committed to research directed toward developing better drugs and vaccines for the treatment and prevention of HIV infection. In addition, government and industry researchers acknowledge the importance of enhanced cooperation. With the urgent need for new scientific knowledge and understanding of HIV infection, both sectors are willing to join in developing mechanisms that promote effective research collaborations.

The proposals discussed at the workshop will, it is hoped, set in motion efforts to foster government and industry collaboration. The proposals identify alternate approaches to NIH's pricing provisions and to its methods of assigning patent rights. They also touch on several operational barriers that inhibit timely research and highlight the need for both government and industry to extend themselves to become more trusting and reliable partners. Efforts to promote collaboration in HIV drug and vaccine development will, many scientists believe, lead to more innovative and effective therapeutic interventions.

Appendix

Workshop Program

Collaboration Between Government and Industry: Challenges and Opportunities for HIV Drug and Vaccine Development

May 6, 1994

9:00 **Welcome and Introduction**
- Paul Volberding, *Chief, AIDS Program and Clinical Oncology, San Francisco General Hospital, and Roundtable Cochair*

9:15 **Importance and Value of Government-Industry Collaboration on HIV Drug and Vaccine Development**
- Patrick Gage, *Chief Operating Officer, Genetics Institute, Inc.*

9:30 **Historical Perspectives on Government Technology Transfer Policy and the Pharmaceutical Industry**

Discussion Leader: Peter Barton Hutt, *Partner, Covington & Burling*

Understanding the Legislative History of Intellectual Property Rights Involving the Pharmaceutical Industry
- Peter Barton Hutt, *Partner, Covington & Burling*

Understanding the History of Fair Pricing Clauses and Their Implementation in Government Licensing of Intellectual Property
- Thomas Mays, *Director, Office of Technology Development, National Cancer Institute*

10:00 Discussion

10:30 *Break*

10:45 **Impediments to Collaboration on HIV Drug and Vaccine Development: Defining the Issues**

Discussion Leader: Patrick Gage, *Chief Operating Officer, Genetics Institute, Inc.*

Commentary from a Government/NIH Perspective
- Bruce Chabner, *Director, Division of Cancer Treatment, National Cancer Institute*

A View from the Pharmaceutical Industry
- Stephen Carter, *Senior Vice President, World Wide Clinical Research & Development, Bristol-Myers Squibb Pharmaceutical Research Institute*

Practical Implications of Rules Governing Intellectual Property Developed from Collaborative Relationships
- Harold Edgar, *Professor of Law, Columbia University School of Law*

11:30 Discussion

1:00 *Lunch*

2:00 **Overcoming Obstacles to Collaboration and Promoting HIV Drug and Vaccine Development: Proposals for Resolution**

Discussion Leader: Martin Delaney, *Founding Director, Project Inform*

Industry Perspective
- David Barry, *Group Director, Research, Development and Medical Affairs, The Wellcome Research Laboratories*

Government/NIH Perspective
- Anthony Fauci, *Director, National Institute of Allergy and Infectious Diseases*

Congressional/Legislative Response
- Timothy Westmoreland, *Counsel, Subcommittee on Health and the Environment, U.S. House of Representatives*

- David Schulke, *Chief Health Policy Advisor, The Honorable Ron Wyden, U.S. House of Representatives, Member, Energy and Commerce Committee, Health and Environment Subcommittee*

2:40 Discussion

4:15 **Consideration of Future Directions: Summary of Salient Issues**

- Daniel Hoth, *Senior Vice President and Chief Medical Officer, Cell Genesys*

4:45 **Closing Remarks**

- Barton Haynes, *F.M. Hanes Professor of Medicine; Director, Duke University Arthritis Center; and Roundtable Cochair*

5:00 *Adjourn*

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