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Institute of Medicine

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

May 6, 1994

Kristine Gebbie

INSTITUTE OF MEDICINE

Roundtable for the Development of Drugs and Vaccines Against AIDS

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WORKSHOP AGENDA

Friday, May 6

8:30 Continental Breakfast

9:00 Welcome and Introduction
- **Paul Volberding,** *Roundtable Co-chair*
- **Barton Haynes,** *Roundtable Co-chair*

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

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

Moderator: **Peter Barton Hutt,** *Covington & Burling*

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

Understanding the History of Fair Pricing Clauses and Their Implementation in Government Licensing of Intellectual Property
- **Thomas Mays,** *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**

Moderator: **Patrick Gage,** *Genetics Institute, Inc.*

Commentary from a Government/NIH Perspective
- **Bruce Chabner,** *National Cancer Institute*

A View from the Pharmaceutical Industry
- **Stephen Carter,** *Bristol-Myers Squibb Pharmaceutical Research Institute*

Practical Implications of Rules Governing Property Developed from Collaborative Relationships
- **Harold Edgar,** *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**

Moderator: **Martin Delaney,** *Project Inform*

Industry Perspective
- **David Barry,** *The Wellcome Research Laboratories*

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

Congressional/Legislative Response
- **Timothy Westmoreland,** *House Subcommittee on Health and the Environment*
- **David Shulke,** *Congressman Ron Wyden's Office*

2:40 Discussion

4:15 **Consideration of Future Directions: Summary of Salient Issues**
- **Daniel Hoth,** *Cell Genesys*

4:45 Closing Remarks
- **Barton Haynes,** *Duke University School of Medicine*

5:00 *Adjourn*

Institute of Medicine
Roundtable for the Development of Drugs and Vaccines Against AIDS

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Duke University School of Medicine

Paul Volberding, M.D.
San Francisco General Hospital

Members:

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

May 6, 1994

Lecture Room
National Academy of Sciences
2101 Constitution Avenue, N.W.
Washington, D.C.

Sponsored by:
INSTITUTE OF MEDICINE
Roundtable for the Development of
Drugs and Vaccines Against AIDS

ACCELERATING DRUG AND VACCINE DEVELOPMENT FOR AIDS AND HIV DISEASE: Tapping the Potential of Collaboration Between the NIH and the Pharmaceutical Industry[1]

Patrick Gage, PhD
Chief Operating Officer
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The National Institutes of Health and the U. S. pharmaceutical industry are far and away the largest investors in health related research in the United States[2]. The mission of the NIH is to "uncover new knowledge that will lead to improved health for everyone"[3], while the mission of the pharmaceutical industry is to develop effective new medicines for the treatment and prevention of disease.[4]

Each of these national institutions has recognized and addressed the challenge of the HIV epidemic with substantial investments: The 1994 NIH investment in AIDS/HIV research totals more than $1.5 billion; although such an estimate is not available for the pharmaceutical industry, the industry's substantial investment in HIV R & D is indicated by PMA survey data.[5] In 1993, 74 companies had 103 products in development, and there have already been 21 products approved by the FDA.

This paper examines whether the substantial U. S. investment in AIDS/HIV R & D can be made more productive in yielding effective drugs and vaccines through more extensive collaboration between the NIH and industry. Would removing or

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[1] A paper prepared for the *Workshop on Barriers to Collaboration Between Government and Industry* of the Roundtable for the Development of Drugs and Vaccines Against AIDS; Institute of Medicine, May 6, 1994.

[2] The Pharmaceutical Manufacturers Association estimates that, in 1994, the pharmaceutical industry will invest $13.8 billion, while the NIH will invest $10.3 billion. [Testimony of Gerald J. Mossinghoff, President, PMA, before Subcommittee on Health and the Environment of the Committee on Energy and Commerce, U. S. House of Representatives, Feb. 8, 1994]

[3] Chen, P. S. Jr., *The National Institutes of Health and Its Interactions with Industry*, in Biomedical Research: Collaboration and Conflict of Interest, Ed. by Porter, R. J. and Malone, T. F. [1992]

[4] The goal of pharmaceutical companies, like any business, is to be commercially successful. I believe it is more and more evident in this era of health care reform, that growth and profitability of the industry depends fundamentally on discovery and development of innovative and effective new therapeutic modalities.

[5] *AIDS Medicines: Drugs and Vaccines In Development, 1993 Survey;* Pharmaceutical Manufacturers Association.

lessening the barriers[6] to collaboration between these two institutions accelerate progress in AIDS/HIV drug and vaccine development?

Challenge and Opportunity: The HIV epidemic arose at a time of profound advances in the life sciences. These advances were driven by discovery and detailed examination of the molecular mechanisms underlying physiological processes and disease. The rise of biotechnology in the 1980s has enabled this explosion of information concerning our biology and also has made possible totally new approaches to the development of innovative disease treatments and preventions. Indeed, the application of biotechnology in the pharmaceutical industry has facilitated and energized an already ongoing transformation of drug discovery from an art to a science.[7]

Drug and vaccine research has been undergoing a transformation for some years from an art, involving little more than phenomenology and luck, to a more scientific, mechanism-based approach. As a result, many of today's most effective new therapeutics modulate the patho-physiology of disease by intervening at the core of its molecular mechanism. These therapeutics most often either are novel, highly specific enzyme inhibitors or receptor blockers that alter the biochemistry of a disease.[8] In the case of biopharmaceuticals, they are manufactured copies of human regulatory molecules used therapeutically to augment their normal physiologic levels, or to replace these agents when they are deficient, in order to prevent or treat disease.[9] A profoundly important feature of this transformation in the pharmaceutical industry and the life sciences is that the divide between basic and applied research has become blurred.

In the mid 1980s, many in academia and some in industry believed that, although AIDS was a truly tragic epidemic, its arrival at the time of the revolution occurring both in the life sciences and in drug discovery promised swift progress in addressing its treatment and prevention. While success with anti-virals in general had been limited, the availability of specific HIV enzymes provided attractive

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[6] These barriers consist principally of intellectual property and product pricing issues associated with government laboratory participation in commercial research efforts. These barriers will be discussed in detail at the workshop, and in other papers prepared for the workshop.

[7] Gage, L. P. *Gene cloning opens up a new frontier in health* in A Revolution in Biotechnology. p.42-55. Editor: Jean L. Marx [1989]

[8] For example, angiotensin converting enzyme inhibitors and beta-adrenergic receptor blockers for cardiovascular diseases.

[9] For example, human interferons for cancer and infectious diseases; and, rhFactor VIII for Hemophilia A and erythropoietin for anemia secondary to renal disease.

had been limited, the availability of specific HIV enzymes provided attractive selective targets for inhibitor discovery. Massive investments by academia and the pharmaceutical industry, while providing a detailed understanding of the virus and identification of many inhibitory agents, have not yet led to the broadly effective treatments or preventives that had been anticipated. Most agree that this disappointment is due primarily to the remarkable complexity of the HIV disease process, the highly mutable character of the virus, and our still incomplete understanding of the details of HIV pathogenesis.

In spite of the disappointments, there have been dramatic advances in our understanding of HIV disease, and some promising short-term results in suppression of HIV in human trials of HIV anti-virals, although often limited by the emergence of resistance. Therefore, instead of calling into question the validity of our strategy, I contend that the task is simply more daunting than first realized. We must continue in this quest, but we must do so more effectively. One major improvement that holds considerable potential is a fundamental enhancement in collaboration between the NIH and pharmaceutical company R & D efforts. A strong case can be made that facilitation of collaboration would make the research programs of both institutions more efficient, yielding faster progress in understanding and, hopefully, better treatments for HIV disease and AIDS.

Value of Government and Industry Collaboration: It is possible to roughly estimate the value, or rate of return, of investments in industrial research, and in relevant academic research, manifest through the introduction of new products and services. Mansfield's analyses across several industries reveals that academic research has had a significant beneficial effect in facilitating industrial product development. Although fraught with uncertainty, estimating the contribution of academic research, when compared across several industries, is greatest by a considerable margin in its benefits to pharmaceutical industry productivity.[10] This contribution reflects the certain impact of at least two major factors:

(1) the significant level of investment in academic research in the life sciences, funded predominantly by the NIH; and,

(2) the central role new understanding plays in discovering innovative therapeutic products.

Mansfield's economic analysis provides strong evidence that academic research

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[10] Mansfield, E. *Social Returns from R & D: Findings, Methods and Limitations.* Research-Technology Management 34, 24-27 [1991]; Mansfield, E. *Academic Research and Industrial Innovation.* Research Policy 20, 1-12 [1991]

benefits society through enhancing the pharmaceutical development process. However, it is dated, representing experience from 1975-85, and therefore does not capture the explosion of knowledge and the transformation of drug discovery that has taken place more recently. Today, the pharmaceutical industry embraces a "rational drug discovery" strategy that depends on the identification of underlying disease mechanisms and focuses on utilizing novel targets revealed by this knowledge for powerful drug design efforts: it depends inherently on state-of-the-art research and modern tools of biotechnology. Drug discovery and biotechnology can, then, be described as "simple technologies"[11] in which advances in basic research rapidly and facilely become manifest in useful products.

Indeed, the biotechnology revolution has significantly modified the "linear model of innovation"[12] as it pertains to R & D in the pharmaceutical industry. Today, academic research in the life sciences, while revealing new information as expected, also very often yields product concepts or actual candidates that immediately go into development. This new innovation pathway has fueled the development of the biopharmaceutical industry. Indeed, this pathway has often by-passed the traditional pharmaceutical industry and has germinated entirely new companies.

Another important change to this sequential model is that information flow in R & D is now much more often reciprocal. Research in the pharmaceutical and biotechnology industry is now so fundamental and of such high quality, that the industry has become an engine of knowledge acquisition, as well as a very important source of fundamentally unique research reagents useful in advancing basic research. Witness the tremendous advance in our understanding of the hematopoietic cascade, directly benefiting from work in the biotechnology industry, and the availability of recombinant cytokines and receptors. Many of these research reagents were first discovered in industry. They happen, also, to be biopharmaceutical development candidates or marketed products. More recently, advances in molecular genetics and the human genome project have fostered the emergence of private company research enterprises that challenge and are likely to transform academic science and ultimately give it tools (genes) that will promote

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[11] Kash, D. E. and Rycroft, R. W. *Direct government investment in valuable commercial technologies must replace our random, inefficient, and obsolete R & D system based on military spinoff and basic research.* Technology Review 96, no. 8, 58-62 [November 1993]

[12] The "linear model of innovation" defines a clear pathway from basic research in academia to subsequent applied research in industry, with products emerging at a considerable time and with a considerable additional investment after the academic contribution. According to this model, the development of pharmaceutical products would be sequential: understanding of disease in academia, leading subsequently to identification of products and their development and commercialization by industry. [see Kash and Rycroft; Mansfield]

dramatic advances in our understanding of life processes.

Lastly, it has always been true that collaboration between scientists interested in a common problem has accelerated the advance of scientific understanding. Today, with the explosion in knowledge, and the discovery of uniquely important technologies, in both academia and in industry, collaboration has become even more important. A prime example of the value of collaboration is the unique initiative taken by sixteen pharmaceutical companies in forming the "Intercompany Collaboration on AIDS Drug Development".[13] Recently, a consensus protocol for the rapid evaluation of triple drug combinations was announced by the Collaboration. This initiative should facilitate the evaluation of investigational drug candidates from competing companies in joint studies that may identify more effective combination regimens than any one company could find on its own. There are few industries were competition is more fierce than in pharmaceuticals, and it is a testament to the potential value of collaboration within the industry that traditional attitudes have been put aside in this initiative.

Summary: [1] Academic research has traditionally contributed more to product development in the pharmaceutical industry than in any other industry;

[2] The 'biotechnology revolution' and the transformation of drug discovery from an 'art to a science' is making fundamental research even more critical to the product development process; and, as a result,

[3] Fundamental research and product discovery are occurring in both academia and industry.

[4] Modern biological research benefits enormously from collaboration,

Conclusion: It is imperative that more be done to accelerate the discovery and development of drugs and vaccines for AIDS and HIV disease. However, rather than simply increasing the investment in HIV R & D, we have an opportunity to enhance the effectiveness and productivity of this research investment by facilitating collaboration between the NIH and industry. Isn't it time that the barriers to this collaboration be reduced or eliminated? Isn't it time to tap the potential of unfettered interaction between scientists in these two major HIV R & D enterprises?

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[13] Current participants in the Collaboration include Aji Pharma USA, Astra, Boehringer Ingelheim, Bristol-Myers Squib, Burroughs Wellcome, Du Pont Merck, Glaxo, Hoechst AG, Hoffmann-La Roche, Lilly, Merck, Miles, Pfizer, Sigma-Tau, SmithKline Beecham, and Syntex. For further information, contact John Doorley at Merck, (908) 423-4081.

April 18, 1994

A Brief and General History of Government Policy Concerning Patent Rights to Federally-Funded Pharmaceutical Inventions

Ever since the federal government began heavily to fund private scientific research in the 1940s, there have been conflicting theories about the proper allocation of rights to inventions arising out of research supported by government funds (whether completely or only in small part). On the one hand, many have argued that inventions supported by any amount of taxpayer money should be freely available to the public. On the other hand, others have contended that such inventions effectively reach the public only when they are commercialized by private companies with exclusive patent rights. Although neither approach has ever entirely prevailed, the general trend over the past four decades has been away from reserving invention rights to the government and toward granting rights in federally-funded inventions to private contractors and grantees.

The 1950s: Diverse Approaches

Federal funding of scientific research in the private arena surged in the years during and after World War II. There was, however, no unified government policy concerning patent rights to inventions arising from federally-supported private research. Each department and agency established its own patent policy.

In the 1950s, the Department of Health, Education, and Welfare (HEW), the parent department of the National Institutes of Health (NIH), promulgated regulations setting out its approach to patent rights. HEW took the position that "the public interest will in general be best served if inventive advances resulting [from research supported by HEW grants and contracts] are made freely available to the Government, to science, to industry, and to the general public."[1/] HEW thus generally required that such inventions be dedicated to public use or, if patented, be made available to the public on a nonexclusive and royalty-free basis.

HEW recognized, however, that it is sometimes necessary to use the patent process "to foster an adequate

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1/ 45 C.F.R. § 8.0(b) (1955), promulgated in 20 Fed. Reg. 6747 (September 14, 1955).

commercial development to make an invention widely available."[2/] The HEW regulations thus permitted the Surgeon General to assign patent rights to a "competent organization," such as the grantee organization, "if he finds that the invention will thereby be more adequately and quickly developed for widest use and that there are satisfactory safeguards against unreasonable royalties and repressive practices."[3/] The regulations also authorized the Surgeon General to enter Institutional Patent Agreements (IPAs) with grantee institutions. These agreements allowed the grantee institutions themselves to determine the ownership and disposition of patent rights in all inventions arising from NIH-funded research, so long as they made the inventions available to the public without unreasonable restrictions or excessive royalties.[4/] The HEW regulations reserved for the government a nonexclusive and royalty-free license under the patent for all governmental purposes.[5/]

In 1957, HEW ruled that contracts with private industry for cancer chemotherapy research would not be subject to the presumption against privately-owned patent rights. According to the new regulation, the Surgeon General, in negotiating such contracts, would "be subject only to such limitations and alternatives as the Secretary may approve for such program."[6/]

In accordance with its general policy of encouraging public access to inventions, HEW freely published the results of most NIH-sponsored research and dedicated many inventions to public use. Between 1953 and 1958, however, NIH entered into IPAs with 18 private institutions, primarily universities. The IPAs gave these private institutions the option to acquire or assign exclusive patent rights to all of their inventions arising from research supported by NIH.

HEW's patent policy was developed within the department and applied only to HEW grants and contracts. Other federal agencies formulated different approaches. The confusing patchwork of policies was itself a disincentive to productive cooperation between the federal government and outside organizations.

[2/] 45 C.F.R. § 8.0(c) (1955).

[3/] 45 C.F.R. § 8.2(b) (1955).

[4/] 45 C.F.R. § 8.1(b) (1955).

[5/] 45 C.F.R. § 8.3 (1957).

[6/] 45 C.F.R. § 8.7 (1957).

The 1960s: The Presumption of Government Ownership

The first effort to establish a uniform patent policy for the federal government was President Kennedy's Memorandum and Statement of Government Patent Policy, issued on October 10, 1963.[7/] Like the HEW regulations, the Kennedy Memorandum attempted to strike a balance between the rights of the public to the fruits of government-sponsored research and the need for incentives to encourage the development and dissemination of these inventions. As applied to pharmaceutical products, however, the Kennedy Memorandum appeared virtually to foreclose the acquisition of patent rights by contractors and grantees.

The Kennedy Memorandum stated that the government should ordinarily acquire the principal or exclusive rights to inventions derived from government-supported research. It set out four situations, encompassing the vast majority of research grants and contracts, in which the government should normally acquire such rights. One such situation -- covering all grants and contracts made by NIH -- was where "a principal purpose of the contract is for exploration into fields which directly concern the public health or public welfare."[8/]

The Kennedy Memorandum allowed that "[i]n exceptional circumstances the contractor may acquire greater rights than a nonexclusive license at the time of contracting, where the head of the department or agency certifies that such action will best serve the public interest."[9/] The Kennedy Memorandum thus appeared to permit IPAs, but only in rare situations. The Kennedy Memorandum also permitted contractors under certain circumstances to acquire greater rights after an invention had been identified -- although it was unclear if this could ever be done when the research touched on the public health. Even if a contractor acquired primary rights to an invention, the government would retain a nonexclusive and royalty-free license under the patent for governmental purposes.

The Kennedy Memorandum proved in practice to be quite flexible. Departments and agencies interpreted the policy in a variety of ways. Some continued routinely to assign patent rights to private contractors. Senator Russell Long repeatedly attacked such "giveaways" and introduced a

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7/ 28 Fed. Reg. 10943 (October 10, 1963).

8/ Id. § 1(a).

9/ Id.

series of unsuccessful bills during the 1960s designed to mandate government ownership.

Senator Long did not direct his wrath at HEW, however, because throughout most of the 1960s, the department steadfastly refused to assign patent rights to private organizations. Between 1958 and 1967, HEW declined to enter into IPAs with any of the 34 universities that requested such arrangements. Moreover, HEW almost never assigned grantees or contractors the rights to particular inventions. When requested to do so, it usually reached a decision only after long delays. During the delays, the development of the inventions remained in limbo. Potential licensees refused to invest in inventions so long as they were afraid that HEW would retain the patent rights.

The 1970s: Transition

In 1968, the General Accounting Office (GAO) issued a report finding that the HEW policy of retaining patent rights deterred industry from cooperating in the development of potentially important new drugs.[10/] In response to the GAO report, HEW agreed to reinstitute the use of IPAs that left the determination of patent rights to universities and nonprofit institutions. Before the reintroduction of IPAs, not one drug arising from HEW-supported research had been successfully developed and marketed. After the department reinstated the IPA program, a number of important new drugs were delivered to the public under IPAs through the involvement of private industry.

HEW's change in policy helped to trigger a general awareness throughout the government that it was often necessary to award exclusive patent rights to grantees and contractors in order to encourage the commercial utilization of federally-sponsored inventions. In the early 1970s, various other agencies copied the HEW IPA program. In 1971, President Nixon retained the Kennedy Memorandum but revised it to authorize departments and agencies to give grantees and contractors greater rights to inventions where necessary to achieve utilization.[11/]

A task group of the Commission on Government Procurement was established to review the federal government patent policy. In its 1972 report, the Commission stressed

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[10/] "Problem Areas Affecting Usefulness of Results of Government-Sponsored Research in Medicinal Chemistry," GAO Rep. No. B-164037(2) (August 12, 1968).

[11/] 36 Fed. Reg. 16887 (August 26, 1971).

the need for a patent policy that would stimulate the commercialization of inventions supported by government funds. The Commission was skeptical of the existing Presidential policy, because it relied primarily on after-the-fact disposition of patent rights, thus causing delays and discouraging firms from participating in government research work. Nonetheless, the Commission urged rapid implementation of the policy so that further assessment could be based on actual experience. If this experience revealed weaknesses in the existing policy, the Commission recommended legislation that would permit the retention of title by grantees and contractors, subject to march-in rights and other safeguards.

In the following years, it became clear that the revised Presidential policy guaranteed neither uniformity among departments and agencies nor the effective commercialization of inventions by industry. By 1978, there were approximately 22 different administrative policies regarding patent rights to government-sponsored inventions. Some of these policies generally permitted contractors to acquire title, but others usually reserved title to the government. In addition, a number of differing statutes were enacted governing the patent policies for specific departments and agencies. These statutes tended to have a title-in-the-government orientation.

By the late 1970s, HEW appeared to have returned to its pre-1968 patent policies, discouraging private ownership. In 1978, Senator Robert Dole compiled a list of 29 important medical discoveries whose development had been significantly delayed because the department was unable to determine whether or not it would retain patent rights. Moreover, HEW became increasingly reluctant to admit new participants to the IPA program. Industry participation in the development of new drugs supported by federal government funds once again began to stagnate.

By the end of the decade, there was a growing movement for legislation to create a government-wide patent policy that encouraged commercialization and utilization of government-supported inventions. The movement received a large boost in 1978 from the publication of a report by the Advisory Subcommittee on Patent and Information Policy, established as part of President Carter's Domestic Policy Review. The report concluded:

> Government ownership of patents with an offer of free public use does not alone result in commercialization of research results. . . . Therefore, all members of this subcommittee recommend transferring the patent rights on the results of Government-sponsored research to the

private sector for commercialization. In the case of university or private contractor work sponsored by the Government, the members of this subcommittee recommend that the title to the patents would go to the university or private contractor . . . .[12/]

The 1980s: The Presumption of Private Ownership

Two years later, Congress enacted the Patent and Trademark Amendments of 1980.[13/] This law, commonly known as the Bayh-Dole Act, essentially mirrored the HEW (now HHS) IPA policy. The statute gives universities, nonprofit institutions, and small businesses a right to retain title to inventions developed in the performance of government grants and contracts. There are exceptions to this rule, but the Bayh-Dole Act reverses the approach established by the Kennedy/Nixon Memorandum. It is now presumed that grantees and contractors covered by the Act will acquire title to patents, and the burden is on the government to justify acquiring title for itself.

Section 202 of the Act provides:

(a) Each nonprofit organization or small business firm may, within a reasonable time after disclosure [of an invention to the federal department or agency] elect to retain title to any subject invention: *Provided, however,* That a funding agreement may provide otherwise (i) when the funding agreement is for the operation of a Government-owned research or production facility, (ii) in exceptional circumstances when it is determined by the agency that restriction or elimination of the right to retain title to any subject invention will better promote the policy and objectives of this chapter or (iii) when it is determined by a Government authority . . . that the restriction or elimination of the right to retain title to any subject invention is necessary to protect the security of [foreign intelligence activities].[14/]

[12/] Draft Report on Patent Policy, Advisory Committee on Patent and Information Policy of the Advisory Committee on Industrial Innovation, pp. 3-4, Proposal V (December 20, 1978).

[13/] 94 Stat. 3015, codified primarily at 26 U.S.C. § 200 ff.

[14/] 35 U.S.C. § 202(a).

The Act requires that any determination under section 202(a)(ii) be in writing and accompanied by a written statement of the facts justifying the determination.[15/] The department or agency must send a copy of each such statement to the Comptroller General, who may at any time inform the department or agency that its pattern of determinations is contrary to the policy and objectives of the Act. These "objectives" include, among other things, the promotion of utilization of inventions, free competition and enterprise, and commercialization and public availability of inventions.[16/] Since these objectives are rarely best achieved by government acquisition of title, the "exceptional circumstances" that justify the retention of patent rights by the government under section 202(a)(ii) are likely to be rare.

Section 203 of the Act provides that, under certain circumstances, a department or agency may exercise "march-in rights" and require a delinquent grantee or contractor that has acquired title to grant a license to a responsible applicant.[17/] The primary situations in which federal departments or agencies may exercise such rights are when the grantee or contractor is not taking effective steps to achieve practical application of the invention or when the action is necessary to alleviate health or safety needs.[18/] In addition, the government always retains the right to use the invention anywhere in the world, royalty-free.[19/]

The enactment of the Bayh-Dole Act represented a striking shift in the federal government's approach to patent rights to inventions developed through federal support. It established a unified government policy favoring the acquisition of patents by nonprofit institutions (including universities) and small businesses. Although the Act does not give similar rights to large businesses, federal grants and contracts with small businesses and nonprofit institutions represent a significant portion of scientific research spending by the federal government. A 1987 Executive Order by President Reagan expanded the Act by directing the heads of all federal departments and agencies to "promote the commercialization . . . of patentable results of federally funded research by granting to all contractors, *regardless of*

[15/] 35 U.S.C. § 202(b)(1).

[16/] 35 U.S.C. § 200.

[17/] 35 U.S.C. § 203.

[18/] 35 U.S.C. § 203(a) & (b).

[19/] 35 U.S.C. § 202(c)(4).

size, the title to patents made in whole or in part with federal funds, in exchange for royalty-free use by or on behalf of the government."[20/]

As a result of the Bayh-Dole Act, the discrete patent policy of HHS was replaced, along with 25 other administrative and statutory policies, by a single federal approach with a presumption that grantees and contractors were to acquire the title to inventions resulting from federal funding. Pharmaceuticals were to be treated like all other government-sponsored inventions. For those nonprofit institutions that already had IPAs with HHS, the enactment of the Act caused few significant changes. For other nonprofit institutions, however, as well as for small businesses (who apparently were not eligible for IPAs under the old HEW policy) the Bayh-Dole Act offered new opportunities. President Reagan's Executive Order extended these opportunities to large businesses.

In 1986, Congress passed another law, the Technology Transfer Act, that further carried out the policy of encouraging private companies to commercialize inventions. This statute permits federal research laboratories to enter into cooperative research and development agreements (CRADAs) with private companies and nonprofit institutions. In exchange for funds, personnel, services, and property, federal laboratories may grant to a collaborating party patent rights to any invention made by a federal employee under the agreement.[21/]

The 1990s: The Return of Greater Government Control?

By the end of the 1980s, therefore, there was a firmly established policy throughout the federal government to give patent rights to private organizations when the inventions were derived from government-supported research. The Bayh-Dole Act and the Technology Transfer Act led to a significant increase in industry involvement in federally-sponsored research and facilitated the development of many new important drugs and devices.[22/]

[20/] Executive Order No. 12591, 52 Fed. Reg. 13414 (April 22, 1987), § 1(b)(4) (emphasis added). President Reagan issued this Executive Order to carry out the policy stated in his Memorandum to the Heads of Executive Departments and Agencies of February 18, 1983. 19 Weekly Comp. Pres. Doc. 252.

[21/] Federal Technology Transfer Act of 1986, 100 Stat. 1785, codified at 15 U.S.C. 3710(a).

[22/] A 1986 GAO report on universities' experience under Bayh-

(continued...)

The new policy also provoked some negative reaction. In 1988, Public Citizen petitioned HHS to change its patent policy regarding AIDS drugs. Public Citizen asked the department to issue only nonexclusive licenses for AIDS drugs developed by government institutions and to include price controls in these licenses.

In 1993, the private ownership of patents arising from government-sponsored research received extensive attention because of an agreement between the Scripps Research Institute and the Swiss-based Sandoz Pharmaceutical Corporation. Scripps, which receives about $70 million a year in grants from NIH, agreed to give Sandoz patent rights to all of its discoveries for ten years in exchange for $300 million. The Scripps-Sandoz agreement was the primary topic of two hearings held before the House Committee on Small Business's Subcommittee on Regulation, chaired by Representative Ron Wyden. Numerous witnesses, including Bernadine Healy, the Director of NIH, criticized the agreement as a giveaway of taxpayer money to a foreign corporation and as a threat to the ideal of unbiased scientific inquiry. Scripps subsequently renegotiated the research agreement with Sandoz.

It was difficult for critics of the Scripps-Sandoz agreement to blame it on the Bayh-Dole Act. Indeed, Dr. Healy suggested that the agreement violated the letter and spirit of the Act, which gives preference to small businesses and American industry. Nonetheless, various witnesses at the hearings called into question the general policy embodied by the Act of granting private organizations relatively unfettered patent rights to inventions arising out of federally-sponsored research. A number of participants in the hearings, including members of the subcommittee, suggested that federal agencies should regulate the prices of drugs developed from NIH-funded research.

Critics of the private commercialization of government-sponsored inventions have rallied around the idea of price controls for drugs. Since 1989, NIH has inserted "fair pricing" clauses into its CRADAs. Representative Wyden,

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22/ (...continued)
Dole stated that although it was too early to assess the full impact of the Act, it was already apparent that "[u]niversities can enter into licensing agreements with private companies easier [sic]." The report also noted that "[p]rivate companies and university representatives collaborate more. Companies are more willing to discuss inventions and give institutions funds to further develop them." "Universities' Research Efforts Under Public Law 96-517," GAO Rep. No. B-207939 (April 4, 1986).

Representative Henry Waxman, and other members of Congress have called for more direct and restrictive participation by the federal government in the pricing of drugs, particularly when the drugs result from federal research or federally-supported research. Indeed, Representative Wyden introduced legislation in March 1993 that would limit "profiteering" by drug companies when the federal government funds the research.

Lewis A. Grossman
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Institute of Medicine
Roundtable for the Development of Drugs
and Vaccines Against AIDS

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

SPEAKERS AND INVITED GUESTS

May 6, 1994

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Industry – Government Collaboration on HIV Drug Development

Issues

1. Industry incentive to take the R&D risk
2. Accelerated development
3. Appropriate labeling

HIV Drug Development

1. Small market

2. Expensive and risky development
   - Compressed time frames
   - Expanded access

3. Public pressures
   - Prioritization not possible

Industry Incentive to Take R&D Risk

1. The specter of price controls
2. Fair pricing clause in CRADAs
3. Congressional attacks

Accelerated Development

Essential Components

1. Expanded access after Phase 1-2 evidence of activity
   - Parallel track
   - Treatment IND
   - Treatment center referral program (TAXOL)
2. Accelerated approval by FDA
   - Surrogate marker package
   - Conditional approval
   - Clinical endpoints to be submitted
3. Surrogate markers
4. FDA – Industry collaboration

Threats to Accelerated Development

1. Attacks on surrogate markers
   - Post concorde depression
   - Research purity
2. Limited labeling
   - Refers to expanded access rather than research trials
3. Therapeutic nihilism

Appropriate Labeling

1. Follow up indication requirement for clinical endpoints
   - Large numbers
   - Long follow up
   - Logistical nightmare
2. Increased discordance between label and actual usage
   - The cancer drug syndrome
   - How to deal with combinations
   - The inability to promote

The ACTG

1. Bureaucratic
2. Inflexible
3. Access to data

April 18, 1994

A Brief and General History of Government Policy Concerning Patent Rights to Federally-Funded Pharmaceutical Inventions

Ever since the federal government began heavily to fund private scientific research in the 1940s, there have been conflicting theories about the proper allocation of rights to inventions arising out of research supported by government funds (whether completely or only in small part). On the one hand, many have argued that inventions supported by any amount of taxpayer money should be freely available to the public. On the other hand, others have contended that such inventions effectively reach the public only when they are commercialized by private companies with exclusive patent rights. Although neither approach has ever entirely prevailed, the general trend over the past four decades has been away from reserving invention rights to the government and toward granting rights in federally-funded inventions to private contractors and grantees.

The 1950s: Diverse Approaches

Federal funding of scientific research in the private arena surged in the years during and after World War II. There was, however, no unified government policy concerning patent rights to inventions arising from federally-supported private research. Each department and agency established its own patent policy.

In the 1950s, the Department of Health, Education, and Welfare (HEW), the parent department of the National Institutes of Health (NIH), promulgated regulations setting out its approach to patent rights. HEW took the position that "the public interest will in general be best served if inventive advances resulting [from research supported by HEW grants and contracts] are made freely available to the Government, to science, to industry, and to the general public."[1/] HEW thus generally required that such inventions be dedicated to public use or, if patented, be made available to the public on a nonexclusive and royalty-free basis.

HEW recognized, however, that it is sometimes necessary to use the patent process "to foster an adequate

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1/ 45 C.F.R. § 8.0(b) (1955), promulgated in 20 Fed. Reg. 6747 (September 14, 1955).

commercial development to make an invention widely available."[2/] The HEW regulations thus permitted the Surgeon General to assign patent rights to a "competent organization," such as the grantee organization, "if he finds that the invention will thereby be more adequately and quickly developed for widest use and that there are satisfactory safeguards against unreasonable royalties and repressive practices."[3/] The regulations also authorized the Surgeon General to enter Institutional Patent Agreements (IPAs) with grantee institutions. These agreements allowed the grantee institutions themselves to determine the ownership and disposition of patent rights in all inventions arising from NIH-funded research, so long as they made the inventions available to the public without unreasonable restrictions or excessive royalties.[4/] The HEW regulations reserved for the government a nonexclusive and royalty-free license under the patent for all governmental purposes.[5/]

In 1957, HEW ruled that contracts with private industry for cancer chemotherapy research would not be subject to the presumption against privately-owned patent rights. According to the new regulation, the Surgeon General, in negotiating such contracts, would "be subject only to such limitations and alternatives as the Secretary may approve for such program."[6/]

In accordance with its general policy of encouraging public access to inventions, HEW freely published the results of most NIH-sponsored research and dedicated many inventions to public use. Between 1953 and 1958, however, NIH entered into IPAs with 18 private institutions, primarily universities. The IPAs gave these private institutions the option to acquire or assign exclusive patent rights to all of their inventions arising from research supported by NIH.

HEW's patent policy was developed within the department and applied only to HEW grants and contracts. Other federal agencies formulated different approaches. The confusing patchwork of policies was itself a disincentive to productive cooperation between the federal government and outside organizations.

[2/] 45 C.F.R. § 8.0(c) (1955).

[3/] 45 C.F.R. § 8.2(b) (1955).

[4/] 45 C.F.R. § 8.1(b) (1955).

[5/] 45 C.F.R. § 8.3 (1957).

[6/] 45 C.F.R. § 8.7 (1957).

The 1960s: The Presumption of Government Ownership

The first effort to establish a uniform patent policy for the federal government was President Kennedy's Memorandum and Statement of Government Patent Policy, issued on October 10, 1963.[7/] Like the HEW regulations, the Kennedy Memorandum attempted to strike a balance between the rights of the public to the fruits of government-sponsored research and the need for incentives to encourage the development and dissemination of these inventions. As applied to pharmaceutical products, however, the Kennedy Memorandum appeared virtually to foreclose the acquisition of patent rights by contractors and grantees.

The Kennedy Memorandum stated that the government should ordinarily acquire the principal or exclusive rights to inventions derived from government-supported research. It set out four situations, encompassing the vast majority of research grants and contracts, in which the government should normally acquire such rights. One such situation -- covering all grants and contracts made by NIH -- was where "a principal purpose of the contract is for exploration into fields which directly concern the public health or public welfare."[8/]

The Kennedy Memorandum allowed that "[i]n exceptional circumstances the contractor may acquire greater rights than a nonexclusive license at the time of contracting, where the head of the department or agency certifies that such action will best serve the public interest."[9/] The Kennedy Memorandum thus appeared to permit IPAs, but only in rare situations. The Kennedy Memorandum also permitted contractors under certain circumstances to acquire greater rights after an invention had been identified -- although it was unclear if this could ever be done when the research touched on the public health. Even if a contractor acquired primary rights to an invention, the government would retain a nonexclusive and royalty-free license under the patent for governmental purposes.

The Kennedy Memorandum proved in practice to be quite flexible. Departments and agencies interpreted the policy in a variety of ways. Some continued routinely to assign patent rights to private contractors. Senator Russell Long repeatedly attacked such "giveaways" and introduced a

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7/ 28 Fed. Reg. 10943 (October 10, 1963).

8/ Id. § 1(a).

9/ Id.

series of unsuccessful bills during the 1960s designed to mandate government ownership.

Senator Long did not direct his wrath at HEW, however, because throughout most of the 1960s, the department steadfastly refused to assign patent rights to private organizations. Between 1958 and 1967, HEW declined to enter into IPAs with any of the 34 universities that requested such arrangements. Moreover, HEW almost never assigned grantees or contractors the rights to particular inventions. When requested to do so, it usually reached a decision only after long delays. During the delays, the development of the inventions remained in limbo. Potential licensees refused to invest in inventions so long as they were afraid that HEW would retain the patent rights.

The 1970s: Transition

In 1968, the General Accounting Office (GAO) issued a report finding that the HEW policy of retaining patent rights deterred industry from cooperating in the development of potentially important new drugs.[10/] In response to the GAO report, HEW agreed to reinstitute the use of IPAs that left the determination of patent rights to universities and nonprofit institutions. Before the reintroduction of IPAs, not one drug arising from HEW-supported research had been successfully developed and marketed. After the department reinstated the IPA program, a number of important new drugs were delivered to the public under IPAs through the involvement of private industry.

HEW's change in policy helped to trigger a general awareness throughout the government that it was often necessary to award exclusive patent rights to grantees and contractors in order to encourage the commercial utilization of federally-sponsored inventions. In the early 1970s, various other agencies copied the HEW IPA program. In 1971, President Nixon retained the Kennedy Memorandum but revised it to authorize departments and agencies to give grantees and contractors greater rights to inventions where necessary to achieve utilization.[11/]

A task group of the Commission on Government Procurement was established to review the federal government patent policy. In its 1972 report, the Commission stressed

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[10/] "Problem Areas Affecting Usefulness of Results of Government-Sponsored Research in Medicinal Chemistry," GAO Rep. No. B-164037(2) (August 12, 1968).

[11/] 36 Fed. Reg. 16887 (August 26, 1971).

the need for a patent policy that would stimulate the commercialization of inventions supported by government funds. The Commission was skeptical of the existing Presidential policy, because it relied primarily on after-the-fact disposition of patent rights, thus causing delays and discouraging firms from participating in government research work. Nonetheless, the Commission urged rapid implementation of the policy so that further assessment could be based on actual experience. If this experience revealed weaknesses in the existing policy, the Commission recommended legislation that would permit the retention of title by grantees and contractors, subject to march-in rights and other safeguards.

In the following years, it became clear that the revised Presidential policy guaranteed neither uniformity among departments and agencies nor the effective commercialization of inventions by industry. By 1978, there were approximately 22 different administrative policies regarding patent rights to government-sponsored inventions. Some of these policies generally permitted contractors to acquire title, but others usually reserved title to the government. In addition, a number of differing statutes were enacted governing the patent policies for specific departments and agencies. These statutes tended to have a title-in-the-government orientation.

By the late 1970s, HEW appeared to have returned to its pre-1968 patent policies, discouraging private ownership. In 1978, Senator Robert Dole compiled a list of 29 important medical discoveries whose development had been significantly delayed because the department was unable to determine whether or not it would retain patent rights. Moreover, HEW became increasingly reluctant to admit new participants to the IPA program. Industry participation in the development of new drugs supported by federal government funds once again began to stagnate.

By the end of the decade, there was a growing movement for legislation to create a government-wide patent policy that encouraged commercialization and utilization of government-supported inventions. The movement received a large boost in 1978 from the publication of a report by the Advisory Subcommittee on Patent and Information Policy, established as part of President Carter's Domestic Policy Review. The report concluded:

> Government ownership of patents with an offer of free public use does not alone result in commercialization of research results. . . . Therefore, all members of this subcommittee recommend transferring the patent rights on the results of Government-sponsored research to the

> private sector for commercialization. In the case of university or private contractor work sponsored by the Government, the members of this subcommittee recommend that the title to the patents would go to the university or private contractor . . . .[12/]

The 1980s: The Presumption of Private Ownership

Two years later, Congress enacted the Patent and Trademark Amendments of 1980.[13/] This law, commonly known as the Bayh-Dole Act, essentially mirrored the HEW (now HHS) IPA policy. The statute gives universities, nonprofit institutions, and small businesses a right to retain title to inventions developed in the performance of government grants and contracts. There are exceptions to this rule, but the Bayh-Dole Act reverses the approach established by the Kennedy/Nixon Memorandum. It is now presumed that grantees and contractors covered by the Act will acquire title to patents, and the burden is on the government to justify acquiring title for itself.

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12/ Draft Report on Patent Policy, Advisory Committee on Patent and Information Policy of the Advisory Committee on Industrial Innovation, pp. 3-4, Proposal V (December 20, 1978).

13/ 94 Stat. 3015, codified primarily at 26 U.S.C. § 200 ff.

14/ 35 U.S.C. § 202(a).

The Act requires that any determination under section 202(a)(ii) be in writing and accompanied by a written statement of the facts justifying the determination.[15] The department or agency must send a copy of each such statement to the Comptroller General, who may at any time inform the department or agency that its pattern of determinations is contrary to the policy and objectives of the Act. These "objectives" include, among other things, the promotion of utilization of inventions, free competition and enterprise, and commercialization and public availability of inventions.[16] Since these objectives are rarely best achieved by government acquisition of title, the "exceptional circumstances" that justify the retention of patent rights by the government under section 202(a)(ii) are likely to be rare.

Section 203 of the Act provides that, under certain circumstances, a department or agency may exercise "march-in rights" and require a delinquent grantee or contractor that has acquired title to grant a license to a responsible applicant.[17] The primary situations in which federal departments or agencies may exercise such rights are when the grantee or contractor is not taking effective steps to achieve practical application of the invention or when the action is necessary to alleviate health or safety needs.[18] In addition, the government always retains the right to use the invention anywhere in the world, royalty-free.[19]

The enactment of the Bayh-Dole Act represented a striking shift in the federal government's approach to patent rights to inventions developed through federal support. It established a unified government policy favoring the acquisition of patents by nonprofit institutions (including universities) and small businesses. Although the Act does not give similar rights to large businesses, federal grants and contracts with small businesses and nonprofit institutions represent a significant portion of scientific research spending by the federal government. A 1987 Executive Order by President Reagan expanded the Act by directing the heads of all federal departments and agencies to "promote the commercialization . . . of patentable results of federally funded research by granting to all contractors, *regardless of*

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[15] 35 U.S.C. § 202(b)(1).

[16] 35 U.S.C. § 200.

[17] 35 U.S.C. § 203.

[18] 35 U.S.C. § 203(a) & (b).

[19] 35 U.S.C. § 202(c)(4).

size, the title to patents made in whole or in part with federal funds, in exchange for royalty-free use by or on behalf of the government."[20/]

As a result of the Bayh-Dole Act, the discrete patent policy of HHS was replaced, along with 25 other administrative and statutory policies, by a single federal approach with a presumption that grantees and contractors were to acquire the title to inventions resulting from federal funding. Pharmaceuticals were to be treated like all other government-sponsored inventions. For those nonprofit institutions that already had IPAs with HHS, the enactment of the Act caused few significant changes. For other nonprofit institutions, however, as well as for small businesses (who apparently were not eligible for IPAs under the old HEW policy) the Bayh-Dole Act offered new opportunities. President Reagan's Executive Order extended these opportunities to large businesses.

In 1986, Congress passed another law, the Technology Transfer Act, that further carried out the policy of encouraging private companies to commercialize inventions. This statute permits federal research laboratories to enter into cooperative research and development agreements (CRADAs) with private companies and nonprofit institutions. In exchange for funds, personnel, services, and property, federal laboratories may grant to a collaborating party patent rights to any invention made by a federal employee under the agreement.[21/]

The 1990s: The Return of Greater Government Control?

By the end of the 1980s, therefore, there was a firmly established policy throughout the federal government to give patent rights to private organizations when the inventions were derived from government-supported research. The Bayh-Dole Act and the Technology Transfer Act led to a significant increase in industry involvement in federally-sponsored research and facilitated the development of many new important drugs and devices.[22/]

[20/] Executive Order No. 12591, 52 Fed. Reg. 13414 (April 22, 1987), § 1(b)(4) (emphasis added). President Reagan issued this Executive Order to carry out the policy stated in his Memorandum to the Heads of Executive Departments and Agencies of February 18, 1983. 19 Weekly Comp. Pres. Doc. 252.

[21/] Federal Technology Transfer Act of 1986, 100 Stat. 1785, codified at 15 U.S.C. 3710(a).

[22/] A 1986 GAO report on universities' experience under Bayh-

(continued...)

The new policy also provoked some negative reaction. In 1988, Public Citizen petitioned HHS to change its patent policy regarding AIDS drugs. Public Citizen asked the department to issue only nonexclusive licenses for AIDS drugs developed by government institutions and to include price controls in these licenses.

In 1993, the private ownership of patents arising from government-sponsored research received extensive attention because of an agreement between the Scripps Research Institute and the Swiss-based Sandoz Pharmaceutical Corporation. Scripps, which receives about $70 million a year in grants from NIH, agreed to give Sandoz patent rights to all of its discoveries for ten years in exchange for $300 million. The Scripps-Sandoz agreement was the primary topic of two hearings held before the House Committee on Small Business's Subcommittee on Regulation, chaired by Representative Ron Wyden. Numerous witnesses, including Bernadine Healy, the Director of NIH, criticized the agreement as a giveaway of taxpayer money to a foreign corporation and as a threat to the ideal of unbiased scientific inquiry. Scripps subsequently renegotiated the research agreement with Sandoz.

It was difficult for critics of the Scripps-Sandoz agreement to blame it on the Bayh-Dole Act. Indeed, Dr. Healy suggested that the agreement violated the letter and spirit of the Act, which gives preference to small businesses and American industry. Nonetheless, various witnesses at the hearings called into question the general policy embodied by the Act of granting private organizations relatively unfettered patent rights to inventions arising out of federally-sponsored research. A number of participants in the hearings, including members of the subcommittee, suggested that federal agencies should regulate the prices of drugs developed from NIH-funded research.

Critics of the private commercialization of government-sponsored inventions have rallied around the idea of price controls for drugs. Since 1989, NIH has inserted "fair pricing" clauses into its CRADAs. Representative Wyden,

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22/(...continued)
Dole stated that although it was too early to assess the full impact of the Act, it was already apparent that "[u]niversities can enter into licensing agreements with private companies easier [sic]." The report also noted that "[p]rivate companies and university representatives collaborate more. Companies are more willing to discuss inventions and give institutions funds to further develop them." "Universities' Research Efforts Under Public Law 96-517," GAO Rep. No. B-207939 (April 4, 1986).

Representative Henry Waxman, and other members of Congress have called for more direct and restrictive participation by the federal government in the pricing of drugs, particularly when the drugs result from federal research or federally-supported research. Indeed, Representative Wyden introduced legislation in March 1993 that would limit "profiteering" by drug companies when the federal government funds the research.

Lewis A. Grossman
Peter Barton Hutt

CASE STUDIES

1. TAXOL®

Paclitaxel (Taxol®) was discovered by the National Cancer Institute (NCI) as a result of its systematic, comprehensive drug discovery and development effort that began in 1955 with the establishment of the Cancer Chemotherapy National Service Center. In 1960, a program for collection, screening, and chemical isolation of plant and other natural products was established, primarily through a collaborative arrangement with the U.S. Department of Agriculture.

In 1962, samples of the Pacific yew, *Taxus brevifolia*, were collected from Washington State and extracts prepared and tested in the standard NCI screen for natural products, the KB in vitro cell culture cytotoxicity test. By 1964, confirmed activity in that system was established, and the product was re-collected and assigned to one of the NCI contractors, Research Triangle Institute, under Dr. Monroe Wall, for chemical purification and isolation. During this period, in vivo activity in several transplanted rodent tumor systems was also observed.

Dr. Wall's group was able to isolate the pure substance and identify its structure, which they published in 1971. Because of the small amounts present in the plant, the difficulty of isolation, and the relatively modest in vivo activity observed until then, paclitaxel was not considered a strong candidate for clinical development. However, by 1974-5, larger amounts of the compound became available and very good activity was observed in another experimental model that had been added to the screen, the B16 melanoma. As a result of this additional information, paclitaxel was accepted as a candidate for preclinical development in 1977.

As the preclinical development efforts were initiated, paclitaxel became of greater and greater interest as a result of further therapeutic studies demonstrating highly significant activity in a human tumor xenograft model, MX-1, and as a result of mechanistic studies by Susan Horwitz and co-workers, who found that the compound stabilized microtubules and thereby served as a mitotic poison in a manner different from any other known drug.

Preclinical development was a long and tortuous process because of problems of supply, isolation, and very poor solubility, but by 1982, it was possible to complete these efforts, including preclinical toxicology, and prepare for the filing of an Investigational New Drug Application with the FDA, in order to initiate Phase I clinical studies. These studies, which began in 1984, were hindered seriously by problems of hypersensitivity reactions, but it was finally found that the drug could be administered safely by utilizing a 24-hour infusion with pre-medication. Suggestions of activity in advanced ovarian cancer were observed and Phase II studies, including studies in ovarian cancer, were initiated in 1985. Activity in that disease was observed and the results published in 1989.

By 1989, NCI recognized that paclitaxel was likely to become a new drug of significant importance, and efforts were initiated to transfer the technology to the private sector, since the NCI does not market drugs. Patents had not been filed by the Government nor by Research Triangle Institute, but even if they had, their term would have expired by the time paclitaxel became recognized as a marketable new agent. Since pharmaceutical companies will not expend their resources without some type of protection, it became necessary to utilize an approach that would provide exclusivity to a pharmaceutical partner. The result was the use of a CRADA (Cooperative Research and Development Agreement), authorized under the Federal Technology Transfer Act of 1986. Under a CRADA, the NCI could provide its preclinical and clinical data to a collaborating organization on an exclusive basis, in exchange for the expenditure of specific efforts and resources by its collaborator.

In August 1989, the NCI solicited proposals from companies to participate in the further development and eventual marketing of paclitaxel. Four applications were received and reviewed, and Bristol-Myers Squibb Company (BMS) was selected as the company best able to carry out the objectives of this collaboration. A CRADA with that company was signed in January 1991.

A number of important terms were included in the CRADA. Supplies of the drug, prepared exclusively from the tree bark, were extremely limited, and the company was to assume responsibility for supplying NCI with the drug for continued clinical trials, producing enough for the commercial market, and developing alternative, renewable sources of the drug, in addition to carrying out all of the other efforts needed to gain approval for marketing. Because of the concerns of environmentalists and others about the maintenance of the species and other impacts of massive harvesting of the tree, particularly on federal lands, these issues became critical but through close collaboration among all of the parties, including the NCI, BMS, the U.S.D.A. Forest Service, and the U.S.D.I. Bureau of Land Management, the problems were rapidly approached and solved, and supply is no longer an issue. Furthermore, BMS is moving rapidly toward gaining approval for an alternate source of the drug, through semi-synthesis from a precursor found in the needles and twigs of other species of *Taxus* growing in many parts of the world.

As a result of its efforts, BMS received approval of its New Drug Application for the use of Taxol® in refractory ovarian cancer in December 1992, and the drug is now on the market. Approval for metastatic breast cancer was recommended by the FDA Oncologic Drug Advisory Committee in December 1993.

The control of drug prices is not within the NCI's mandate or competence. Fair pricing is of concern to the institute, however, and the CRADA includes the following language:

13. B. NCI has a concern that there be a reasonable relationship between the pricing of taxol, the public investment in taxol research and development, and the health and safety needs of the public. Bristol-Myers Squibb acknowledges that concern, and agrees that these factors will be taken into account in establishing a fair market price for taxol.

C. Bristol-Myers Squibb is concerned that, because taxol in not patentable, market exclusivity for a period necessary to recover its investment in taxol research and development may not be available. In addition, due to the limited supply of natural resources for production of taxol and the complexity of the manufacturing process, taxol will be expensive to develop and manufacture. NCI acknowledges these concerns, and agrees that these factors may be taken into account in establishing a fair market price for taxol.

The CRADA mechanism under which the pricing clause has been included is an extremely useful vehicle. It has made the pricing issue a matter of public interest. In doing so, this clause has undoubtedly exerted considerable pressure on the company to moderate its pricing strategy. Specifically, as detailed below, it has allowed the NCI to argue forcefully for total access to the drug, both for those that can afford it and those unable to pay. It has allowed us to guarantee that the thousands of patients already receiving Taxol® on a compassionate basis continued to receive it free even after FDA approval.

Since NIH lacks the expertise to undertake cost-based analyses, we chose to measure the fairness and reasonableness of the price by comparison with other products marketed for the same indication, as well as other considerations. Beginning in the summer of 1992, as the time of expected FDA approval neared, several discussions were held between senior officials of NCI and BMS in order to reach an agreement on the general principles that would be used by the company in establishing a fair price for the drug. Among these principles were: 1. the establishment of a price that is comparable to that of other drugs for the same indication, specifically in the lower 50% of such products, 2. a discounted price to the Government, 3. free drug to those unable to pay, and 4. modification in the price as the market expands and/or new indications are added. In addition, we requested that free drug continue to be supplied to the NCI for its research trials and for the many patients already receiving the drug under the compassionate release program. These factors were all agreed to and incorporated in the final company marketing plan.

The initial wholesale price of the drug led to a cost per treatment cycle of $980 for the average patient, which is less than the cost of carboplatin. The net-weighted cost of the drug is equal to that of cisplatin, despite the fact that cisplatin is inexpensive to produce, has a larger market, and has been under patent protection for the first 15 years of its commercial sale. In addition, we had considerable experience with the production of paclitaxel and knew that it was far more expensive to produce than cisplatin, which we had also produced. Thus, NCI believes that the pricing strategy announced by Bristol meets every reasonable test of fairness, if one considers the price of similar products, its lack of patent protection, and the significant problems in

production. In this instance, the Federal Technology Transfer Act allowed a very effective transfer to the private sector, with all the advantages of rapid scale-up of production and rapid commercialization, and with assured access of all women with ovarian cancer who require this treatment.

2. DDI

In contrast to the discovery of Taxol®, DDI (dideoxyinosine) evolved from research carried out by intramural investigators at the NCI, who were exploring possible new agents for the treatment of HIV-infected patients. Realizing the potential importance of purine and pyrimidine nucleosides to inhibit viral replication through inhibition of reverse transcriptase, Dr. Broder and his colleagues in the Clinical Oncology Program, Division of Cancer Treatment, purchased a number of compounds from commercial suppliers, including DDA, DDI, DDC and others. All three of these compounds were highly active in their in vitro test system.

In 1987, both DDA and DDI were approved for further development, and the necessary preclinical toxicology and other studies needed for IND filing were undertaken by the Developmental Therapeutics Program. In the course of these studies, it became clear that, after administration in vivo, DDA was rapidly deaminated to DDI and we were therefore dealing effectively with just one drug. Although work progressed with DDA to the IND stage and the initiation of a clinical trial since it was further advanced in development, eventually DDA was dropped in favor of DDI, once the IND for DDI was approved.

Clinical trials with DDI, carried out under the auspices of both NCI and the National Institute of Allergy and Infectious Diseases (NIAID), clearly established its utility in patients with HIV. Since the discovery of the activity of these agents was solely a government invention, patent applications were filed, which included both DDA and DDI. As with most inventions made at NIH, the licensing was carried out by the National Technical Information Service (NTIS). Of six applications received, that from Bristol-Myers Squibb (BMS) was judged best and an exclusive license was awarded. A New Drug Application for DDI was approved by the FDA in 1991.

Although the license agreement does not contain a clause controlling the price of DDI, it does contain the following clause relating to fair pricing:

> 3.2 LICENSEE acknowledges the concern of the Government that there be a reasonable relationship between LICENSEE'S pricing of Licensed Product and the health and safety needs of the public and that this relationship be supported by evidence. If , during the exclusive marketing term of this Agreement, as provided under Paragraph 2.1 above, LICENSEE fails to provide such evidence upon reasonable request of the Director, Division of Cancer Treatment, National Cancer Institute, NTIS has the right to require LICENSEE to grant sublicenses

under Licensed Patent(s) to responsible applicants on reasonable terms when necessary to fulfill health and safety needs. It is agreed that any such evidence will be treated in a confidential manner. Any requirements to grant sublicenses shall be deemed a modification of this agreement and shall be subject to the provisions of Paragraphs 9.2 and 11.4.

The discussions with Bristol-Myers Squibb on the pricing of DDI were somewhat simpler than those relating to Taxol®. In essence, we requested that the price be well below the entry price of AZT ($10,000 per year). They set a price of $2,000, which is we consider reasonable and appropriate.

Clearly, although approval to award an exclusive license to BMS required approval at the level of the Assistant Secretary for Health, DHHS, the licensing process for DDI was still simpler than the effort needed to implement the CRADA for paclitaxel. In addition, of course, a patent provides a much higher degree of proprietary protection, which is very important in attracting collaborators from the private sector. We therefore believe that every effort should be made to obtain patent protection, although the CRADA is certainly a feasible alternative where necessary. The current procedures required to initiate a CRADA are rather cumbersome and time-consuming, but efforts are underway to simplify the process.

In summary, we feel comfortable with the current guidelines and procedures related to drug pricing. Our experiences in dealing with Bristol-Myers Squibb to reach appropriate agreements for both paclitaxel and DDI were highly satisfactory, and we have every reason to believe that similar dealings with other companies would result in similarly acceptable agreements.

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TODAY's NEWS

NATIONAL SPENDING CAP IS INEVITABLE UNDER HEALTH CARE REFORM, according to Senate Majority Leader George Mitchell (D-Maine). Speaking before the Independent Insurance Agents of America annual meeting in Washington, D.C. April 19, Mitchell stated that "all [nations] except the U.S. have in common the existence of some expenditure cap, and I think inevitably it will have to occur in our society."

The majority leader, who will retire at the end of this session, explained that a national limit is necessary because the "normal laws of supply and demand" do not apply to health care. "It is an extraordinary economic transaction because [health care] is one of the few transactions in which the seller determines what the purchaser will buy." Mitchell has an academic background in economics as well as law.

Senators currently are discussing two variations of a global budget, the Maine Democrat reported. "Some advocate setting up the new system of so-called managed competition, seeing if it works and setting [spending] targets. If it meets those targets voluntarily, then...global caps only kick in at a later time," he explained. The other alternative is implementing the ceiling "at the outset."

Late on the afternoon of April 19, Senate Minority Leader Robert Dole (R-Kan.), chased by reporters as he left a closed Finance Committee meeting, was asked to comment on Mitchell's assertion that expenditure caps were a prerequisite for achieving cost control. "He's probably right," Dole conceded.

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Many advocates for the pharmaceutical industry have argued that the Medicare drug benefit structure outlined in President Clinton's Health Security Act would create disincentives for companies to engage in breakthrough drug R&D, by virtue of the law's mandated Advisory Council on Breakthrough Drugs. However, it has also been suggested that companies with weaker product pipelines might prefer the 17% Medicare rebate required under the Clinton plan to the market forces of PBM management.

Wagner noted the difficulty of defining a breakthrough drug, suggesting that "from the market's point of view, a breakthrough drug is one which is so uniquely beneficial that it must be accepted onto a formulary regardless of its price." Wagner reported that OTA is currently studying breakthrough drugs at the request of Sen. David Pryor's (D-Ark.) Aging Committee. One of the goals of the study is to answer a number of questions about breakthroughs, such as "how often will we expect them to come along, how long will they stay on the market alone without close competitors developing, just how beneficial will such drugs have to be to operate as breakthroughs in the market, and just how price-insensitive will health plans be to such products."

Wagner noted that any pharmaceutical benefit under health care reform "will be layered on top of the emerging marketplace" for drugs. "If the prescription drug benefit is compatible with managed care pharmacy approaches, it will share in the cost-moderating forces that are at work," she advised. "If the prescription drug benefit is structured as a fee-for-service benefit, then more direct regulation of prices and utilization will be necessary to control the cost of prescription drug benefits."

While declining to state her preference for either the "market approach to cost moderation or the regulatory approach," Wagner maintained that the decision "deserves careful consideration by this committee and the Congress."

One major problem with price regulation, she advised, "is that it's very difficult to know what the right price of a drug is, and any price control structure runs, in the long run, the risk of creating unintended incentives that may lead to inefficient patterns of prescription drug pricing, utilization and, ultimately, innovation and new drugs." On the other hand, she noted, "there are problems with the suggestions to turn the Medicare drug benefit over to pharmacy benefit managers, but the approach has not been fleshed out enough to examine problems in detail."

NIH "REASONABLE COMPENSATION" APPROACH SHOULD REPLACE "REASONABLE PRICE" clauses in National Institutes of Health Cooperative Research and Development Agreements, Regeneron Director of Technology Transfer Barbara Conta testified before the Senate Judiciary/Patents Subcommittee at an April 19 hearing on the Bayh-Dole Act.

Speaking on behalf of Regeneron and the Biotechnology Industry Organization, Conta said that BIO "supports the goals" of the Technology Commercialization Act of 1993 (S 1537) sponsored by subcommittee Chairman Dennis DeConcini (D-Ariz.) and Sen. Jay Rockefeller (D-W.Va.). If enacted, S 1537 should be interpreted to mean that NIH will receive "reasonable compensation" and prevent "further regulation like the 'reasonable price' clause" that would be "inconsistent with the purpose and effectiveness of technology transfer," Conta maintained.

BIO has been opposing efforts by Rep. Ron Wyden (D-Ore.) and others to expand the "reasonable price" clause included in CRADAs to other forms of technology transfer involving federally funded research. NIH CRADAs currently require corporate partners to promise to set a "reasonable price" for any products resulting from the licensed technology.

Many biotechnology firms, including Regeneron, have said they will no longer enter CRADAs on the grounds that the potential for pricing oversight by the federal government does not allow them to risk capital on the development project.

The Deconcini/Rockefeller bill advocates a "reasonable compensation" approach to NIH technology transfer. At the hearing, Deconcini asked witnesses specifically about the feasibility of introducing a "user fee"

approach to Bayh-Dole, whereby payments made by companies to federally funded research centers would be subject to a royalty to be paid to the federal government.

DeConcini asked whether "a small percentage of the license fee going to the federal government, or an additional small percent" added to a licensing arrangement would damage the success of Bayh-Dole. Additionally, DeConcini questioned whether there were objections to a "legislative royalty for the government to participate in profits" of successful ventures.

"BIO member companies are willing to negotiate royalties or other arrangements with the government when they license and then commercialize intellectual property transferred by the government," Conta said. Regeneron is only concerned about "the overall royalty rate." It is "irrelevant to us" if the company pays a 3% royalty to a university that has to pay 1% of it to the government, Conta added.

The remainder of the witnesses were opposed to the proposal on the grounds that the research centers/universities would pay the royalties. Massachusetts Institute of Technology President Charles Vest said that "the federal government should support research and provide incentives" for universities, and anything that detracts incentives should be avoided.

Sen. Edward Kennedy (D-Mass.) spoke favorably on behalf of Bayh-Dole. Referring to one of Rep. Wyden's concerns with technology transfer arrangements, Kennedy declared that suggestions of tax-payer funded research being exported to other countries at the expense of the U.S. "is a misinterpretation of what has been happening." There has been "misinterpretation and distortion and misrepresentation" of Bayh-Dole, he maintained. The act has been an "enormously important trigger in terms of the movement of technology and innovativeness into the commercial world," Kennedy said.

Senate Majority Leader Robert Dole (R-Kan.) testified that Bayh-Dole has been a success, and changing the bill "would be a mistake." Sen. Dole said that he would be "happy to explore at the staff level" Sen. DeConcini's provision to include user fees in the legislation.

ORPHAN DRUG-STYLE INCENTIVES FOR ANTI-ADDICTION DRUG R&D could be added to the pending crime bill, Sen. Joseph Biden (D-Del.) and Orrin Hatch (R-Utah) agreed at a April 19 hearing before the Biden's Senate Judiciary Committee. Hatch said the measure would be designed to provide pharmaceutical companies with incentives to develop anti-addiction medications in the face of the high cost of drug development.

The Utah Republican said when the Orphan Drug Act sponsored by him and Rep. Henry Waxman (D-Calif.) originally was passed in 1983, the number of orphan drugs in development went from "eight to 60 or 70" within eight months, "and now there are over 100." At present, three medications are approved for treatment of drug addiction: methadone, ***ORLAAM*** (LAAM) and ***Trexan*** (naltrexone). Only a handful of other anti-drug abuse drugs are in the pipeline now, and most are in very early stages of development, the hearing was told.

Hatch proposed that orphan drug-style language be added to the Senate crime bill (S 1607) when it goes to conference with the House version (HR 4092) within the next three weeks. "I believe that Sen. Biden and I could be creative enough with the help of others," and "I am going to challenge both staffs to get together and see what we can do," he remarked. While not as optimistic as Hatch about the timeframe, Biden said he would "support anything [Hatch] proposes."

Neither Hatch nor his staffers offered any specifics about the proposal. Under the Orphan Drug Act, manufacturers of drugs for treatment of a "rare disease or condition" that affects fewer than 200,000 people are eligible for marketing exclusivity for seven years after approval may apply for FDA orphan research grants and contracts, and are eligible for tax credits for the costs of clinical trials conducted in the U.S. An amendment to the Orphan Drug Act introduced in both the House and Senate March 24 would lower market exclusivity to four years.

The hearing was held to discuss a report released by the Institute of Medicine March 17 entitled "Development of Anti-Addiction Medications: Issues for the Government and Private Sector." The report highlights the

need for federal leadership in developing anti-addiction medications, better economic incentives for pharmaceutical companies and an expedited FDA review process for anti-addiction drugs.

Testifying before the Committee, IoM committee Chairman Laurence Earley, MD, University of Pennsylvania, approved of Hatch's suggestion: "That is, so to speak, on the tip of our tongue," he said, adding that the committee's second report, to be released in December, is expected to contain a similar recommendation. The report also is expected to include a recommendation that an expedited review process of anti-addiction medications be formalized at the FDA.

Biden noted that the hearing was the first in a series of hearings intended to change the public perception that drug addiction cannot be successfully treated with pharmaceuticals. At the next hearing, pharmaceutical companies will be invited to discuss their concerns about bringing anti-addiction medications to market. A hearing date has not been set.

FDA's MEDICAL DEVICE APPROVALS WOULD INCREASE TO 820 510(K)s, 9.5 PMAs PER MONTH two years after a user fee program is implemented, according to a draft document on FDA user fee performance goals prepared by the majority staff of the House Energy and Commerce Committee. Under the plan, 510(k)s clearances would increase 95% from an initial base level of 425, while PMA productivity would jump 111% from a base average output of 4.5 per month.

The figures, which represent the average number of applications logged out monthly during the six months prior to the date specified, are two of the "interim productivity goals" for device premarket evaluation set for FDA during the first two years of a user fee program. If current trends persist, the Center for Devices and Radiological Health appears to be in a position to accomplish at least the one-year 510(k) productivity goal of 630 per month. The center cleared over 600 510(k)s in both February and March.

The draft document lists a number of additional performance objectives to which FDA would commit in conjunction with enactment of device user fee legislation. FDA's commitment would be embodied in a letter from FDA Commissioner David Kessler to Congress and industry.

The method of including the agency's medical device performance goals in a letter of agreement separate from the actual bill was first used when the Prescription Drug User Fee Act was passed in 1992. A letter from Kessler accompanying that measure spells out goals for backlog elimination in two years, as well as premarket application review timeframes to be achieved five years after enactment. By 1997, FDA is committed to reviewing 90% of all prescription drug applications within stipulated timeframes.

As expected, the medical device performance goals would require FDA to eliminate essentially the entire premarket application backlog within two years. According to the draft performance goals, FDA would "take final action on 95% of the backlogged 510(k)s and 90% of the backlogged PMAs with 24 months of enactment of appropriating legislation and hiring authority." The document defines the backlog as "those applications pending at the agency upon enactment of appropriating legislation and hiring authority."

Long-term goals of the user fee program spelled out in the draft include completion of final action on 95% of 510(k)s within 90 days and completion of "substantive review" on 90% of PMAs within 180 days. These goals would apply to applications submitted 25 months after commencement of the program.

The document defines "final action" as "a determination that the device is substantially equivalent, not substantially equivalent, [or] not approvable." The draft defines "substantive review" as "a determination that: the device is approved; the device is approvable with final action to follow within 30 days of resubmission; FDA is refusing to approve the device;...the device is not approvable due to major deficiencies;...[or] the device is ready to go to the advisory panel." If a firm submits "an unsolicited major amendment" to a PMA during the second three months of the review period, "FDA will have an additional 90 days to review the information."

Timeframes for review of PMA supplements are also addressed in the draft goals. Supplements that require clinical data share the same review timeframes as original PMAs, while those supplements without data

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MEMORANDUM

TO: Members, Roundtable for the Development of Drugs and Vaccines Against AIDS

FROM: Leslie Hardy LH

DATE: July 7, 1994

SUBJECT: Draft Summary of May Roundtable Workshop on Government-Industry Collaboration

Enclosed is a draft summary report of the May workshop, *Collaboration Between Government and Industry: Challenges and Opportunities for HIV Drug and Vaccine Development*. Because there was considerable redundancy, the panels have each been summarized as one section. The whole section is attributed to all those who presented or offered comments rather than attributing each point to a particular person.

Shortly following the workshop, we asked that each panel moderator (Hutt, Gage, and Delaney) prepare a brief synopsis of their respective panel discussions. Where possible, we have relied on the panel moderators' summaries in developing the workshop report. This means, however, that many sections are presented with a particular point of view, which does not present a problem unless other Roundtable members disagree with the characterization or have an alternative interpretation of the discussion. Striking the appropriate balance and tone in the report will be critical. We also have incorporated passages from the workshop background papers (e.g., the paper prepared by Pat Gage on the value of collaboration, and the paper by Lewis Grossman and Peter Barton Hutt on the history of government policies in this area). We thought it would be more effective to integrate the relevant material from the papers into the full summary rather than appending them at the end of the report.

Please **review the draft carefully** for mistakes, problems in emphasis or tone, inaccuracies in content, awkward phrasing of legal points, etc. Keep in mind that this draft has not been thoroughly edited: inconsistencies in terms or acronyms, grammatical errors, and awkward sentence structure will be corrected. Also, there are a number of specific questions or notes (in bold type) for you embedded in the text. Throughout the workshop, for example, many participants asserted that government-industry collaboration (in particular, the number of CRADAs) is declining; however, the attached bar graph, prepared by NIH's Office of Technology Transfer (June 1994) would seem to indicate otherwise. If there are other sources that document a real diminution (and the possible causes thereof) in collaborations, we should note these in the report. You will find the phrase "need documentation" sprinkled throughout the text.

Please either mark up the draft and return it to me via Federal Express, or fax (202-334-2939) your comments and revisions **by Tuesday, July 19** at the latest. We hope to submit the report for IOM/NAS review by the last week of July, and plan to publish the report in mid-September. Many thanks to all of you for your help and cooperation. Please call me if you have any questions.

NIH CRADAs EXECUTED BY FISCAL YEAR, 1985 - 1993

ICD	FY85	FY86	FY87	FY88	FY89	FY90	FY91	FY92	FY93	TOTAL[1]
CC	0	0	0	0	0	1	0	1	2	4*
DCRT	0	0	0	0	0	1	0	0	0	1
FIC	0	0	0	0	0	0	0	0	0	0
NCHGR	0	0	0	0	0	0	0	0	0	0
NCI	1	2	8	6	16	9	10	7	10	69*
NCRR	0	0	0	2	0	1	0	0	0	3
NEI	0	0	0	0	0	3	0	1	1	5
NHLBI	0	0	0	0	1	0	2	3	2	8*
NIA	0	0	0	1	0	0	0	0	0	1
NIAAA	0	0	0	0	0	0	0	0	0	0
NIAID	0	0	0	0	4	4	4	9	7	28*
NIAMS	0	0	0	0	1	0	0	0	0	1
NICHD	0	0	0	3	0	0	1	1	1	6
NIDA	0	0	0	0	0	0	2	1	0	3
NIDCD	0	0	0	0	0	0	0	0	0	0
NIDDK	0	0	1	1	3	4	4	2[2]	4	19*
NIDR	0	1	1	0	2	3	0	2	3	12
NIEHS	0	0	0	0	0	0	0	0	1	1
NIGMS	0	0	0	0	0	0	0	0	0	0
NIMH	0	0	0	3	9	3	0	2	6	23
NINDS	0	0	0	3	4	3	2	0	3	15*
NINR	0	0	0	0	0	0	0	0	0	0
NLM	0	0	0	0	0	0	0	0	0	0
JOINT ICD	0	1	0	1	2	0	1	1	1	7
NIH TOTAL	1	4	10	20	42	32	26	30	41	206

NOTE: The FY 85 and FY 86 columns include information about certain collaborative research agreements that were executed before the Federal Technology Transfer Act was signed into law on October 20, 1986 but have been reclassified as CRADAs as of the enactment date of the statute.

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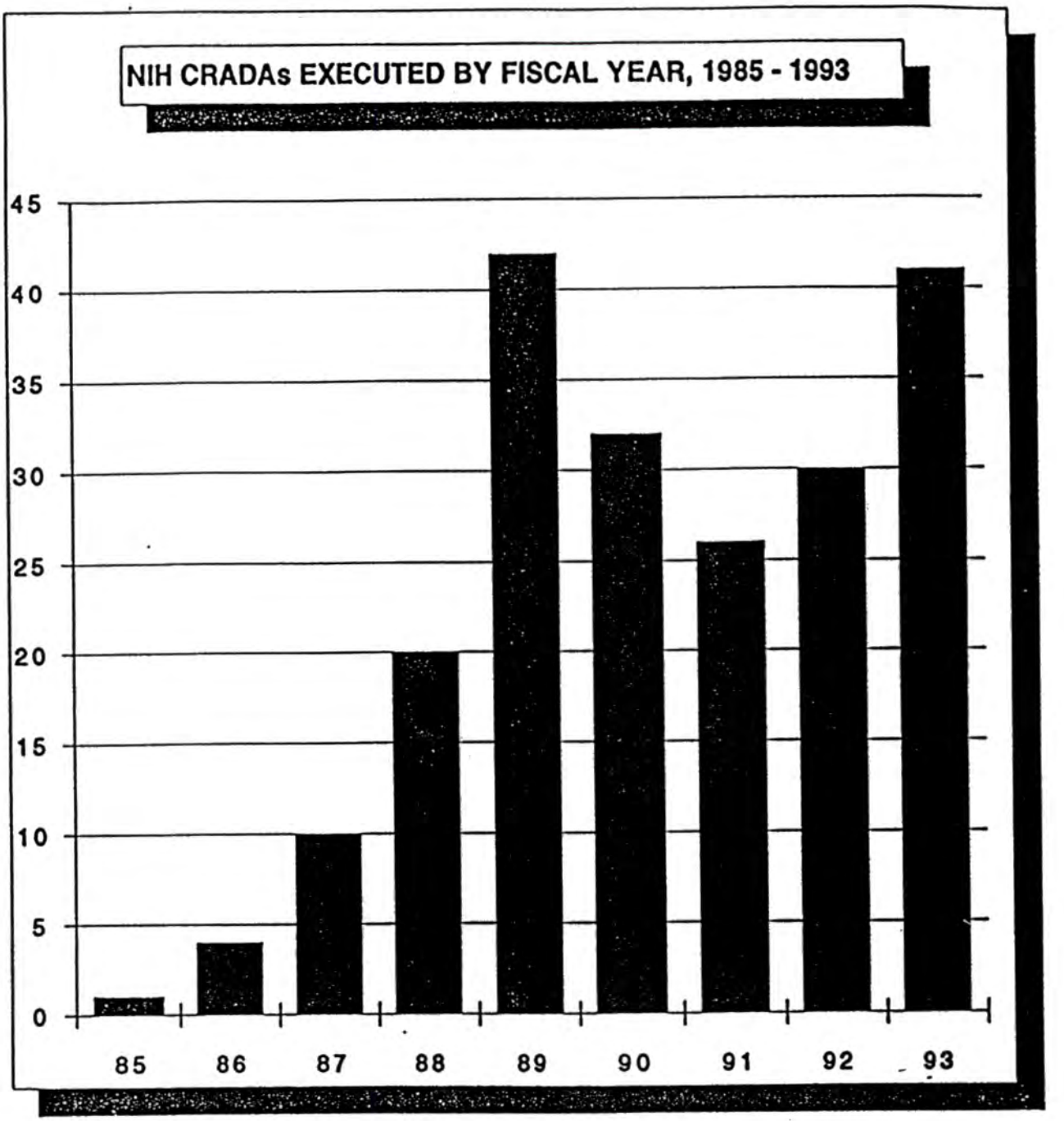
1 Several ICDs, denoted by asterisk, have entered into joint ICD CRADAs which are reported separately as "joint ICD" CRADAs. These joint ICD CRADAs are not "double-counted" and are not reflected in the individual ICD totals but are included in the NIH total. The seven joint ICD CRADAs are:

FY 86	NCI(Glatstein)/CC(Doppman) - Thompson CGR
FY 88	NCI(Gallo)/NIAID(Moss) - Immuno-U.S.
FY 89	NHLBI(Anderson)/NCI(Gallo) - Genetic Therapy, Inc.
FY 89	NHLBI(Anderson)/NCI(Blaese) - Genetic Therapy, Inc.
FY 91	NCI(Kelly)/NIAID(Siebenlist) - Sandoz Forschungsinstitut
FY 92	NIDDK(Rice)/NINDS(Rogawski) - Neurogen Corporation
FY 93	NINDS(Karlson)/NHLBI(Dunbar/Donahue) - Genetic Therapy, Inc.

2 On 7/27/93 the FY 92 NIDDK/GalaGen CRADA was amended to include NIEHS. This amendment is noted in the CRADA inventory but, for the purpose of this table and associated graph, this CRADA is counted only once as a FY 92 NIDDK CRADA.



Prepared by NIH Office of Technology Transfer 6/3/94

COLLABORATION BETWEEN GOVERNMENT AND INDUSTRY: CHALLENGES AND OPPORTUNITIES FOR HIV DRUG AND VACCINE DEVELOPMENT

Workshop Summary
May 6, 1994

Roundtable for the Development of Drugs
and Vaccines Against AIDS

Institute of Medicine

ROUNDTABLE FOR THE DEVELOPMENT OF DRUGS AND VACCINES AGAINST AIDS

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Sent From:

Kristine Gebbie, RN, MN, National AIDS Policy Coordinator

Number of Pages: 9 + Cover Fax Number: 202 334-2939 Date: 7/22

Message:

Leslie —

Sorry I'm slow. Here are the pages on which I had a comment or suggestion — give me a call if I've not been clear —

Kristine

Importance and Value of Government-Industry Collaboration on HIV Drug and Vaccine Development[1]

As the toll from AIDS and HIV disease continues to mount in the United States and 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 on HIV/AIDS research, however, is not the sole answer; some observers question whether substantial additional funds could indeed be spent productively. A complementary strategy would be to enhance the effectiveness of current investments in research and development. One major opportunity that holds considerable potential is to increase collaborations among HIV researchers in the public and private sectors, because cross-fertilization among scientists interested in a common problem can accelerate the advancement of scientific knowledge and understanding.

HIV-related research is under way in three sectors: government (primarily through the National Institutes of Health [NIH]), academia, and the pharmaceutical industry. Collaboration in research between industry and academia and between NIH and academia generally are regarded as going well. Indeed, numerous joint efforts have helped provide a detailed understanding of the virus and identification of the first generation of antiretroviral agents that provide therapeutic value, albeit of limited duration. But collaboration between

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

NIH and the pharmaceutical industry is limited at best, and the past several years have seen an increased skepticism about the effectiveness of what is in place ~~a rise in troublesome tensions~~ in their relationship **[Is this characterization accurate?]**.

Magnifying the importance of improving government and industry collaboration is the considerable investment each sector makes in HIV/AIDS research. The government has spent more than $3 billion during recent years, and in 1994 NIH will spend more than $1.5 billion. Although monetary estimates are not available for industry, survey data collected by the Pharmaceutical Research and Manufacturers of America (formerly Pharmaceutical Manufacturers Association) indicate that companies are making a substantial--perhaps comparable--investment.[2] In 1993, for example, 74 companies had 103 products in development, and there already have been 21 products approved by the Food and Drug Administration (FDA). Promoting a fundamental enhancement in collaboration between these two major research enterprises is expected to make both programs more effective, hopefully yielding faster progress in HIV drug and vaccine development.

Fueling the potential value of increased collaboration, too, is the recent blending of research goals, methods, and outcomes that 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. The strategy focuses on elucidating underlying disease mechanisms and then using novel targets identified by this fundamental knowledge for powerful drug-design

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[2] *AIDS Medicines: Drugs and Vaccines in Development, 1993 Survey*; Pharmaceutical Manufacturers Association.

efforts. Research in government and university laboratories, while continuing to reveal new basic information as expected, also increasingly yields product concepts or actual therapeutic candidates that immediately go into development. 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 stage would seem set, then, for greater collaboration between government and industry, ~~yet just the opposite has~~ been true **~~[Does this statement need qualification?]~~**. While industry collaboration and licensing agreements with academia are growing in number, industry collaboration with NIH has ~~declined~~ not grown. **~~[need documentation]~~**. As one indicator, the number of cooperative research and development agreements (CRADAs)--federal mechanisms intended to foster the private commercialization of government technology--between pharmaceutical companies and NIH has ~~diminished.~~ not increased, nor **~~[NOTE: NO STATISTICS PRESENTED]~~** Moreover, some of the clinical trial agreements (CTAs)--in which government and industry join to assess the efficacy, safety, method of use, and other aspects of candidate drugs--are perceived as addressing issues of secondary importance **[Accurate? Needs explanation?]**.

Workshop participants identified a number of barriers to research collaboration between government and the pharmaceutical industry. They involve such issues as intellectual property rights, the government's role in establishing drug prices, and access to data in clinical trials. Eliminating or lowering the barriers in these and other areas, done

carefully and appropriately, will allow the nation to tap more fully the potential of scientific interaction. Indeed, fostering government and industry collaboration promises to benefit not only HIV/AIDS research, but all drug discovery and development efforts.

Historical Perspectives on Government Technology Transfer Policy and the Pharmaceutical Industry[3]

Ever since the federal government began to invest heavily in private scientific research in the 1940s, there have been conflicting theories about the proper allocation of rights to inventions arising out of 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 commercialized by private companies with exclusive patent rights. Neither approach has ever entirely prevailed, and government policy has often meandered around the issue of intellectual property rights.

There has been some consistency, however. The government has generally maintained that any invention developed (even in part) with federal funds automatically gives the federal government a property right in that invention. If the government decides to relinquish its property right, it has always retained a nonexclusive right to use that

[3]This section is based on material presented by Peter Barton Hutt and Thomas Mays.

invention without paying royalties. While these two policies have remained constant, still in question is whether the federal government will grant no rights, nonexclusive rights, or exclusive rights in an invention to private institutions or companies.

Prior to the 1950s, the government had no uniform policy concerning patent rights to inventions arising from federally-funded private research, and the various agencies and departments followed their own patent guidelines or policies. In 1955, the Department of Health, Education, and Welfare (HEW)--the parent department of NIH--promulgated regulations spelling out its approach to patent rights. HEW (now the Department of Health and Human Services [DHHS]) 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, NIH freely published the results of research it sponsored and dedicated many inventions to public use.

HEW recognized, however, that it is sometimes necessary "to foster an adequate commercial development to make an invention widely available." **[cite?]** Toward this end, HEW's regulations allowed the 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 government-wide patent policy came in 1963, when President Kennedy issued an executive order **[cite?]** 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 public health. While 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 General Accounting Office (GAO) issued a report stating that HEW's policy of retaining patent rights deterred industry from cooperating in the development of potentially important new drugs **[cite?]**. Without the certainty of obtaining exclusive rights, companies could not afford the investment needed to develop promising compounds into commercial products. Indeed, the report concluded that not one drug arising from HEW-supported research during this period had been successfully developed and marketed. In response, HEW agreed to reinstate the IPA program, and a number of important new drugs were delivered to the public under IPAs through the involvement of private industry **[documentation?]**.

The next ten years, however, saw a return to government confusion about how and

when to grant patent rights. By the late 1970s, 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 compiled a list of 29 important medical discoveries whose development had been substantially delayed because of HEW's inability to readily determine whether it would retain or transfer patent rights. **[documentation?]**

By the end of the decade, there was growing support for legislation to create a government-wide patent policy to encourage 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. The law gives universities, nonprofit institutions, and small businesses the right to retain title to inventions developed in the performance of government grants and contracts. (This was extended to large businesses in 1987, not by statute but by an executive order issued by President Reagan.)

The Bayh-Dole Act places the burden on the federal government to justify title acquisition for itself. However, 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 primary situations in which the government may exercise such rights are when a grantee is not taking effective steps to achieve practical application of the invention or when the action is necessary to address pressing health or

147 safety needs.

148 To further encourage private companies to commercialize federal inventions,
149 Congress passed the Federal Technology Transfer Act of 1986. This statute permits federal
150 research laboratories to enter into cooperative research and development agreements with
151 non-profit institutions and private companies, with special attention to be given to small and
152 domestic businesses. Through CRADAs, federal agencies can provide personnel, services,
153 facilities, equipment, and other resources, but not funds, to nonfederal organizations for the
154 conduct of specific research projects. The organizations can contribute similar resources as
155 well as funds, and in return the government agrees to grant them exclusive patent rights to
156 inventions arising from the research, including inventions made by federal employees
157 working under the agreement (who receive compensation through royalties and cash award
158 programs).

159 Under these statutes, cooperation in drug development among government, industry,
160 and academia flourished, and a large number of drugs whose discovery and development
161 had been supported with federal funds reached the marketplace. **[NOTED BY SEVERAL**
162 **PARTICIPANTS WITHOUT EVIDENCE, need documentation]** But controversy has
163 continued to simmer, and additional issues have arisen that contribute to the unstable
164 relationship between government and industry.

165 Some observers have charged that private commercialization of government-
166 sponsored inventions represents bad policy and, at a minimum, the government should
167 exercise some type of price control over drugs whose development has been supported by

federal funds. Criticism vocally entered public debate in 1987, when consumer advocates and some government representatives claimed that the introductory price for the AIDS drug zidovudine (AZT) was excessively high, which 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. Congress took up the issue, perhaps most notably in a House subcommittee hearing chaired by Representative Henry Waxman that received wide media coverage **[need more information on specifics of hearing?]**.

NIH responded to such pricing concerns--and some industry representatives say to unfair public and political pressure--by making an administrative decision in 1989 to adopt a policy of inserting a "fair pricing" clause into its CRADAs with private organizations. This clause states: "NIH has a concern that there be 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. Accordingly, exclusive commercialization licenses granted for NIH intellectual property rights may require that this relationship be supported by reasonable evidence." (The language of the clause has been amended in some CRADAs.) NIH also includes fair pricing provisions in many, perhaps most, of the clinical trial agreements it strikes with industry.

Impediments to Collaboration on HIV Drug and Vaccine Development: Defining the Issues[4]

Pharmaceutical research and development is inherently risky, time-consuming, and expensive--and industry representatives maintain that the problems are compounded in HIV/AIDS research. Among the reasons cited are: the ultimate market is relatively small, development time is accelerated (which means more resources must be invested in a compressed period), and public pressure often interferes with the customary methods of prioritizing research. Industry, then, is reluctant to enter into collaborations with government that they believe may complicate--even worsen--this already complex picture.

Industry representatives perceive a number of impediments that hinder more fruitful collaboration. Many people in government also agree that, while federal policies guiding collaborative research were implemented with good intentions, pressing problems have arisen that must be addressed.

The single most significant obstacle identified is the role government has assumed in how the pharmaceutical industry sets prices for products that emerge from research collaborations. A second major impediment is the potential that government may assign rights to new intellectual property developed during collaborative research in ways that

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

benefit a company's competitors or lead to uncertain licensing arrangements. Other impediments identified include government's operating policies regarding the management of clinical trials under the auspices of the AIDS Clinical Trials Group (ACTG), a network of clinical centers under the control and funding of the National Institutes of Allergy and Infectious Diseases (NIAID), and the burdensome, lengthy, and bureaucratic process of establishing cooperative research and development agreements.

Underlying these specific barriers, there exists an environment of uncertainty, instability, and fear fed by the periodic shifts in governmental policies. There also is what many observers regard as a mutual lack of trust and respect between government and industry. Faced with the daunting scientific challenges presented by HIV disease, there is general agreement that government and industry collaboration will be improved by the measure that each party can extend itself to become a more trusting and reliable partner.

Fair Pricing

NIH adopted fair pricing as a means to achieve a balance between its statutory mission to conduct and promote biomedical research and education to benefit the public health with its statutory mission to foster the transfer of federal technology. It is one of several mechanisms NIH uses to help ensure that the broadest spectrum of individuals have access to medical products arising from collaborative research. NIH officials point to the successful commercialization of two drugs--the cancer drug Taxol and the AIDS drug Videx (ddI)--through collaborative research with Bristol-Myers Squibb that carried fair

price provisions requiring that the public's investment be considered along with the company's investment in setting market prices for the drugs **[Would further discussion of Taxol and ddI experience be useful here or more detail than is necessary?]**. Yes — short description of the process used

The pharmaceutical industry generally views fair price provisions as being too broad and too threatening to their proprietary interests in a highly competitive marketplace. Companies maintain that they will not know for years whether the prices allowed under fair pricing will permit a reasonable return on investment. Faced with a choice of investing in the development of their own proprietary compounds or becoming involved in a government collaboration encumbered with price restrictions, most companies are choosing the former. Only the smallest companies, which have no other sources of income, can afford to take this risk **[documentation?]**.

Industry dislikes fair price provisions across the board--in both CRADAs and CTAs, and when the drug of interest belongs to either government or industry. Both industry and government representatives agree that conflicts have been most common--and the risk to companies perhaps greatest--when the drug belongs to industry and NIH seeks to join in clinical trials or other research. An NIH official notes, for example, that every company approached by the National Cancer Institute in recent years has declined to participate in CTAs. Industry's worry is that only minor participation by NIH in a drug's development could lead to a major government role in its pricing.

Much of industry's concern centers around the various uncertainties associated with fair pricing provisions. Industry representatives say they must agree to the provisions

without knowing how NIH will attempt to implement their intent when it comes time to market a product. In addition, there is no ready definition of what a "fair price" should be, and experience has demonstrated that perceptions about drug prices--within industry, government, and the public--are subjective and can vary widely, often to industry's disadvantage. Industry therefore considers it impossible to calculate risk and make responsible financial projections. Offers from NIH to "negotiate" when problems occur are considered equally vague and uncertain. Even the examples of Taxol and Videx cited by NIH are widely viewed in industry as evidence of the potentially heavy hand of government. A Bristol-Myers Squibb official expresses 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 in the future.

Industry argues that there are, in fact, only a limited number of examples where abuse might have occurred, and thus it is inappropriate to saddle the entire industry with pricing constraints. Additionally, the cost of drugs in the United States represents only 6 to 9 percent of the overall health care budget, and the percentage paid out for drugs has been decreasing at the rate of 1/2 percent per year for the last several years **[documentation?]**. Industry representatives note that the cost of a typical hospital stay is approximately $1,200 per day, yet there seems to be much less tendency in government to fault this aspect of health care costs. Industry feels that the cost of drugs is perhaps being singled out for criticism primarily because it is the only expense that many people pay or partially pay out

of their own pockets. Thus, there is heightened and perhaps misguided sensitivity to drug pricing. **[Is this paragraph an accurate characterization or analysis?]**

NIH readily acknowledges that it lacks the appropriate expertise to undertake meaningful analyses of private-sector product pricing decisions. 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) that bind collaborators to fair pricing provisions **[documentation?]**.

NIH officials express willingness to consider the implications for industry of fair pricing policies, but stress the overarching need to safeguard the public's interest. Consumer representatives also caution that mechanisms to control prices and ensure the broadest possible access to drugs should not be left entirely outside of the public policy arena. For their part, industry representatives maintain that government and public interest is best served by increasing the flow of innovative medicines and letting market mechanisms, such as competition, exert their customary control of prices. They say that rather than assuring access and lowering costs, fair pricing provisions are in fact discouraging collaboration and thereby the accelerated development of innovative drugs. Society, in turn, is denied the benefits of their broad utilization.

Intellectual Property

[Is there a need for some introductory explanation of intellectual property, patents, etc.?]

Patents are more important in the pharmaceutical industry than in any other major industry. They protect markets for the developer of medical products and processes that allow for an eventual return on investment that companies need to survive. Patents on successful products help pay for research and development on the many others that never reach the marketplace. **[Is this paragraph an accurate characterization?]**

The government clearly has an obligation to administer its patent rights in a manner that benefits society. This means, for one thing, not privatizing patents covering "core research" technologies that are critical to creation of a pool of common scientific knowledge on which everyone can draw equally. While recognizing government's social contract, industry widely perceives government as guarding patents and licenses too closely and not providing companies the property-right assurances they require to engage in collaborative research.

Industry generally accepts CRADAs as a useful framework for collaborative research. Their major advantage 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 cannot agree in advance to assign property rights to the industrial collaborator. If the research leads to inventions--including new ways to administer the drug and new uses or combinations of uses for the drug--the government is not obligated to

assign 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 companies offering similar products based on its own initial research and development. The patent issue is perhaps less troubling in CTAs involving government-discovered drugs, although some industry representatives warn that even here a company often places a substantial investment at risk. For industry-discovered agents, many companies are finding the risks simply overwhelming.

Industry also would like to see improved definition of the patent process itself. The increasing number of "use" patents, "compound" patents, and "process" patents **[need to define types of patents?]** make it difficult to know just who has or should have what level of rights or expectations in regard to intellectual property. What matters most to industry in this area is consistency and assurance that principles will remain stable as political leadership changes.

ACTG and CRADA Complexities

Industry considers the process of working through the AIDS Clinical Trials Group to be mired in bureaucracy and inflexibility. This has led many companies to conclude that they can move more quickly on their own, without government partnerships. Another particularly divisive issue for industry is the question of sponsor access to data in ongoing clinical trials. Industry argues that since NIH staff people are being allowed early access to data without apparently threatening the statistical validity of the studies, there should be a

way to permit senior officials from industry to have early access to data as well. While such early examinations of data should not be permitted to affect the conduct of the clinical trials, industry considers it important for sponsors to be aware of the data for long-term planning purposes.

Industry also considers CRADAs to be plagued by bureaucratic drawbacks. Developing the agreements involves too many government officials and entails lengthy negotiations regarding follow-on intellectual property rights **[define "follow-on" property rights?]**. The process typically takes about a year, which many believe is far too long for advancing innovative research. At the other end of the CRADA pipeline, another problem is that government often proves a weak partner in intellectual property disputes because it does not actively enforce its own patents.

Overcoming Obstacles to Collaboration and Promoting HIV Drug and Vaccine Development: Proposals for Resolution[5]

Industry and government are committed to the importance of improving collaborative research efforts. Both also believe that the relationships must be as clear, consistent, and stable as possible. Industry representatives stress that if collaborations are

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

often subject to future revisions or added expectations from other parts of government or new political leadership, entering into collaboration will be seen as a poor business practice because of the many uncertainties involved.

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

Fair Pricing

Industry representatives argue that NIH should simply eliminate the fair price clauses from all CRADAS and CTAs. At minimum, NIH could eliminate the price provisions in HIV 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 fair price 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, since the administrative discretion was exercised (after?)(with?) Congressional oversight on the issue.

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 inability to pay. Many companies already have special "indigent" 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 leave some people in a bind, not sufficiently impoverished to meet the standard set for special access provisions but unable to pay for the drug without incurring substantial financial hardship. Government also could increase the use and perhaps size of royalty payments. For example, in exchange for exclusive license, the industry partner could pay the government a negotiated royalty, which would be predictable and measurable. It could also be factored into the company's financial planning calculations and marketing decisions.

Some combination of these options may be required, and industry and government representatives express their readiness to negotiate an agreeable solution to pricing concerns.

Intellectual Property

Since patents are a keystone of the pharmaceutical industry, its representatives propose that both CRADAs and CTAs should automatically guarantee prospective property rights to company collaborators. Companies receiving patents would pay to government

appropriate royalties agreed upon in advance. Some industry and government representatives suggest that this solution should be accomplished through legislation, in order to insulate the policy mandate from being buffeted by the winds of political change. Others say that while legislation may be welcome, contract law may offer more immediate relief. If permitted administratively, NIH and companies entering CTAs could contractually agree to the automatic flow of property rights to the industrial collaborator. Contracts also offer a solution in cases where clinical trials involving industry drugs are conducted through universities. The Bayh-Dole Act now requires 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 cite the success of the Intercompany Collaboration on AIDS Drug Development. **[Footnote with brief description of ICC mission]** Sixteen pharmaceutical companies, ordinarily fierce competitors who closely guard their intellectual property, have joined together under a cooperative contract to conduct collaborative research on anti-HIV drugs. The companies completed their contractual agreements in about six weeks, which industry contrasts to the lengthy negotiations typically required in government collaborations.

~~Both~~

All participants need to clearly identify ~~the~~ types of study data, which access should be limited to protect ~~the~~ study integrity and quality.

The ACTG and CRADAs

While 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 recent reorganization and reform of the group may address industry's concerns about its responsiveness. The ACTG apparently will operate in the future in a manner similar to the more successful model of the clinical trial groups sponsored by the National Cancer Institute. **[Is this an accurate characterization of organizational changes underway in ACTG?]**

In addition, the ACTG representatives want to address industry's interest in gaining early access to clinical trial data. Industry and NIH representatives identified two key components of a possible resolution to this issue. ~~First,~~ companies ~~need to understand the reasons for limiting access to study data,~~ make a clear and convincing argument for gaining access to ~~the~~ data, and develop ways to protect the quality of studies if such access is provided. ~~Second,~~ government in turn needs to recognize and accept the role that access to such data plays in the corporate planning process and find ways to either accommodate necessary access, or it must develop and adhere to a more consistent policy that ~~also denies~~ access to NIH staff. **[~~Does the above paragraph artificially dichotomize or oversimplify what may be a complicated solution? Need to amplify?~~]**

NIH also recognizes the need to simplify and accelerate the negotiation process

involved in developing CRADAs, and officials say this already is receiving attention. One suggestion is that NIH assign additional staff members to handle the negotiations. **[Other changes occurring?]** CRADA streamlining will allow this type of collaborative research to better keep pace with a steadily changing commercial and scientific environment. **[We will add any information from July 21 NIH CRADA forum, if appropriate.]**

Political Overview

Congress seeks to reconcile the need to stimulate and support pharmaceutical research and development with the public need for access to drugs. Congressional representatives often believe they are representing the interests of the public 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 proposes a two-fold approach. One step would establish an enforcement mechanism for negotiating "reasonable prices" for products resulting from CRADAs or NIH grants. A second bill, designed to create incentives to conduct clinical research to answer common clinical questions, would authorize NIH to enter into CTAs and stipulate up front that the institute will not claim intellectual property rights and will not assert a reasonable pricing clause for products that result. **[Accurate summary of the bills' intent?]**

While industry representatives support the proposal to eliminate price provisions in

CTAs, they question the basis for attaching price provisions to all CRADAs. Workshop participants argued that differentiation among the various types of CRADAs is important with respect to application of "reasonable pricing" considerations. While CRADAs sometimes include a critically important invention or contribution from government, however, its role in some CRADAs amounts to little more than providing screening techniques or other testing procedures, **[need more specific examples of minimal government role in CRADAs]** situations in which the government acts more like a contractor than an inventor. Thus, industry maintains it is critical to avoid regulations or requirements that would assume similar major government contributions and rights in all CRADAs. Instead, discussion of government rights should at least be proportional to its actual contributions. For example, in collaborations where government has had a minimal role in developing a pharmaceutical product (i.e., a company develops a drug, but then brings it to government for additional screening or clinical studies), fair pricing provisions are less defensible. Industry executives argue that a broad, generic assertion of government rights is likely to discourage or deter industry from entering into such research collaborations.

Much of the concern in Congress about drug pricing stems from what industry representatives and other participants judged to be "worst-case" scenarios. An example would be a company that develops a product, based upon government invention, which produces a significant therapeutic advantage over other alternatives. The company sets a price that is clearly exorbitant, causing problems of both access and financial hardship on

government health care reimbursement. ~~Such behavior should not be tolerated. But rather than turning to pricing provisions as a remedy,~~ NIH and industry representatives believe it would be possible to work out a narrow form of agreement that would create effective mechanisms for dealing with "bad-apple" behavior, but there is no readily available ~~What is needed is a~~ forum for refining such measures. ~~**[Is this paragraph necessary?]**~~

The message, then, is that NIH and industry must find ways to work together to address pricing concerns in ways that reduce industry's fear 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, many 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.

Summary

Government and the pharmaceutical industry are the nation's major investors in HIV research. Promoting a fundamental enhancement in collaboration between these vast

research enterprises offers perhaps our best hope to accelerate the development of innovative HIV drugs and vaccines. Unfortunately, recent years have seen a rise in tensions in their relationship, and collaborative research between the National Institutes of Health and industry has perhaps reached low ebb.

Workshop participants highlighted a number of barriers that contribute to diminished collaboration. The two most important are the role that government has assumed in how industry sets prices on products, and the government's control of rights to intellectual property developed during collaborative research. The impediments are compounded by industry's ingrained fear of the unpredictable shifts in government policy, and by a mutual lack of trust and respect between the two parties.

Still, there is room for optimism. This is founded in part on the fundamental, if unstated, partnership between government and industry that has proved to be the world's most successful model for training scientists, acquiring knowledge, and improving public health. It also rests on the underlying commitment in both NIH and pharmaceutical companies to better understand HIV infection and to devise improved methods of treatment and prevention.

The proposals of this 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 touch on several operational barriers that inhibit timely research. And they 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.