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Biotechnology, Breakthrough Drugs, And Health Care Reform: Lessons From The NIH-University-Industry Relationship

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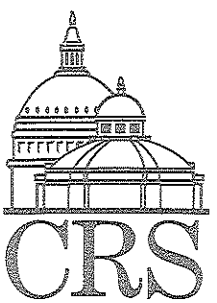

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BIOTECHNOLOGY, BREAKTHROUGH DRUGS, AND HEALTH CARE REFORM: LESSONS FROM THE NIH-UNIVERSITY-INDUSTRY RELATIONSHIP

SUMMARY

President Clinton's health care proposal (H.R. 3600, S. 1757) includes the establishment of an Advisory Council to monitor the prices of new, "breakthrough" drugs and a mechanism to allow the Secretary of the Department of Health and Human Services to negotiate the cost to the Government of such therapeutics if they are found "excessive" under threat of exclusion from expanded Medicare prescription reimbursements. Such proposals reflect the Administration's concerns over cost containment as well as arguments that the pharmaceutical industry is receiving undue profits which are contributing to the high cost of health care. Indirect price control techniques have been considered, particularly by several Members of Congress, based on the rationale that the Federal Government's financial, research, and/or clinical support contributes to the development of new drugs and thus entitles it to commensurate cost considerations.

The argument that the Government should control drug prices based upon its contribution to product development is also the basis for inclusion of a "fair pricing clause" in cooperative research and development agreements (CRADAs) between the National Institutes of Health (NIH) and the private sector. In response to concerns over anticipated high costs, this requirement mandates that any commercial therapeutic or diagnostic resulting from a CRADA be sold at a price which reflects the relative contributions of both the Government and the company. While all Federal R&D agencies utilize CRADAs, NIH is the only laboratory which stipulates that this clause be included.

Some view such efforts as a move away from congressional activity over the past 15 years designed to facilitate the commercialization of federally-funded R&D. The intent of this legislation is to provide the business and/or academic communities with incentives to bring the results of Government-supported research to the marketplace where they can generate profits, improve productivity, or meet other important national needs. Earlier Congresses determined that, despite arguments of unfair advantage or additional Government costs, the payback to society brought about by increased innovation was of paramount importance. The development and growth of the biotechnology industry and the emergence of new therapeutics to improve health care are prominent examples of the benefits of innovation.

Since NIH has chosen to utilize the fair pricing clause, fewer firms are interested in cooperative work with the laboratory. This experience may be illustrative of the consequences if similar conditions are imposed on the development of breakthrough drugs. Companies which do not control the results of their investments appear to be less likely to engage in R&D. The implications may be significant, not just for the companies involved, but for the development of new biotechnology drugs to meet the health, public welfare, and economic growth needs of this Nation.

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INTRODUCTION

President Clinton's health care proposal (H.R. 3600, S. 1757) includes the establishment of an Advisory Council to monitor the prices of new, "breakthrough" drugs and a mechanism to allow the Secretary of the Department of Health and Human Services to negotiate the cost to the Government of such therapeutics if they are found "excessive" under threat of exclusion from expanded Medicare prescription reimbursements.[1] Such proposals reflect the Administration's concerns over cost containment as well as the arguments that the pharmaceutical industry receives undue profits which contribute to the high cost of health care and the elderly pay too much for prescription drugs. Indirect price control techniques have been considered, particularly by some members of Congress, based on the rationale that the Federal Government's financial, research, and/or clinical support contributes to the development of new drugs and thus entitles it to commensurate cost considerations.[2]

The argument that the Government should control drug prices because it contributes to product development is also the basis for inclusion of a "fair

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[1] Note: Other legislative initiatives to reform health care have been introduced which ". . . impose some kind of restraint on the ability of manufacturers to set prices for prescription drugs," including H.R. 2624, S. 223, S. 491, and H.R. 1200; see: U.S. Library of Congress. Congressional Research Service. Prescription Drug Prices: Should the Federal Government Regulate Them? CRS Issue Brief No. IB92097, by Gary Guenther. However, the Clinton proposal has provisions that specifically target new, breakthrough drugs which are the focus of this discussion.

[2] For example see: U.S. Congress. Senate. Special Committee on Aging. The Federal Government's Investment in New Drug Research and Development: Are We Getting Our Money's Worth? Hearing, 103d Cong., 1st Sess. Feb. 24, 1993; and U.S. Congress. House. Committee on Small Business. Subcommittee on Regulation, Business Opportunities, and Technology. Conflict of Interest, Protection of Public Ownership in Drug Development Deals Between Tax-Exempt, Federally Supported Labs and the Pharmaceutical Industry. Hearing, 103d Cong., 1st Sess. Mar. 11, 1993.

pricing clause" in cooperative research and development agreements (CRADAs) between the National Institutes of Health (NIH) and the private sector. In response to concerns over anticipated high costs to the consumer, this requirement mandates that any commercial therapeutic or diagnostic resulting from a CRADA be sold at a price which reflects the relative contributions of both the Government and the company. While all Federal R&D agencies utilize CRADAs, NIH is the only laboratory which stipulates that this clause be included.

Some view Government intervention in price decisions based upon initial Federal support as contrary to a long-term trend of Government promoting innovation, technological advancement, and the commercialization of technology by the business community. Over the last 15 years, Government policies, congressional legislation and, more recently, Administration directives have established a policy to promote the acceleration of private sector commercialization of the results of federally-funded R&D, often through cooperative ventures between Government, industry, and academia. Economic incentives for investment in research and development by companies are a major part of this approach. This policy has been adopted for various reasons including the economic growth and increased productivity which comes from many new products, processes, and services.

In many areas, major joint Government-industry efforts to facilitate the development and commercialization of new technologies are pointed to by some as the "wave of the future." The Administration has made Government-industry-university cooperation a cornerstone of its technology policy as well as part of its strategy for economic growth. President Clinton has stated that at least 20 percent of Federal laboratory budgets should be used to provide support for joint ventures with industry. Federal funding for cooperative efforts has increased substantially. A dramatic example is the Advanced Technology Program at the National Institute of Standards and Technology, which provides seed funding to companies or consortia of universities, industries, and Government laboratories to accelerate the development of generic technologies with broad application across industries. This program has seen its budget grow from $47 million in FY 1992, to $68 million in FY 1993, to $199 million in FY 1994. The FY 1995 budget request for this effort is $451 million. The Advanced Battery Consortium, the Clean Car Initiative, and the American Textile Consortium (AMTEX) have all made headlines as models of cooperation following both the letter and spirit of the relevant laws. There has been no public discussion of imposing direct or indirect price controls on any resulting products or processes, nor do the attendent CRADAs include a fair pricing clause.

Despite the Government's efforts to promote technological advancement, the biomedical community is sometimes subject to criticism, scrutiny, and doubt over similar, long established cooperative efforts between Federal laboratories, academia, and industry. A question is why and what could this mean to the cost of health care? In light of the initiatives included in the Clinton health care proposal, this paper will look at the possible effects of price control strategies

on the biotechnology community; on its pursuit of research, development, and commercialization; and ultimately on the availability of new, genetically engineered therapeutics and diagnostics. This will be done in the context of parallel concerns over drug costs to the consumer which led to the inclusion of the fair pricing clause in NIH CRADAs. The approach taken here is to provide the reader with (1) an understanding of the reasons behind Government promotion of technological advancement, (2) an explanation of Federal legislation establishing the policies and practices to facilitate this technological progress, and (3) an exploration of the implementation of these laws by the National Institutes of Health. Analysis of both the current interaction between NIH and companies involved in R&D and the results of the application of the fair pricing clause may prove illustrative of the issues surrounding the imposition of similar conditions on new, breakthrough, biotechnology drugs.

Throughout this report, an effort has been made to distinguish to the extent possible between the biotechnology industry and the pharmaceutical industry. Although they do overlap, the former is characterized by a preponderance of small firms which are research intensive, have few products on the market, and generally are dependent for funding on venture capital or public stock offerings. Most have been established within the last 10 years; several have grown significantly in size over that time. The pharmaceutical sector tends to be made up of larger companies which do work in biotechnology, but which predominantly produce chemically derived therapeutics. The majority of these firms are well established and have a record of high profitability. Some of the available data used in this paper was generated by studies of only the pharmaceutical industry. However, this information is included because of its relevance to the biotechnology sector and the debate over price limitations.

THE CLINTON HEALTH CARE PROPOSAL: POSSIBLE PRICE CONTROLS ON BREAKTHROUGH DRUGS

The Clinton health care proposal contains several initiatives dealing with drug prices, including new, breakthrough therapeutics. According to Administration testimony in February 1994, "The President's commitment to the country is to make prescription drugs available to all Americans at reasonable prices."[3] Among the measures included to "contain drug costs" is the creation of an Advisory Council on Breakthrough Drugs (Title I, Subtitle F, sec. 1572) which would review the price of such new advances and report to the Secretary of Health and Human Services on its "reasonableness."

> The Council would base its determinations on prices of other drugs in the same therapeutic class, cost information supplied by the

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[3] Lee, Philip and Helen M. Smits. U.S. Dept. of Health and Human Services. Written statement submitted to the House Committee on Energy and Commerce, Subcommittee on Health and the Environment, Feb. 8, 1994. p. 1. [Unpublished hearings]

> manufacturer, the prices charged for the drug in other industrial countries, the projected prescription volume, economies of scale, product stability, special manufacturing requirements and research costs. Also included are evaluations of cost-effectiveness relative to the cost of alternative course of treatment options, and improvements in quality of life offered by the new product.[4]

The Secretary of the Department of Health and Human Services (DHHS) has the option to publish the Advisory Council's findings in the *Federal Register* with the understanding that "this information should help health alliances and consumers make appropriate and cost-effective decisions."[5] In addition, because the Clinton plan would require that Medicare pay for outpatient prescriptions, the Secretary would be permitted to negotiate with the manufacturer of a new drug and exclude its use under Medicare if an acceptable rebate amount could not be agreed upon (Title II, Subtitle A, sec. 2003). In doing this, the Secretary must take into consideration prices of other drugs in the same therapeutic class, cost data supplied by the producer, prescription volume estimates, ". . . economies of scale, product stability, special manufacturing requirements, . . ." and foreign prices for the drug, among other things. This reflects the Administration's concerns with

> . . . the possibility that the lack of market competition combined with guaranteed private health insurance for every American could lead to pharmaceutical prices that are much higher than they would be in the current health care system . . . The American people need to know that the prices they pay bear a reasonable resemblance to the costs of research, development, and production.[6]

ECONOMIC DIMENSIONS OF BIOTECHNOLOGY

At issue is whether or not such provisions would have a serious adverse effect on the biotechnology industry in light of the general assumption that a significant number of future breakthrough drugs will be the result of biotechnology--genetically engineered drugs, biologics, and diagnostics. Biotechnology therapeutics are important not just to the health of the individual but ultimately may have far reaching effects on the economy in terms of labor productivity and national health care costs, among other things. Biotechnology

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[4] Ibid., p. 3.

[5] Ibid., p. 3.

[6] Ibid., p. 3.

also has the potential to enhance the world's food supply and environmental quality.[7]

Currently U.S. biotechnology companies generate annual sales of $7 billion;[8] the National Academy of Sciences has projected that this will increase to $50 billion by the year 2000.[9] An industry which did not exist 15 years ago, biotechnology has provided new products and processes for the international marketplace with vast potential for many more advances. Along with medical devices and traditional pharmaceuticals, this sector has consistently generated a positive trade balance for the United States.[10] It is estimated that the industry employs 97,000 people directly[11] and an additional 100,000 indirectly.[12] In addition, Americans hold 70-80 percent of all U.S. biotechnology patents.[13]

As noted above, most biotechnology companies are **small** firms involved in a highly competitive, research intensive industry. In addition, an estimated 33 percent of R&D projects in the major pharmaceutical companies now involve work on genetically engineered therapeutics.[14] The biotechnology sector's R&D expenditures are 81 percent of sales.[15] This compares to 10 percent in the pharmaceutical industry and typically 3 percent in manufacturing. Currently, with only 27 products approved for marketing, much of the present

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[7] U.S. Congress. House. Committee on Small Business. Subcommittee on Regulation, Business Opportunities, and Energy. The National Institutes of Health and Its Role in Creating U.S. High-Technology Industry Growth and Jobs. Hearings, 100th Cong., 1st Sess., Dec. 9, 1991. p. 5.

[8] Burrill, G. Steven and Kenneth B. Lee, Jr. Biotech 94, Long-Term Value Short-Term Hurdles. San Francisco, Ernst and Young, 1993. [Unnumbered page]

[9] National Academy of Sciences. Putting Biotechnology to Work: Bioprocess Engineering. Washington, 1992.

[10] The National Institutes of Health and Its Role in Creating U.S. High-Technology Industry Growth and Jobs, op. cit., p. 5.

[11] Biotech 94, op. cit. [Unnumbered page]

[12] Widder, Kenneth J. Why the Biotech Industry is in Peril. The San Diego Union-Tribune, June 20, 1993. p. G3.

[13] The National Institutes of Health and Its Role in Creating U.S. High-Technology Industry Growth and Jobs, op. cit., p. 14.

[14] Number of Biotech Projects in Pharmaceutical R&D on the Rise. Washington Fax, Oct. 14, 1993. p. 2.

[15] Biotech 94, op. cit., p. vii.

value of biotechnology firms is in R&D. According to some surveys, the top public U.S. biotechnology companies have over 270 new drug therapies undergoing clinical trials and approximately 2,000 new compounds in the early stages of development.[16] Safeguarding this investment in research and development will inherently depend on intellectual property protection. As will be discussed later, Wharton School economist Edwin Mansfield and others have found the drug industry to be more dependent on patents than other industrial sectors.

FY 1994 Federal funding for health related biotechnology (41 percent of the total Federal biotechnology research budget) is an estimated $1.7 billion.[17] Analysts at Ernst and Young estimate that the biotechnology industry spent $5.7 billion on research and development in calendar year 1993.[18] Dependent on private sector, high risk funding for much of the difference, biotechnology companies are faced with enormous costs associated with a new therapeutic. Various studies have calculated that a pharmaceutical company may have to spend between $125 million to $359 million to bring a new drug to the marketplace.[19] The larger costs reflect research spending on drugs which never make it out of the laboratory. These figures are so high because of the uncertain nature of biomedical research, clinical trials, and the FDA approval process, among other things. Yet even after reaching the marketplace, only about one in three drugs are able to recoup R&D costs through sales.[20] Nonetheless, U.S. pharmaceutical firms have maintained high net profits for decades.

According to the Food and Drug Administration, 80 percent of the drug approvals between 1985 and 1990 were for small improvements to existing products.[21] However, in the future it may be the breakthrough drugs which will have the most impact. In 1992, FDA estimated that 40 percent of the new

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[16] Ibid., p. 31.

[17] U.S. Office of Science and Technology. Federal Coordinating Council for Science, Engineering, and Technology. Committee on Life Sciences and Health. Biotechnology for the 21st Century: Realizing the Promise. U.S. Govt. Print. Off., Washington, June 30, 1993. p. 13-14.

[18] Biotech 94, op. cit. [Unnumbered page]

[19] Ibid, p. 12. Also: U.S. Office of Technology Assessment. Pharmaceutical R&D: Costs, Risks, and Rewards. Washington, U.S. Govt. Print. Off. p. 16.

[20] Steere, William C., Jr. The Pharmaceutical Industry's Role in Health-Care Reform. The NPC Report, Fall 1993. p. 2.

[21] Biotech 94, op. cit., p. 10.

drugs approved were major advances over existing products.[22] But despite the potential, this remains a complex sector. As described by industry analysts:

> . . . the biotechnology industry's progress has been governed by a unique confluence of factors: massive breakthroughs in science and technology, enormous capital needs with a long horizon to payback, financial markets that turn alternately hot and cold, the heavy hand of regulation, uncertainty about intellectual property rights, and a cost crisis in its primary market (health care). No other major industry has had to grow up with so many hurdles to surmount in order to bring value-added products to its customers and earn commensurate profits.[23]

GOVERNMENT SUPPORT FOR RESEARCH AND DEVELOPMENT[24]

Because of the arguments put forth that the Government's imposition of price controls derives, in part, from the Federal investment in R&D, it is important to determine the rationale behind such support. An understanding of the foundation for these research efforts is important to the assessment of this justification. The U.S. Government funds research and development to meet the mission requirements of the Federal departments and agencies (e.g., defense, public health, environmental quality). It also finances work in areas where there is an identified need for research, primarily basic research, not being performed in the private sector.

Federal support for basic research is founded, in large part, on the understanding that the rate of return to society as a whole generated by investments in research is significantly larger than the benefits that can be captured by any one firm performing it.[25] This Government support reflects a consensus that basic research is the foundation for many innovations, but that incentives for private sector financial commitments are dampened by the fact that spending for R&D runs a high risk of failure. Even results of fruitful R&D

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[22] Stone, Peter H. An Industry in Pain, National Journal, Oct. 23, 1993. p. 2529.

[23] Burrill, Steven G. and Kenneth B. Lee, Jr. Nurturing Biotechnology Companies. Chemtech, Apr. 1993. p. 49.

[24] For additional discussion see: U.S. Library of Congress. Congressional Research. Industrial Competitiveness and Technological Advancement: Debate Over Government Policy. CRS Issue Brief No. IB91132, by Wendy H. Schacht; and The Debate Over a National Industrial Policy Toward Technology and Economic Growth. CRS Rept. No. 92-426 SPR, by Wendy H. Schacht.

[25] Mansfield, Edwin. Social Returns From R&D: Findings, Methods, and Limitations. Research/Technology Management, Nov.-Dec. 1991. p. 24.

often are exploited by other domestic and foreign companies, thus resulting in underinvestment in research by the private sector. The returns from basic research are generally long-term, sometimes not marketable, and not always evident.

The Government's interest has been expanding beyond the traditional role of funding R&D. The concern for technological advancement has extended to meeting other national needs including the economic growth that flows from commercialization of new products and processes in the private sector. While a basic tenet is that commercialization of technology is the responsibility of the private sector, over the past several years there have been additional efforts by the Government to stimulate innovation and technological advancement in industry.

The actual and expected innovations flowing from biotechnology go beyond economic considerations of the importance of technological progress to the Nation. The potential life saving quality of many of the products associated with biotechnology provides an additional dimension. The biotechnology industry not only generates profits on sales of products, provides jobs, and stimulates investments, but advances in this arena could also facilitate economic growth through improvements in productivity resulting from a healthier population and a possible decrease in public costs associated with health care.

Technological advancement is an important factor in economic growth and long-term increases in the Nation's standard of living. Industrial expansion historically was based on the use of technology to develop natural resources. Today, industrial growth tends increasingly to be based on the development of scientific discoveries and engineering knowledge (e.g., electronics, biomedical applications) and is even more dependent than before on the development and use of technology. Technology contributes to the creation of new goods and services, new industries, and new jobs. New technology expands the range of services which can be offered and extends the geographic distribution of these services. The development and application of technology also play a role in determining patterns of international trade by affecting the comparative advantages of industrial sectors. It is now widely accepted that ". . . from one-third to one-half of all [U.S.] growth has come from technical progress, and that it is the principal driving force for long-term economic growth and the increased standards of living of modern industrial societies."[26] Technological progress can clearly contribute to the resolution of those national problems which are amenable to technological solutions.

Technological progress is achieved through innovation, the process by which industry provides new and improved products, processes, and services. An invention becomes an innovation when it has been integrated into the

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[26] Landau, Ralph. Technology, Economics, and Public Policy. In: Landau, Ralph and Dale W. Jorgenson, eds. Technology and Economic Policy. Cambridge, Ballinger Publishing Co., 1986. p. 2.

economy such that the knowledge created results in a new or improved product or service that can be sold in the marketplace or is applied to production to increase productivity and quality. It is only through commercialization that a significant stimulus to economic growth occurs. Yet, while the United States has a strong basic research enterprise, foreign firms have at times appeared more adept at taking the results of these scientific efforts and making commercially viable products. Often U.S. companies are competing in the global marketplace against goods and services developed by foreign industries from research performed in the United States. Thus, there has been increased congressional interest in mechanisms to accelerate the development and commercialization processes in the private sector.

The majority of innovations are the result of incremental improvements to existing products or processes. Some of these are based on R&D, but many others are the result of changes in engineering and the production process, or reflect new ideas generated by intuition, experience, or skill. However, research and development are critical to technological progress in many ways. It has been demonstrated that the innovations arising from R&D are the more important ones in terms of their effects on society.[27] Profound changes have been brought about by advances in research resulting in new products and processes in the areas of medicine, semiconductors, computers, and materials, just to name a few. Biotechnology may be the next frontier.

The Federal response to stimulating innovation has taken various forms, among them: (1) facilitation of "technology transfer" from Government laboratories to the private sector; (2) promotion of cooperative research and development among Government, industry, and academia; (3) support for small, high technology companies; and (4) incentives for increased private sector investment in R&D. Of particular interest to this study are several laws which affect the way the National Institutes of Health interacts with the academic community and industry in the R&D arena. Underlying these efforts is a series of legislative provisions designed to promote and protect private sector investments in related research and development to encourage the participation of the business community as discussed below. It is in this area where the sometimes competing goals of health care cost containment and encouragement of technology-based breakthroughs may conflict.

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[27] Mansfield, Edwin and Anthony Romeo, Mark Schwartx, David Teece, Samuel Wagner, Peter Brach. Technology Transfer, Productivity, and Economic Policy. New York, W.W. Norton and Co., 1982. p. 5.

TECHNOLOGY TRANSFER[28]

The Federal Interest

The Federal Government spends approximately $70 billion per year on research and development to meet the mission requirements of all the Federal departments and agencies. Of this figure, in FY 1993 approximately $23 billion was spent for research and development carried out by Federal laboratories; $1.7 billion was expended by the National Institutes of Health for intramural research.[29] While the major portion of the total Federal R&D spending is in the defense arena, Government support has led to or contributed new products and processes for the commercial marketplace including, but not limited to, antibiotics, plastics, jet aircraft, computers, electronics, and genetically engineered drugs (e.g., insulin, human growth hormone) and diagnostics.

Given the increasing competitive pressures on U.S. firms in the international marketplace, as well as demands for new products to meet the Nation's needs, proponents of technology transfer argue that there are many other technologies and techniques generated in the Federal laboratory system which could have commercial value if further developed by the industrial community. The movement of technology from the Federal laboratories to industry is achieved through technology transfer, a process by which technology developed in one organization, in one area, or for one purpose is applied in another organization, in another area, or for another purpose. Technology transfer can have different meanings in different situations. In some instances, it refers to the transfer of legal rights, such as the assignment of patent title to a contractor or the licensing of a Government-owned patent to a private firm. In other cases, the transfer endeavor involves the informal movement of "know-how" (information, knowledge, and skills) through person-to-person interaction.

Until recently, despite the potential offered by the resources of the Federal laboratory system, the commercialization level of the results of federally-funded research and development remained low. There are various reasons for this, one of which is the fact that many technologies and patents have no commercial application or have little value in the marketplace. Additional barriers to transfer involve costs. It has been estimated that research accounts for

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[28] For more information on this and the following chapter see: U.S. Library of Congress. Congressional Research Service. Technology Transfer: Use of Federally Funded Research and Development. CRS Issue Brief No. IB85031, by Wendy H. Schacht.

[29] U.S. National Science Foundation. Federal Funds for Research and Development: Fiscal Years 1991, 1992, and 1993. Washington, U.S. Govt. Print. Off., 1993. p. 58. Note: the total Federal agency intramural figure includes the "Federally Funded Research and Development Center" funding columns under which NSF reports support for several of the Department of Energy laboratories categorized as FFRDCs.

approximately 25 percent of expenditures associated with bringing a new product or process to market.[30] Thus, while it might be advantageous for companies to rely on Government-funded research, there are still significant added investments necessary to achieve commercialization after the transfer of technology has occurred. This is particularly relevant in the biomedical field where clinical trials and FDA regulations place additional requirements. However, industry unfamiliarity with these technologies, the "not invented here" syndrome, and ambiguities associated with obtaining title to or exclusive license for federally-owned patents also contribute to the limited level of commercialization.

The Legislative Foundation

Congress has enacted several laws to facilitate technology transfer from the Federal Government to the private sector, beginning in 1980 with P.L. 96-480, the Stevenson-Wydler Technology Innovation Act. Recognizing the benefits to be derived from the transfer of technology, the law explicitly states that:

> It is the continuing responsibility of the Federal Government to ensure the full use of the results of the Nation's Federal investment in research and development.

P.L. 96-480 "legitimized" the transfer effort and mandated that technology transfer be accomplished as an expressed part of each agency's mission.

Section 11 created the institutional mechanisms by which Federal agencies and their laboratories can transfer technology.[31] Additional incentives for the transfer and commercialization of technology are contained in several amendments to Stevenson-Wydler. Of particular interest to this discussion, is the creation of a specific legal instrument, the "Cooperative Research and Development Agreement" (CRADA), to initiate joint research and development activities between a Federal laboratory and the business and/or academic communities. P.L. 99-502, the Federal Technology Transfer Act, permits Government-owned, Government-operated laboratories to enter into CRADAs; this authority was extended to Government-owned, contractor-operated laboratories (generally the laboratories of the Department of Energy) in the FY 1990 Defense Authorization Act (P.L. 101-189). Decisions to participate in CRADAs may be made by the director of a laboratory who may also negotiate licensing agreements for related Government-owned inventions previously made at that laboratory. There is expected to be limited agency headquarter review of CRADAs; they are intended to be developed at the laboratory level. In

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[30] See: The Debate Over a National Industrial Policy Toward Technology and Economic Growth, op. cit.

[31] For more information see: U.S. Library of Congress. Congressional Research Service. Technology Transfer: Use of Federally Funded Research and Development. CRS Issue Brief No. IB85031, by Wendy H. Schacht.

pursuing these joint efforts, the laboratory may accept funds, personnel, services, and property from the collaborating party and may provide personnel, services, and property (but **not** funds) to the other organization. The work performed must be consistent with the laboratory's mission.

Under a CRADA, title to, or licenses for, inventions made by a laboratory employee may be granted in advance to the participating company, university, or consortium by the director of the laboratory. In addition, the director can waive, in advance, any right of ownership the Government might have on inventions resulting from the collaborative effort regardless of size of the company. This diverges from other patent law which requires that title to inventions made under Federal R&D funding be given only to small businesses, not-for-profits, and universities (see below). In all cases, the Government retains a nonexclusive, nontransferable, irrevocable, paid-up license "to practice, or have practiced," the invention for its own needs.

Laboratory personnel and former employees are permitted to participate in commercialization activities if these are consistent with the agencies' regulations and rules of conduct. Federal employees are subject to conflict of interest restraints. Preference for CRADAs is given to small businesses, companies which will manufacture in the United States, or foreign firms from countries that permit American companies to enter into similar arrangements. According to Senate report 99-283, which accompanied the legislation, "the authorities conveyed by [the section dealing with CRADAs] are permissive" to promote the widest use of this arrangement. To date, over 2,000 CRADAs have been signed across all Federal departments and agencies; NIH was involved in 206 through the end of FY 1993. In the Administration's FY 1995 budget request, the President has recommended that the number of CRADAs involving all Federal institutions increase to 3,200 by 1995.

COOPERATIVE R&D

The Rationale

While much of the focus of technology transfer has been on the formal CRADA mechanism, there are various other ways to promote cooperation between Government laboratories, industry, and academia. Many of these also have a legislative basis, reflecting congressional intent to establish an environment where industry expands its utilization of the results of federally-funded research and development. These include non-CRADA cooperative agreements, personnel exchanges and visits; direct funding for projects through grants; licensing of Government-owned patents; educational initiatives; information dissemination (publication); participation at meetings; and the spinoff of new firms. In addition, P.L. 102-564, the Small Business Innovation Development Amendment Act, created a new pilot program designed to facilitate the commercialization of Federal laboratory R&D by small companies, among other things. The Small Business Technology Transfer Program will provide funding for research proposals developed and executed cooperatively between a

small firm and a research scientist in a laboratory (Federal, university, or non-profit institution) which fall under the mission requirements of the Government funding agency. This will be financed by a 0.05 percent set-aside of the agency's R&D budget in 1994, 0.1 percent in 1995, and 0.15 percent in 1996.

Efforts to foster joint ventures between academia, industry, and Government are an attempt to utilize and integrate what these sectors do best and to direct these activities toward the goal of generating new products and processes for the marketplace. Collaborative projects allow for shared costs, shared risks, shared facilities, shared expertise, and possibly shared profits. Opponents argue that joint ventures stifle competition; proponents assert that they are designed to accommodate the strengths and responsibilities of each participant in the innovation process.

The lexicon of current cooperative activity covers various different institutional and legal arrangements. Collaborative ventures can be structured either "horizontally" or "vertically." The former involves efforts in which companies work together to perform research and then use the results of this research within their individual organizations. The latter involves activities where researchers, producers, and users work together. Both approaches are seen as ways to address some of the perceived obstacles to the competitiveness of American firms in the marketplace. Issues of patent ownership, disclosure of information, licensing, and antitrust are resolved within the guidelines established by law governing joint ventures as discussed below.

Of particular interest to NIH is industry-university cooperation. Traditionally, universities perform much of the basic research integral to certain technological advancements. They are generally able to undertake fundamental research because it is part of the educational process and because they do not have to produce for the marketplace. The risks attached to basic research in this setting are fewer than those in industry where companies must earn profits. Universities also educate and train the scientists, engineers, and managers employed by companies.

Academic institutions do not have the commercialization capacity or responsibility available in industry and necessary to translate the results of research into products and processes that can be sold in the marketplace. Thus, if the work performed in the academic environment is to be integrated into goods and services, a mechanism to link the two sectors must be available. Prior to World War II, industry was the primary source of funding for basic research in universities. This financial support helped shape priorities and build relationships. However, after the war, the Federal Government supplanted industry as the major financial contributor and became the principal determinant of the type and direction of the research performed in academic institutions. This situation resulted in some disconnection between the university and industrial communities. Because industry and not the Government is responsible for commercialization, the difficulties in moving an idea from the research stage to a marketable product or process appear to have been compounded.

Efforts to encourage increased collaboration between the academic and industrial sectors might be expected to augment the contribution of both parties to technological advancement. It is of benefit to the Government, particularly for NIH which extensively funds university R&D ($5.2 billion in FY 1994),[32] to see that the results of this Federal investment are commercialized. In response, the Congress enacted P.L. 96-517, Amendments to the Patent and Trademark Laws, commonly known as "Bayh-Dole" after its two main sponsors. The intent of the legislation is to utilize patent ownership of inventions arising out of Government-sponsored R&D to facilitate the development of new technologies through cooperation between the research community, small business, and industry.

Patents, the Bayh-Dole Act, and Related Law

P.L. 96-517 was passed by the Congress in 1980 to address the low utilization rate of patents resulting from Government sponsored research. The House report to accompany H.R. 6933 notes that at the time the bill was considered there were 26 different agency policies regarding the use of the results of Government-funded R&D. The intent was to replace this with a "single, uniform national policy designed to cut down on bureaucracy and encourage private industry to utilize government funded inventions through the commitment of the risk capital necessary to develop such inventions to the point of commercial application."[33] This was to be accomplished by utilizing the patent system to (1) provide for increased participation of small firms in the Federal R&D enterprise under the assumption that these companies tend to be more innovative and (2) augment collaboration between universities (as well as other non-profit institutions) and the business community to ensure that inventions are brought to market.

Prior to the passage of Bayh-Dole in 1980 and subsequent related legislation, the Government generally retained title to inventions made under Federal funding and issued to companies either an exclusive license in rare cases, or, more commonly, a nonexclusive license. However, it was argued that without title (or at least an exclusive license) to an invention and the protection it conveys, a company would not invest the time and money necessary for commercialization. This contention was supported by the fact that, although a portion of ideas patented by the Federal Government have potential for further development, application, and marketing, by 1980 only about five percent of these were ever used in the private sector.

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[32] Federal Funds for Research and Development: Fiscal Years 1991, 1992, and 1993, op. cit., p. 58.

[33] U.S. Congress. House. Committee on the Judiciary. Report to Accompany H.R. 6933. House Report No. 96-1307, Part 1, 96th Cong., 2d Sess. Washington, U.S. Govt. Print. Off., 1980. p. 3.

The patent system was created to promote innovation. Based on Article I, Section 8 of the U.S. Constitution which states: "The Congress Shall Have Power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries . . .," the patent system encourages innovation by simultaneously protecting the inventor and fostering competition. It provides the inventor with an exclusive right for 17 years to further develop his idea, commercialize, and thereby realize a return on his initial investment. Concurrently, the process of obtaining a patent places the concept in the public domain. As a disclosure system, the patent can, and often does, stimulate other firms or individuals to invent "around" existing patents to provide for parallel technical developments or meet similar market needs.

Not everyone agrees that the patent system facilitates innovation. Critics argue that patents provide a monopoly which induces additional social costs and that cross licensing between companies can result in exploitation of markets. It has also been claimed that the patent system was designed to assist the individual inventor and the shift toward more R&D being performed in large companies has diminished the patent's value to society since these firms can utilize other methods to protect their investments (e.g., trade secrets). For example, in the pharmaceutical arena, a firm can strengthen its competitive position over other companies because of the long lead time necessary to bring a product to market and by utilizing the FDA approval process, clinical trials, and the data generated, among other things, to capture "monopoly profits" prior to similar goods reaching the marketplace.[34]

However, these arguments may not hold up well when considering the biotechnology industry where similar products can be made by different processes or identical processes used to make different products. Process patents,[35] which are of vital importance for much of the biotechnology and pharmaceutical industries, are often harder to enforce and thus protect the companies investment.

> Not only is it difficult to detect and prove infringement of such a patent [one that claims products or processes that are used only during product development], but often the only effective remedy even for proven infringement will be damages, because an injunction against future use of the invention will not thwart the efforts of a competitor who has already finished using the invention.[36]

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[34] Technology Transfer, Productivity, and Economic Policy, op. cit., p. 134-135.

[35] A process patent is a patent on the methodology used in creating or producing a product.

[36] Eisenberg, Rebecca S. Genes, Patents, and Product Development. Science, v. 257, Aug. 14, 1992. p. 906.

In particular, as University of Pennsylvania professor Edwin Mansfield and his colleagues found, patents are more important in the drug industry than in others studied (e.g., electronics, machinery) because of the ease which a drug can be reproduced. These findings parallel ". . . Taylor and Silberston's conclusion that the lack of patent protection would reduce the rate of expenditure on innovative activity to a greater extent in drugs than in other industries."[37] In the drug industry, more than other industrial sectors, many patented innovations would not have been introduced without patent protection.[38] Other relevant considerations include the fact that the majority of the biotechnology companies seeking patent protection are likely to be small firms originally intended to be protected by the patent system and which do not have access to some of the resources of the larger companies. In addition, the time lag traditionally found between research and application (but not commercialization) is often substantially decreased in biotechnology because of the nature of the industry and the type of R&D performed.

Despite the argument put forth during consideration of Bayh-Dole that title should remain in the public sector where it is accessible to all interested parties since Federal funds were used to finance the work, the Congress has accepted (to some extent) the proposition that vesting title to the contractor will encourage commercialization. The law states:

> It is the policy and objective of the Congress to use the patent system to promote the utilization of inventions arising from federally-supported research or development; . . . to promote the commercialization and public availability of inventions made in the United States by United States industry and labor; [and] to ensure that the Government obtains sufficient rights in federally-supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions. . .[39]

Each nonprofit organization (including universities) or small business is permitted to elect (within a reasonable time) to retain title to any "subject invention" made under federally-funded R&D; except under "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."[40] The institution must commit to commercialization within a predetermined, agreed upon, time frame. As stated in the House report to accompany the bill, "the legislation establishes a **presumption** [emphasis added] that ownership of all patent rights in

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[37] Technology Transfer, Productivity, and Economic Policy, op. cit., p. 148.

[38] Ibid., p. 150.

[39] P.L. 96-517, sec. 200.

[40] Ibid.

government funded research will vest in any contractor who is a non-profit research institution or a small business."[41]

Certain rights are reserved for the Government to protect the public's interests. The Government retains ". . . a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world . . ." The Government also retains "march-in rights" which enable the Federal agency to require the contractor (whether he owns the title or has an exclusive license) to ". . . grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants . . ." (with due compensation) or to grant a license itself under certain circumstances. The special situation necessary to trigger march-in rights involve a determination that the contractor has not made efforts to commercialize within an agreed upon time frame or that the "action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor. . ."[42]

The Government is "authorized" to withhold public disclosure of information for a "reasonable time" until a patent application can be made. This supplements additional law (35 U.S.C. 205) which prohibits the Patent and Trademark Office from releasing information associated with a patent until it is issued. However, at NIH, the grant recipient is required to publish the results of the federally-funded research. This is augmented by tax code regulations mandating expeditious publication of actual research results in order for a university or research institution to retain its tax exempt status. NIH also requires that the patented work be available for use by other scientists for research purposes without acquisition of a license.

Licensing by any contractor retaining title under this act is restricted to companies which will manufacture substantially within the United States. Initially, universities were limited in the time they could grant exclusive licenses for patents derived from Government-sponsored R&D to large companies (5 of the 17 years of the patent). This restriction, however, was voided by P.L. 98-620, Amendments to the Patent and Trademark Laws. According to Senate Report 98-662, extending the time frame for licensing to large firms ". . . is particularly important with technologies such as pharmaceuticals, where long development times and major investments are usually required prior to commercialization."[43]

It continues to be argued that patent exclusivity is important for both large and small firms. In a February 1983 memorandum concerning the vesting of

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[41] Report to Accompany H.R. 6933, op. cit., p. 5.

[42] P.L. 96-517, sec. 203.

[43] U.S. Congress. Senate. Committee on the Judiciary. Report to Accompany S. 2171. Senate Report No. 98-662, 98th Cong., 2d Sess. Washington, U.S. Govt. Print. Off., 1984. p. 3.

title to inventions made under Federal funding, President Reagan ordered all agencies to treat, as allowable by law, all contractors regardless of size as prescribed in P.L. 96-517. This, however, does not have a legislative basis. In addition, as noted previously, the Federal Technology Transfer Act allows firms regardless of size to be awarded patents generated under a CRADA with a Federal laboratory.

NIH-UNIVERSITY-INDUSTRY COLLABORATION: THE RESULTS

Implementation of the Laws

Funding by the National Institutes of Health in biotechnology has proven effective in terms of new products both on the market and in the pipeline, leading to cost savings. According to Dr. Jay Moskowitz, former NIH Associate Director for Science Policy and Legislation, "[f]or a total investment of $800 million in applied research, NIH research advances provide the Nation with a yearly total cost savings of $5.2 billion. This is a conservative estimate."[44] The system of incentives to innovate and bring new products on the market embodied in the patent and technology transfer laws--reflecting congressional and Administrative mandates--appears to be working well. The CRADA process at NIH has accelerated clinical development of several therapeutics and hastened the development of animal models for a variety of human diseases.[45] University patent and licensing activities have increased substantially since the passage of Bayh-Dole. There has also been growth in the number of "spin-off" companies emerging out of academic institutions. In the 10 years between 1980 and 1990, the number of applications for patents on NIH supported R&D increased from 890 to 2,600, according to Dr. Bernadine Healy, former Director of the National Institutes of Health. In addition, universities are receiving licensing royalties of over $80 million annually as compared to approximately $30 million in 1986.[46] And, perhaps most meaningful to this discussion is the statement by the former Director of NIH, Dr. Bernadine Healy that Bayh-Dole is responsible for the development and growth of the biotechnology industry.[47] This was achieved by both the expansion of cooperative efforts among Government, industry, and academia and by the intellectual property protection this Act provided.

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[44] The National Institutes of Health and Its Role in Creating U.S. High-Technology Industry Growth and Jobs, op. cit., p. 12.

[45] Ibid., p. 9.

[46] Bayh-Dole May Need "Reasonable Amendment and Adjustment." Washington Fax, June 23, 1993. p. 2.

[47] U.S. Congress. House. Committee on the Judiciary. Biotechnology Development and Patent Law. Hearings, 102d Cong., 1st Sess., Nov. 20, 1991. Washington, U.S. Govt. Print. Off., 1993. p. 48.

NIH is faced with two interrelated goals: "promoting the health of the American people and all mankind through research in the biosciences, and fostering a vigorous domestic biotechnology industry."[48] The legislation discussed above provides a general framework to achieve these objectives. However, there are specific issues associated with health research which have generated concerns not raised in other industrial sectors. Given the particular interest in health-related R&D, the increased commercial potential, and cost considerations, questions are being raised as to the adequacy of current arrangements. Most agree that closer cooperation can augment funding sources (both in the public and private sectors), increase technology transfer, stimulate more innovation (beyond invention), lead to new products and processes, and expand markets. However, others point out that cooperation may provide an increased opportunity for conflict of interest, redirection of research, less openness in sharing of scientific discovery, and a greater emphasis on applied rather than basic research.

These issues were extensively explored in the discussion surrounding changes to the patent laws in 1980 and 1986, and the debate over technology transfer since the late 1970s. As a result of these concerns, safeguards have been built into the activities authorized by law. As discussed previously, march-in rights, the Government's retention of a irrevocable license to these patents, publication requirements, and commercialization schedules, among other things, all are incorporated into the process to protect the public interest. While there is a potential for creating an "unfair" advantage for one company over another, this is balanced against the need for new technologies and techniques and their contribution to the well-being of the Nation. During the 1980s, Congress determined that the dispensation of patent rights to universities, small businesses, and nonprofit institutions and the issuance of CRADAs takes precedence because of the greater good generated by new products and processes which improve the country's health and welfare and by the understanding that the economy gets a significant payback through increased taxes on profits, through new jobs created, and expanded productivity. The Government benefits through increases in tax revenues from profits, wages, and salaries.

The National Institutes of Health, in its cooperative ventures, has taken into account many of the concerns arising specifically from the health-related field, as well as from political considerations. Thus, the NIH approach to cooperative research and development agreements differs from that of other Federal laboratories. Although CRADAs are exempt from disclosure under the Freedom of Information Act, "[c]onsistent with our mission responsibilities, ... NIH declines to protect the results of CRADA research as trade secrets for collaborators. This allows the results of CRADA research to join intramural research results in being communicated broadly to the scientific and medical

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[48] President's Council of Advisors on Science and Technology. Achieving the Promise of the Bioscience Revolution: The Role of the Federal Government. Washington, Dec. 1992. Introductory letter. [No page number]

community."[49] Open dissemination of research data is promoted[50] with the agency reserving the right to publish information on NIH generated R&D even under a CRADA.[51]

The Fair Pricing Clause

The major difference, however, in the way the National Institutes of Health and other Federal laboratories do joint work with the private sector is the inclusion of a "fair pricing clause" in NIH's cooperative research and development agreements and most licensing arrangements. This clause, adopted by NIH in 1989, requires that any commercial product (e.g., a new drug) resulting from a CRADA be sold at a price which reflects both the Federal and private sector contributions to the technology's development as well as the "health and safety needs of the public." The official language states that there be a "reasonable relationship" between these factors. Dr. Healy testified that the emphasis is on "reasonableness:"

> . . . NIH is not in the business, and does not intend to get into the business, of price fixing or being a regulatory agency for pharmaceutical prices. It does, however, intend to take seriously the reasonable pricing clause in the sense of dialogue, discussion, and persuasion, when necessary, in dealing with industry.[52]

The fair pricing clause was instituted in response to public and political pressures resulting from concern over the cost of AZT, a drug used in the treatment of HIV infection, as well as the past director's judgement that it is "... important for the public health."[53] There is no legislative mandate for such a requirement, although a bill has been introduced to augment the clause. [H.R. 1334, introduced March 11, 1993, would prohibit NIH from entering into a CRADA that does not include a set formula for pricing any future commercial products.] At this point, it is unclear if the clause can be enforced as written

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[49] U.S. Congress. House. Committee on Science, Space and Technology. Subcommittee on Technology and Competitiveness. Transfer of Technology from Federal Laboratories. Hearings, 102d Cong., 1st Sess., May 30, 1991. Washington, U.S. Govt. Print. Off., 1991. p. 158.

[50] The National Institutes of Health and Its Role in Creating U.S. High-Technology Industry Growth and Jobs, op. cit., p. 13.

[51] Ibid., p. 29.

[52] Ibid., p. 19.

[53] Ibid., p. 22. For a discussion of the concerns expressed over the price of AZT see: Pharmaceutical R&D: Costs, Risks, and Rewards, op. cit.

and NIH is reluctant to make definitive decisions on pricing.[54] Currently, reasonable pricing is defined as a price within the range of existing therapies.[55] However, it is necessary to differentiate between the reasonable pricing clause and "price setting:" the latter is regulation and has been considered inappropriate for NIH. As Healy testified, the laboratory is ". . . probably . . . unqualified" to undertake drug pricing because it has not been involved in such activities. Instead, NIH ". . . should approach fair pricing as a co-inventor of a fundamental discovery and use . . . leverage as an agency that knows what we brought to the table." Guidelines should be established ahead of time. The laboratory should not be "too intrusive" or get ". . . too involved in the financial and proprietary activities of companies."[56]

The reluctance of a Federal laboratory to enter into determinations of "fair" pricing may be understood within the context of the wide range of variables which might need to be taken into consideration. Among these are: (1) What is the value of the Federal contribution since the Government is specifically prohibited from providing **direct** funding under a CRADA? (2) What is the cost of Government-sponsored research in relation to the total costs incurred by the company (including research, development, clinical trials, FDA approval, production, distribution, marketing)? (3) What costs were incurred in related work which did not result in a marketable product or process? (4) Who owns the intellectual property rights and what is their value to the company? (5) What are the costs of **not** having the drug available? (6) What are the replacement and/or substitution costs associated with the therapeutic?

Representatives from NIH have argued that as a result of the reasonable pricing clause, ddI (an antiviral drug used in the treatment of AIDS) came to the market at a cost to the consumer which was several hundred dollars less than expected.[57] However, this requirement has generated additional uncertainties in a process already fraught with risk. Not knowing what the determination of "fair" will be at the end of a long and expensive research, development, and commercialization process, is a strong deterrent to entering into a cooperative arrangement. Accordingly, ". . . many pharmaceutical and biotechnology companies are reconsidering CRADAs, and NIH officials say four of the largest--Pfizer, Abbott Laboratories, Merck and The UpJohn Company--have told the laboratory that they plan to forego new CRADAs unless the pricing clause is

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[54] Anderson, Christopher. Rocky Road for Federal Research Inc. Science, v. 262, Oct. 22, 1993. p. 497.

[55] NCI Seeking Prices for CRADA Products in Line with Existing Therapies; Indigent Care Important. "The Blue Sheet," Jan. 27, 1993. p. 10.

[56] The National Institutes of Health and Its Role in Creating U.S. High-Technology Industry Growth and Jobs, op. cit., p. 22-23.

[57] Ibid., p. 22.

removed."[58] Some firms are even declining opportunities for joint clinical trials with NIH in anticipation of future price control demands.[59] Some observers are concerned that similar problems might arise with the cost containment mechanisms proposed in the Clinton health care plan.

A study by the DHHS Inspector General found that companies viewed the clause as a major problem in the NIH CRADA approach.[60] It appears that fewer companies are interested in entering into cooperative research and development agreements with the laboratory since the implementation of the fair pricing requirement and other arrangements are being used to avoid it. For example, Pfizer gave up exclusivity to commercial rights in a cooperative effort with NIH to develop a drug to treat tooth pain in exchange for a waiver of the clause. They were able to enter into a non-exclusive CRADA because of the company's strong patent position regarding previous work. Several companies are using a similar approach.[61] However, some other firms, particularly small ones like many biotechnology companies, can not afford to avoid the fair pricing clause or make other cooperative arrangements. Thus, the sector which was provided preference in entering into CRADAs--the small business community--arguably could be the most adversely affected by the reasonable pricing clause.

THE HEALTH CARE PLAN: IMPLICATIONS

To date, the U.S. system of research, development, and commercialization appears to be working in the biotechnology arena. As noted previously, it is one of the industries where American firms have had a continual positive trade balance, where 70-80 percent of all U.S. patents are held by Americans, and where NIH officials argue that by 1992 Federal investments of under $1 billion have resulted in cost savings of over $5 billion a year, among other things. The application of NIH fundamental and clinical R&D can provide improved health care through better diagnosis, screening, prevention, and more effective therapeutics. However, if the trend towards private sector avoidance of cooperative R&D with NIH continues due to the imposition of the fair pricing clause, it might have significant effects on the future of the biotechnology industry.

The same concerns over the cost of new drugs which resulted in the use of the fair pricing clause in NIH CRADAs have entered into the debate over the proposed Clinton health care plan. As reflected in 20 years of congressional

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[58] Rocky Road for Federal Research, Inc., op. cit., p. 497.

[59] Rhein, Reginald. Will NIH's Fair Price Clause Make CRADAs Crumble? The Journal of NIH Research, v. 6, Mar. 1994. p. 41.

[60] Ibid., p. 41.

[61] NIH CRADA Review Rate of 4-6 per Month Reflects Industry Wariness of "Reasonable Price Clause." The Blue Sheet, May 12, 1993. p. 6.

deliberation over patents and cooperative R&D, as well as indicated by recent circumstances at the National Institutes of Health, it appears that firms which are unable to control the results of their investments because of Government policies may be less willing to engage in related R&D. Companies can avoid both licensing Government-owned patents or entering CRADAs with NIH in response to the fair pricing clause if they have access to other means by which to support research and protect their resources. However, if under pricing restraints, the biotechnology community can not convince investors that the returns on risk capital will be sufficient, the major funding sources may disappear with few alternatives.

In attempting to ascertain what the potential effects of price control mechanisms might be, the following discussion first describes briefly the various reasons put forth for such restraints on breakthrough drugs.[62] These reasons are, for the most part, derived from the Administration's assessment of pricing practices within the pharmaceutical industry. However, as noted earlier, although there is overlap, the biotechnology and pharmaceutical industries are not identical. While pharmaceutical companies do perform R&D in biotechnology (estimates are 33 percent of current research), they are generally large entities which fund their own work out of profits from sales of existing, primarily chemically derived, drugs. Most of these firms have been in existence for many years and have a record of high profitability. The biotechnology industry is composed primarily of small companies which are research intensive, have few, if any, products on the market, fewer profits, and are dependent on venture capital, public stock offerings, or cooperative efforts with larger pharmaceutical companies for funding. Several of these firms have evolved into larger companies over the last few years, but the majority remain small and have been in operation 10 years or less.

The Clinton health care proposal would institute price control mechanisms that could affect all new breakthrough drugs regardless of whether they emerged from an established pharmaceutical company or a small biotechnology firm. In light of this, the discussion below explores whether the affects of such provisions on the biotechnology sector might be significantly different than that which could be expected on the traditional pharmaceutical industry. Are current assumptions still valid? Might there be unintended consequences to biotechnology firms because of assumptions based on the activities of pharmaceutical companies?

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[62] For additional discussion see: U.S. Library of Congress. Congressional Research Service. The President's Health Care Reform Plan and Drug Development in the Biotechnology Industry, by Gary Guenther. Washington, Mar. 9, 1994.

Rationale for Price Controls

There are several underlying considerations associated with the price control provisions included in the Clinton health care proposal.[63] They are based, in part, upon cost containment concerns and information that shows very high profits in the pharmaceutical industry with drug prices rising in the 1980s at twice the rate of inflation. For example, in 1991 it was estimated that pharmaceutical companies had profit levels four times that of the average Fortune 500 firm.[64] Because Medicare does not currently reimburse for most outpatient prescriptions, the elderly have to pay for drugs out of pocket and are acutely aware of price increases. For the population as a whole, prescription drug purchases are necessary and not deferrable. A recent study by the General Accounting Office comparing prices of prescription drugs in the United States and the United Kingdom found prices lower in Great Britain for most therapeutics reviewed. In introducing the report, Representative Henry Waxman noted that the regulation of prices in Great Britain has not diminished the performance of the indigenous drug industry.[65]

The argument has been put forth that biotechnology products are unique and therefore would not be subject to the type of intense competition which would lower prices. Critics also charge that the pharmaceutical companies spend more money on marketing and advertising than on research and development.[66] The Senate Select Committee on Aging has published data indicating that the pharmaceutical industry is spending $1 billion more per year on public relations than on research.[67] According to testimony by Hillary Clinton before the House Energy and Commerce Committee in October 1993, there is no

> . . . longer doubt that we have a problem with the pricing of drugs in the country. And what we are trying to do is to strike the right balance between encouraging and motivating research, but not permitting the public either through government programs or through

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[63] For additional discussion see: Prescription Drug Prices: Should the Federal Government Regulate Them? op. cit.

[64] U.S. Congress. Senate. Special Committee on Aging. Prescription Drug Prices: Out-Pricing Older Americans. Hearings, 103d Cong., 1st Sess., Apr. 14, 1993. p. 3.

[65] GAO Report on Drug Prices Hits U.S. Pharmaceutical Companies Hard. Washington Fax, Feb. 4, 1994. p. 2.

[66] An Industry in Pain, op. cit., p. 2529.

[67] Prescription Drug Prices: Out-Pricing Older Americans, op. cit., p. 3.

private insurance to bear more than a fair share of the costs of any company recouping its research and development costs.[68]

Paralleling the arguments surrounding the NIH CRADA "fair pricing clause," there are critics who contend that biotechnology and pharmaceutical companies receive identifiable benefits from the Federal Government and should price resulting therapeutics accordingly.[69] If, as proposed by the Clinton plan, Medicare covers outpatient prescriptions, the Government should not have to pay excessive prices under Medicare reimbursements for drugs resulting from Federal support. Proponents of the use of price reviews argue that in determining guidelines for these assessments, relevant criteria can be established which adequately reflect a company's financial investment.

Concerns of the Biotechnology Industry

As these proposals are discussed, it might be helpful to examine the related literature in this area, to review the current situation, and reiterate the effects of the fair pricing clause on cooperative R&D between NIH and the private sector. Several avenues of inquiry which might be explored include: Are the indicators of price correct and relevant to the biotechnology industry? What do recent studies show about the effects of price controls on biotechnology companies? What has happened in the biotechnology industry since controls have been suggested?

According to supporters of the biotechnology community, the focus on "excessive" costs and "undue" profits is, in part, a result of misperceptions. Of the $839 billion spent in 1992 on health care, drug expenditures were seven cents for every one dollar expended elsewhere on health. Yet because 75 percent of this seven cents is paid for directly by the consumer, the industry claims that the public perceives drug prices as being too expensive.[70]

Recent figures indicate that increases in prescription drug prices have fallen to below 3 percent in 1993, from the over 10 percent rise which occurred in

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[68] Quoted in: Clinton, Shalala Testify on Future of Biomedical Research, Pharmaceutical R&D Under Health Care Reform. Washington Fax, Oct. 13, 1993. p. 1.

[69] U.S. Congress. House. Committee on Small Business. Subcommittee on Regulation, Business Opportunities and Technology; and U.S. Congress. Senate. Special Committee on Aging. Hearings for discussion of the political considerations advanced by the Hon. Ron Wyden and the Hon. David Pryor. Hearings held Mar. 11 and Feb. 24, 1993.

[70] Biotech 94, op. cit., p. 7-8.

1991.[71] This is considered less than inflation. It is argued the rate of drug price increases is declining because of managed care, competition from generics, and cost consciousness.[72] The movement towards large scale drug purchases by HMOs, mail order drugs, and State Medicaid agencies has shifted market share by making doctors prescribe drugs from formularies; the ability to shift market share is a key to keeping drug prices competitive.[73] It is also argued that the "threat" of price controls has had a significant impact on slowing the rate of drug price increases.

The price increases which are pointed to as the primary reason for imposition of cost control measures are typically descriptive of new **chemical** entities rather than **biotechnology** derivatives (of which there are still few products). According to the testimony of Kirk Raab, President and CEO of Genentech,

> Virtually no biopharmaceutical drug has increased its price beyond the rate of inflation. Our medicines tend to be priced two to three times higher abroad than here in the United States. Most have NEVER had any price increases at all and some have actually declined in price. Moreover, the manufacturer of every biopharmaceutical has instituted a "free goods" program to ensure that no American is denied treatment because of inability to pay.[74]

Additional information from the GAO study of drug pricing in the United States and Great Britain appears to support this argument to some extent. Analysis of the data show that while drugs sold before 1980--prior to the development of the biotechnology industry--were 121 percent more expensive in the U.S., the differentials were only 17 percent for those drugs--both chemical and biotechnology--first marketed between 1986 and 1993.[75] In addition, these breakthrough drugs may not remain unique for long as competing therapeutics are developed and introduced. The Boston Consulting Group found that those drugs marketed during 1991 and 1992 had an average price 14 percent lower

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[71] Economists Dispute Clinton Claim Health System is Anti-Competitive. Inside the White House, Jan. 6, 1994. p. 20.

[72] The Pharmaceutical Industry's Role in Health-Care Reform, op. cit., p. 2.

[73] Tully, Shawn. The Plots to Keep Drug Prices High. Fortune, Dec. 27, 1993. p. 121.

[74] Raab, Kirk. Written Statement submitted to the House Committee on Energy and Commerce, Subcommittee on Health and the Environment, Feb. 8, 1994. p. 7. [Unpublished hearings]

[75] GAO Report on Drug Prices Hits U.S. Pharmaceutical Companies Hard, op. cit., p. 2.

than the leading medicine in the same therapeutic category.[76] If, in fact, **chemically** derived drug prices are excessive, controls on new, breakthrough therapeutics which are expected to result from **biotechnology** may not have application or produce the intended effects.

The majority of companies doing R&D in the biotechnology arena have few if any products now on the market and therefore few if any profits. Drug profits pay for more research; as noted previously, biotechnology companies invest a larger percentage of sales revenue into R&D than other types of firms. Supporters argue that if profits, where they exist, are curtailed there will be less money for reinvestment particularly by the smaller firms. At the same time, other sources of financial support seem to be diminishing. Under current budgetary constraints, the increased demand for NIH grants means a smaller percentage are being funded. Most firms in this community are dependent on private sector, high risk funding. However, it appears that the public equity market is moving away from biotechnology investments.

According to the Ernst and Young report, 1992 biotechnology initial public offerings (IPOs) were $900 million, 31 percent less than the previous year.[77] The Biotechnology Industry Organization (BIO) reports that the value of IPOs through June 30, 1993 was $253 million. This figure appears to reflect a recent trend of decreasing value of IPOs as evidenced by BIO's figures of $1.203 billion for 1992 and $1.542 billion in 1991.[78] Reasons for the decline include the inability of certain therapeutics to meet their expectations both on the market and in clinical trials and reduced profits in the industry. A 25 percent decline in the value of biotechnology companies between December 31, 1992, and March 31, 1993, has been attributed by some analysts to announcements concerning price constraint aspects of the Clinton health care proposal.[79] CommScan has figured that, in 1993, $520.8 million in public and private stock offerings for drugs and medical devices were canceled due to the specter of price controls. The potential for the approximately 4,000 jobs which reportedly would have been created due to this financing was eliminated. J.D. Kleinke of HCIA, a health care data analysis and research firm, points out that 35,000 actual positions have been cut by pharmaceutical companies since this debate began. Most of these jobs were well paid, high tech, highly skilled positions.[80] However, others have attributed this to drugmakers downsizing due to a more

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[76] Ibid., p. 12.

[77] Biotech 94, op. cit., p. 55.

[78] Biotechnology Industry Organization. September 1993 Report on the Financial Markets for Biotechnology Companies. Unpublished report. [Unnumbered pages]

[79] Biotech 94, op. cit., p. 6.

[80] Kleinke, J. D. Expensive Drugs Lower Health Care Costs. Wall Street Journal, Feb. 16, 1994. p. 18.

competitive environment. It has also been reported that biotechnology firms raised approximately $3 billion in 1993, the second largest yearly total to date which may mean other funding sources are being utilized.[81]

The rate of R&D investment in both the pharmaceutical and biotechnology sectors is expected to decline. This year, pharmaceutical industry increases in R&D of as little as 4 percent to approximately $13.1 billion are anticipated in contrast to last year's 13.5 percent increase; and there are concerns that health care reform may "curtail" spending even further.[82] Last year's increase in funding was less than the 16 percent average between 1980 and 1992.[83] Yet, it can be noted that this decline comes following a decade of substantial yearly increases in profits. According to Standard and Poor's, between 1982 and 1992 the pharmaceutical industry had an average annual earnings growth rate of 18 percent.[84]

Similar declines in R&D growth rates are expected in the biotechnology sector. The effects of this change in R&D may be dramatic, if, as P. Roy Vagelos, M.D., Chairman and Chief Executive Officer of Merck and Company, Inc. argues, R&D investment decisions are based on the availability of funding. "Numerous academic studies have documented the responsiveness of R&D to changes in cash flow: for every $100 drop in cash flow, R&D investment declines $30 to $40."[85] In a survey undertaken by the industry association BIO of its member firms in the area of cancer research, 44 percent of companies have delayed or canceled their research activities and 41 percent attributed this to a decline in investment resulting from uncertainty generated by the Clinton proposal for price restraint mechanisms in the health care plan. Sixty-two percent of respondents felt there would be additional cutbacks if this provision became law.[86] In the field of AIDS research, 47 percent of the firms indicated

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[81] Hamilton, Joan O'C. A Little Dose of Government Won't Kill Biotech. Business Week, Feb. 28, 1994. p. 65.

[82] Weber, Joseph. A Big Dose of Uncertainty. Business Week, Jan. 10, 1994. p. 85.

[83] Mossinghoff, Gerald J. Written statement submitted to the House Committee on Energy and Commerce, Subcommittee on Health and the Environment, Feb. 8, 1994. p. 6. [Unpublished hearings]

[84] Health Care Products and Services, Basic Analysis. Standard and Poor's Industry Surveys, v. 161, Sept. 9, 1993. p. H18.

[85] Vagelos, P. Roy. Written testimony submitted to the House Committee on Energy and Commerce, Subcommittee on Health and the Environment, Feb. 8, 1994. p. 8. [Unpublished hearings]

[86] Biotechnology Industry Organization. Cancer Research Suffers From Investment Crunch, Biotech Industry Sees Further Cuts. BIO News Release, Feb. 2, 1994. p. 1.

that R&D spending had declined, 40 percent blamed the fear of price controls. Sixty-three percent noted that further cuts would be made if the plan became law.[87] A recent study by The Gordon Public Policy Center at Brandeis University authored by Robert Goldberg found that of the 107 biotechnology firms surveyed, 67 percent would be deterred from R&D for the population served by Medicare because price controls would limit the availability of investment capital.[88] However, the study also found that if, as intended under health care reform, Medicare would pay for prescriptions, the number of prescriptions filled may increase substantially and may offset some of the effects of drug price limitations.

Several other recent studies have predicted that price controls would be detrimental to innovation in the biotechnology arena. F. M. Scherer at Harvard concluded that such a provision would "seriously impair" investment in new products. Because, as he sees it, price controls would not take into account the costs associated with drugs which did not make it to the market,

> [i]f profits were held to "reasonable" levels on blockbuster drugs, aggregate profits would almost surely be insufficient to sustain a high rate of technological progress. This tendency would be aggravated when, as is likely, individual companies are too small to pool internally the combination of (highly skewed) market and regulatory risks. If in addition developing a blockbuster is riskier than augmenting the assortment of already known molecules, the rate at which important new drugs appear could be retarded significantly.[89]

According to George M. Milne, President of Central Research at Pfizer Inc., "The stronger the focus on prices, the greater the danger that companies will be too risk-adverse."[90] Under price controls, it thus becomes increasingly important to pick only winners if other investments which do not make it to the marketplace can not be compensated for by those products that do. Some analysts believe that the avoidance of risk may hinder the progress of science where failures often are instructive and promote the evolution of new ideas and approaches.

Robert Goldberg, Brandeis University, found that in the global marketplace ". . . there is a perfectly inverse relationship between drug price regulation and new product innovation as measured by product introductions and world-wide

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[87] Ibid., p. 3.

[88] Price Controls Would Force Biotech Companies to Look Offshore for Funding, Says Survey. Washington Fax, Mar. 16, 1994. p. 1.

[89] Scherer F. M. Pricing, Profits, and Technological Progress in the Pharmaceutical Industry. Journal of Economic Perspectives, v. 7. Summer 1993. p. 113.

[90] A Big Dose of Uncertainty, op. cit., p. 85.

market share relative to domestic market size."[91] Similarly, industry analyst Heinz Redwood concluded that there is "an indisputable link between pricing freedom and successful innovative research and development in the pharmaceutical industry."[92] A 1991 study by the U.S. International Trade Commission reported that foreign efforts to implement cost-containment programs, price controls, or both, on a national level, resulted primarily in decreased R&D investments such that the pharmaceutical industries in several countries have been weakened or have shifted their activities elsewhere.[93]

The industry and many analysts argue that the long-term cost effectiveness of a therapeutic is more relevant to health care improvements than the drug's initial price. Most medicine tends to be less expensive than surgery, hospitals, or nursing home care. A recent study found that restrictions on the availability of medicines (restricted formularies) may lower expenditures for drugs, but increase expenditures for other health related services including hospitalization and administrative costs.[94] For example, it costs approximately $46,000 for a coronary bypass in contrast to $60 per month for a drug designed to lower cholesterol and prevent surgery.[95] At Duke University, cost efficiencies have been achieved in a bone marrow transplantation program though the use of a biotechnology-derived product that stimulates the growth of bone marrow. Application of granulocyte colony-stimulating factor has decreased hospital stays from weeks in isolation to only four to five days and lowered the per-patient cost by $75,000 (from $140,000 in 1990). As described by Charles Sanders, M.D., Chairman and Chief Executive Officer of Glaxo Inc., this therapy has ". . . turned what was a high-mortality, inpatient procedure into a highly successful procedure performed largely on an outpatient basis."[96]

An interesting analogy was offered by Dr. John Curd, Clinical Director at Genentech during testimony at recent hearings. He pointed out that in the early stages of development, satellite technology was extremely expensive but now telecommunications technologies are both cheap and ubiquitous. Ultimately, biotechnology research may result in drugs that are so medically

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[91] Quoted in: Expensive Drugs Lower Health Care Costs, op. cit., p. 18.

[92] Quoted in: Sanders, Charles A. Written statement submitted to the House Committee on Energy and Commerce, Subcommittee on Health and the Environment, Feb. 8, 1994. p. 4. [Unpublished hearings]

[93] Mossinghoff testimony, op. cit., p. 13.

[94] Kozma, C. M. et. al. Economic Impact of Cost-Containment Strategies in Third-Party Programmes in the United States. PharmacoEconomics, 1993. p. 187-202, as summarized in: The NPC Report. The National Pharmaceutical Council. Fall 1993. p. 7.

[95] Expensive Drugs Lower Health Care Costs, op. cit., p. 18.

[96] Sanders testimony, op. cit., p. 2-3.

effective they will be cost effective also.[97] The "learning curve" is part of the process of decreasing costs, argues Dr. Thomas Brown, Associate Professor, Duke University School of Medicine. The cost of breast cancer treatment is being lowered by new drugs and technologies which allow women to stay out of hospital while receiving therapy. Similarly, three times the initial NIH investment in R&D for testicular cancer has been recouped by the lives saved and all the accompanying benefits.[98]

OBSERVATIONS

Some proponents of price reviews on breakthrough drugs maintain that Federal support for biotechnology R&D, which often leads to new therapeutics, provides a rationale for Government participation in price determinations, particularly for drugs involved in expanded Medicare reimbursements under the Clinton health care proposal. This justification is also the basis for the inclusion of a fair pricing clause in cooperative research and development agreements between the National Institutes of Health and the private sector. It is argued that criteria can be established which take into consideration the relative investments of both the Government and the company.

The position that the Federal Government should receive commensurate cost considerations for its financial support of research and development was part of the legislative debate over patent policy and cooperative R&D. Congress, over 20 or more years, weighed the issues and the arguments and decided that, in the case of patent and technology policies, the benefits to the Nation brought about by increased innovation are paramount. It has been estimated that the returns to society generated by investments in basic research are approximately twice those to the company performing the work. The payback to the country includes increased revenues from taxes on profits, new jobs created, improved productivity, and economic growth. The growth of the biotechnology industry and the development of new therapeutics to improve health care are prominent examples of such benefits. These benefits have been considered more important than the initial cost of the technology to the Government or any unfair advantage created.

Actual experience and cited studies point to the conclusion that companies which do not control the results of their investments--either through ownership of patent title, exclusive license, or pricing decisions--tend to be less likely to engage in related R&D. This fact is reflected in the legislative approaches to

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[97] Curd, John. Oral testimony presented to the House Committee on Science, Space and Technology, Subcommittee on Technology, Environment and Aviation, Feb. 2, 1994. [Unpublished hearings]

[98] Brown, Thomas. Oral testimony presented to the House Committee on Science, Space, and Technology, Subcommittee on Technology, Environment and Aviation, Feb. 2, 1994.

both patents institutionalized by Bayh-Dole and cooperative research mandated by Stevenson-Wydler, as amended. Universities, non-profit institutions, and small businesses are provided title to any patent arising from federally-funded research and development as an economic incentive to encourage the commercial application of these technologies or techniques. Cooperative R&D is designed to facilitate the emergence of new products, processes, and services by fostering an environment where the participants in the technology advancement process can work together. There are provisions for the non-federal partners in the joint effort to obtain certain rights to any resulting intellectual property. In these ways, the business community can obtain a return on their financial contribution to the endeavor.

NIH has decided to implement a "fair pricing clause" in its cooperative research and development agreements. This limits the decisions that a company can make in commercializing any result of federally-supported R&D. As a result, fewer firms appear to be interested in joint research with the National Institutes of Health. Speaking to the situation at the NIH, Robert Taber, DuPont Merck Vice President for Extramural R&D, warned "'Until this pricing issue ends up getting settled, it's going to cast a pall over our ability to work with NIH at a time when the opportunities have never been greater.'"[99] This experience may be illustrative. The results of the pricing clause in NIH CRADAs demonstrate, in practice, some of the actual effects of the imposition of such conditions. Companies avoidance of cooperative R&D is contrary to congressional initiatives to promote increased innovation. There is concern that this may be a harbinger of the possible impact of price controls on breakthrough drugs under the proposed Clinton health care plan. This is where the competing goals of health care cost containment and the encouragement of technology-based breakthrough drugs may conflict. The implications could be significant, not just for the companies involved, but for the development of new biotechnology drugs to meet the health care, public welfare, and economic growth needs of this Nation.

[99] NIH CRADA Review Rate of 4-6 Per Month Reflects Industry Wariness of "Reasonable Price Clause," op. cit., p. 6.