Federal Support for Pharmaceutical Research and Development 9

Economic theory suggests that without help from the government, the private sector alone will underinvest in research (19,5 13). It makes sense for a firm to invest in research whose results lend competitive advantage to the company. But, much research creates knowledge that the firm cannot keep to itself. The patent system and the legal protections afforded trade secrecy are attempts by governments to confer exclusive ownership rights to knowledge, but not all discoveries can make use of these privileges. Basic research increases the storehouse of fundamental scientific understanding and is often necessary for commercial applications. Yet, a private industrial firm lacks the incentive to adequately support basic research because the firm cannot ensure it will capture all the benefits of such support. To realize the benefits of basic research and research training, the public sector must participate in its funding.

Underwritten largely by Federal and State Governments, research-intensive universities serve as the public sector's principal agents in the conduct of both biomedical research and training of biomedical researchers. The goal of this support is to realize the economic and public health benefits that can follow from the commercialization of research results (131).

The pharmaceutical industry is particularly adept at mining the motherlode of knowledge created by government-sponsored biomedical research and training. In a recent survey of firms in seven research-based industries, Mansfield (253) found over one-quarter of products and processes in use in the pharmaceutical industry could not have been developed without substantial delay in the absence of recent academic research (figure 9-l).

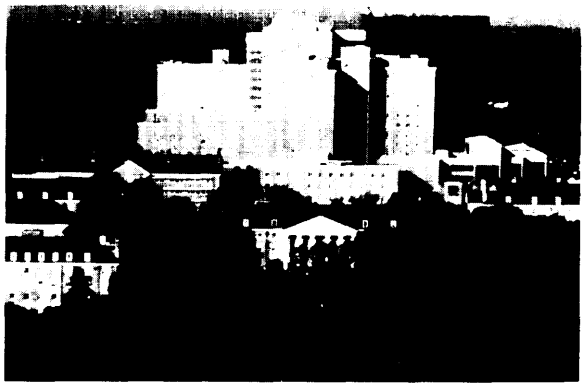


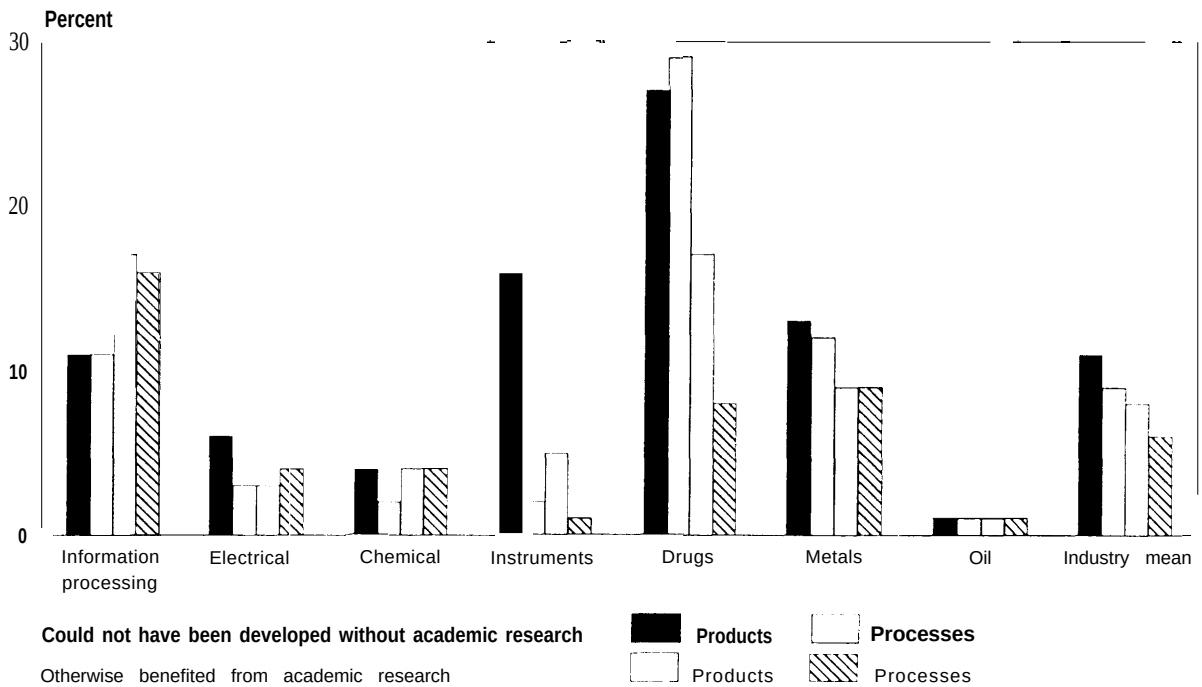
Photo credit: NATIONAL INSTITUTES OF HEALTH

The National Institutes of Health conducts targeted drug discovery and testing programs. The transfer of the scientific knowledge with commercial value from this agency to the pharmaceutical industry is one of the ways that pharmaceutical companies directly benefit from Federal research support.

Respondents to a survey of biotechnology firms conducted by Blumenthal and colleagues (52) reported that collaboration with academic institutions helped keep firms current with important research (83 percent) and that it reduced the cost of mounting research and development (R&D) programs in new fields (60 percent). Indeed, most of the biotechnological techniques developed during the early 1980s, upon which the pharmaceutical industry now depends, came from academic laboratories (445).

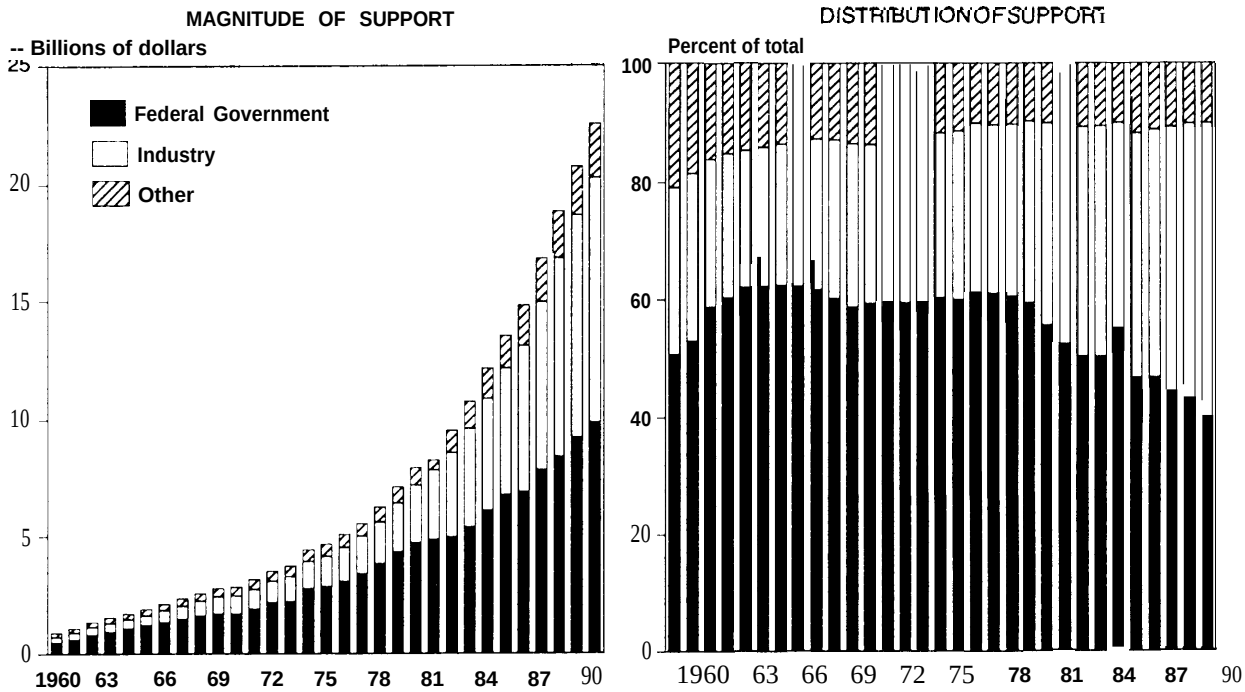
The Federal Government provides even more direct subsidies to industrial pharmaceutical R&D than general support for biomedical research and training. The National Institutes of Health (NIH) and other Federal laboratories themselves conduct targeted drug discovery and testing in disease areas deemed particularly important. In addition, the Federal Government offers a series of subsidies specifically designed to encourage the development of orphan drugs, treatments that might not otherwise be commercially viable. And finally, the Federal Government may unintentionally defray some of the cost of clinical research through its Medicare and Medicaid programs.

Figure 9-l—Percent of New Products and Processes Based on Recent Academic Research, 1975-85



SOURCE: **Office of Technology Assessment, 1993. Based on data from E. Mansfield, "Academic Research and Industrial** Innovation," *Research Policy* 20:1 **-12, 1991.**

Figure 9-2—Sources of Support for Health-Related R&D in the United States, 1960-90



NOTE: Other sources of support include State and local government, private, and nonprofit support.

SOURCE: Office of Technology Assessment, 1993. Based on data from U.S. Department of Health and Human Services, Public Health Service, National Institutes-of Health, *Data Book 1989* (Washington, DC: U.S. Government Printing Office, 1989).

This chapter describes direct Federal contributions to the pharmaceutical knowledge base as well as indirect support through its funding of the biomedical research and training infrastructure. In addition to assessing the extent of such Federal subsidies, this chapter describes how federally funded knowledge produced in academic institutes and government laboratories is transferred to pharmaceutical companies.

The transfer of scientific knowledge with commercial value to private companies that can develop and commercialize the resulting products or services unquestionably has benefits. This chapter describes powerful financial incentives recently put in place through Federal legislation to transfer technologies to the private sector. Whether the public pays too much for the resulting products, however, is a question that needs more attention from public policymakers.

FEDERAL SUPPORT FOR THE LIFE SCIENCES

In 1990, the Federal Government and industry each funded approximately 45 percent ($9.9 billion) of health R&D undertaken in **the** United States (483). Of the Federal portion, 75 percent came from NIH. In the post-World War II period as a whole, the contribution of the Federal Government to biomedical R&D has been much greater than that of industry. Figure 9-2 shows the Federal portion of health R&D conducted in the United States was consistently over twice that of industry throughout the 1960s and 1970s. NIH's investment in biomedical research continued to increase at 2.6 percent per year between 1981 and 1991, after adjusting for inflation. But, the dramatic spurt in industrial pharmaceutical R&D spending beginning in the early 1980s is responsible for the increase in industry's share of total biomedical R&D since 1980.

The Federal investment in R&D over the postwar period has created a physical and organizational infrastructure that continues to be productive today. Over 60 percent of all health-related academic and nonprofit research facilities built between 1958 and 1968 were financed with 50-50 matching funds available through the Federal Health Facilities Research Act (Ch. 779, 70 Stat 717).[1] The National Science Foundation (NSF) and several NIH institutes also had their own authority and appropriations to support building and renovation. Although Federal support for construction has fallen since the 1960s, the Federal Government's contribution over the entire period provided the necessary capacity to conduct subsequent research funded by government, industry and the nonprofit sector.

Industry, on the other hand, has never been a significant contributor of research facilities other than its own in-house laboratories (207).[2] When industry has provided research grants or contracts to academic institutions, its support for indirect and overhead expenses (which pay for facilities and administration) has generally been below the standard Federal contribution for such costs.

Dollars devoted to research and facilities do not fully reflect the importance of Federal support for the academic research infrastructure upon which industry depends. Not only did institutions of higher education receive 62 percent of NIH R&D funds and 53 percent of all Federal health R&D money, but colleges and universities receive virtually all Federal funds for research training (482).[3] Academia, in turn, has used these resources to produce one of the most important components of the R&D infrastructure—scientific talent. The Federal investment in training includes not only scholarship and fellowship support, but also research support to principal investigators who employ trainees in their laboratories, thus giving them a vital part of their education, a research apprenticeship.

Although data limitations preclude comprehensive measurement of Federal support for training,[4] the Office of Technology Assessment (OTA) estimates that in 1989 the Federal Government spent over $325 million on training support for over 14,000 postgraduate trainees in the biological sciences (see table 9-1).5 (This does not include the billions of dollars spent on general training support for undergraduate and graduate education through the Federal student financial aid programs administered by the U.S. Department of Education.) About 25 percent of graduate students pursuing a doctoral degree in the biomedical sciences receive a training grant from NIH (207).

Over the last 10 years, the number of doctoral-level biomedical research jobs in industry has grown about 12 to 13 percent per year compared with an average 4.9 percent increase for biomedical research jobs in all sectors (207). Pharmaceutical companies make more intensive use of trained scientific personnel than do firms in other industries. While all industries together employ 27 trained scientists or engineers per 1,000 employees, the pharmaceutical industry hires 62 per 1,000 employees (figure 9-3).

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1 The other most common sources of funding for biomedical research facilities are State and local government and debt financing by the research institution itself (207).

2 Well-publicized agreements between universities and industry in the health sciences that include the construction of new facilities are noteworthy for their size, but they have been limited to a few of the most research-intensive universities.

3 Remaining Federal and NIH research money went to industry, Federal, State and local governments, and private nonprofit organizations not engaged in higher education.

4 OTA published a more detailed discussion in 1991 of the strengths and limitations of data on scientific research and training in the united States (452).

5 Most awards for training biomedical researchers are funded as National Research Service Awards (NRSAs). Most NRSA traineeships go to educational institutions that in turn award them to predoctoral trainees for up to 5 years and postdoctoral for up to 3 years. After completing their training, awardees must conduct biomedical research for 1 month for every month they received support. Those who do not provide this research ''payback' must reimburse the government for their awards.

Table 9-I—Federal Research Training Support Targeted for the Life Sciences *In* 1989

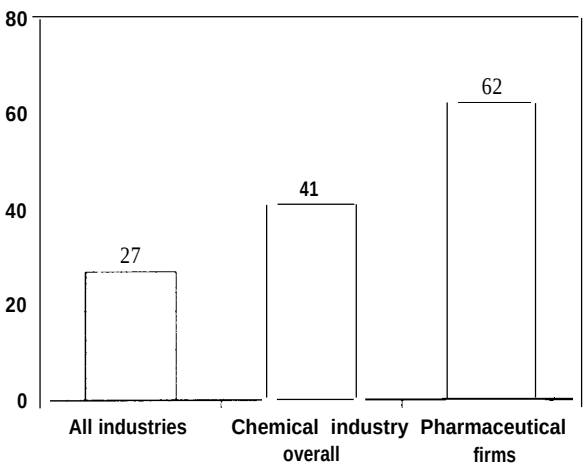
Agency	Number of trainees supported			Funds for research training ($ millions)	Other characteristics
	Predoctoral	Postdoctoral	Total		
National Institutes of Health (NIH)	6,216	5,369	11,585	$256.0	For both NIH and ADAMHA, all but 1,150 awards require recipients to conduct research 1 month for each month supported after completing training.
Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA)[a]	720	567	1,287	27.1	Includes approximately 630 awards for behavioral research training
National Science Foundation (NSF)	NA	NA	1,361	12.8	Training support is provided through research funds to principal investigator who hire trainees.
U.S. Department of Energy (DOE)	200	10	210	30.7	
Totals			14,443	$326.6	

a In 1992, the research institutes administering ADAMHA's training awards were made part of NIH under Public Law 102-321. The remainder of ADAM HA became the Substance Abuse and Mental Health Services Administration.

KEY: NA = not available.

SOURCE: Office of Technology Assessment, 1993.

Figure 9-3-Number of Trained Scientists and Engineers Per 1,000 U.S. Employees



SOURCE: Office of Technology Assessment, 1993. Based on data from J.P. Swarm, *Academic* Scientists *and the* Pharmaceu*tical Industry: Cooperative Research in Twentieth Century America* (Baltimore, MD: The Johns Hopkins University Press, 1988).

Training support for graduate students and postdoctoral fellows comes not only through formal training grants, but also through employment as research assistants (RAs) on grants or contracts supported by Federal funds. About 52 percent of all graduate students with training support from DHHS in 1988 reported their work as RAs was the major form of such aid (289) compared with only 31 percent in 1981.

The Federal investment in R&D infrastructure outlined above made possible the fundamental knowledge and techniques upon which current drug discovery depends. The advances in molecular biology, which form the core of biotechnology (445), include recombinant DNA processes, monoclinal antibodies, and gene synthesis and splicing. Chapter 5 discusses the importance of these techniques in today's pharmaceutical R&D process. These advances were made, for the most part, in university laboratories and relied heavily on Federal support.

Private industrial firms also provide predoctora1 or postdoctoral training in the life sciences

through scholarships, fellowships, and other training grants as well as other research support in universities. About 6 percent of life science trainees (advanced graduate students and postdoctoral fellows) at six research-intensive universities surveyed by Blumenthal and colleagues in 1985 received training grants or scholarship support from industry (151).6 Other types of involvement with industry also provided financial benefit to trainees. In all, about 19 percent of life science trainees in the six universities studied by Blumenthal and colleagues reported receiving research salary, training grants, or scholarships directly from industry; another 15 percent worked in the laboratories of faculty advisers who received industrial research support.

Industry support appears to be more restrictive than that of government. Of students and fellows reporting scholarships or training grants from industry, about 35 percent were required to perform some activity of direct benefit to the sponsoring firm, such as working for the company (151). And, while the average research training award at NIH in 1984 was $12,385 for graduate students and $22,425 for postdoctoral fellows, the mean award for training grants or scholarships from firms involved in biotechnology ranged from approximately $4,551 to $9,181 per award (150). Thus even when industry has provided training support for universities in the life sciences, the support is more restrictive than is Federal support.

COLLABORATION BETWEEN PHARMACEUTICAL FIRMS AND ACADEMIA

Collaborative arrangements between academic researchers and pharmaceutical firms represent an implicit transfer of federally supported research and knowledge to the private sector. As opportunities to commercialize; research findings in the life sciences have grown, so too has interest in commercial relationships designed to make use of these results in the marketplace (445).

The pharmaceutical industry has a long tradition of cooperation with academia (415). When World War I eliminated the supply of pharmaceuticals from Germany, American drug companies realized the need to develop their own products. They established ties with universities in order to recruit scientific manpower and to capitalize on academic research with pharmaceutical potential.

Academics were receptive to such cooperation (415). During the postwar period, U.S. pharmaceutical firms established multifaceted strategies for cooperation with universities. They built ties with academic scientists by attending scientific meetings in force, visiting academic laboratories on a regular basis, sponsoring lectures by academic scientists at company facilities, sponsoring awards through academic societies, and developing lists of leading scientists within relevant fields to receive regular written updates on advances occurring within industrial laboratories. They also began to sponsor fellowships and trainees in universities. Between 1925 and 1930, for example, Squibb spent a seventh of its research budget on such fellowships (415).

Collaboration between academia and the pharmaceutical industry on *basic research* diminished steadily between 1940 and the 1970s as alternative sources of support for university research (mainly the government) increased and as the growth in industrial research laboratories reduced firms' reliance on academia (415). Yet, the amount of *clinical research* sponsored by the industry and conducted by academia grew significantly over this period, particularly after the 1962 amendments to the Food, Drug and Cosmetic Act (21 U.S.C. 301 et seq.) required drug sponsors to establish effectiveness as well as safety of new products.

Clinical research requires collaboration with academic medical centers that have the physician-

[6] Although these six universities are not representative of all institutions that train young biomedical researchers, the survey does provide insight into the role of industry in the training of students and fellows in very research-intensive universities. Such young researchers are Likely to constitute the next generation of scientific leadership (151).

researchers, the patients, and the infrastructure to test new drugs. Hence, even as university-industry relationships revolving around laboratory research diminished in the 1950s to 1970s, pharmaceutical firms maintained formal and informal clinical relationships with academia.

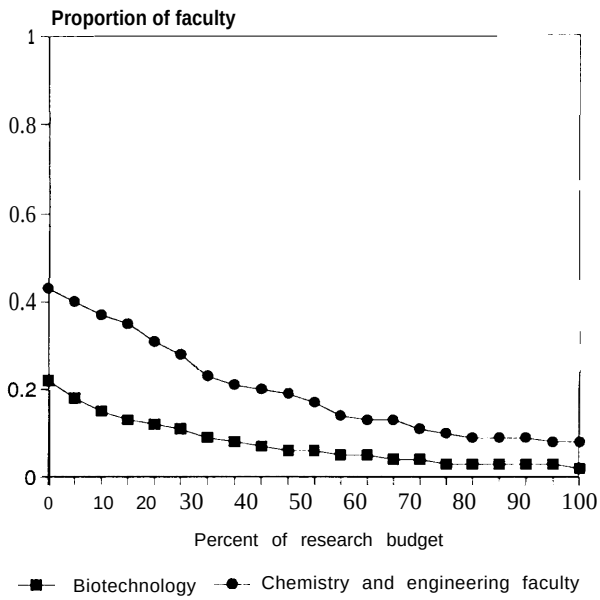
Beginning in the late 1970s, the number of collaborations with universities during the discovery phase of research began to expand once more. Most observers have tied this trend to the development of biotechnology techniques in university laboratories (228,415,445). Large pharmaceutical firms turned to academia to learn these techniques. In many instances, the principal founders of new biotechnology companies came from academia and attempted to keep their university affiliations. In the 1980s academic scientists and venture capitalists, recognizing the value of these advances in the life sciences, sought to commercialize university research through startup firms that also maintained close relationships with academic laboratories (228).

Today's collaborations take place against a backdrop of pervasive government funding for biomedical research in academia. Even within the individual academic research laboratory, financial support from industry coexists with more extensive government support. As figure 9-4 indicates, in 1984 less than one-quarter of principal investigators in the life sciences who used biotechnological techniques at 40 of the 50 most research-intensive universities received *any* support from industry (53). In addition, the vast majority of those faculty who received *any* research support from industry still get most of their research support from government and the nonprofit sector; only 10 percent of principal investigators receive more than 25 percent of their research support from industry. In comparison, faculty members in chemistry and engineering receive industrial funds almost twice as frequently.

Four Kinds of University-Industry Collaborations

There are at least four kinds of collaboration between academia and the pharmaceutical industry. The two most common are project-specific research support and consulting arrangements with pharmaceutical firms. Two less common forms of collaboration-large-scale, multiyear, investments in academic research centers by private companies and ownership or control of industrial firms by a university or its faculty—have received much more popular attention in recent years, perhaps because of their novelty in the life sciences and their potential impact on traditional academic values and norms of behavior (228).

Figure 9-4—Proportion of Faculty Receiving a Given Percent or More of Research Budgets From Industry, 1984



SOURCE: Reprinted with permission from D.B. Blumenthal, M.E. Gluck, K.S. Louis, et al., "University-Industry Relationships in Biotechnology Implications for the University," *Science* 232:1361-1366, 1986.

[7] The **data** also indicate that the vast majority of life scientists responding to the survey (81 percent) used biotechnological techniques.

Table 9-2—Large-Scale Pharmaceutical R&D Agreements Between Universities and Industry

Partners (university/firm)	Funds ($ millions)	Duration (years)	Year established	Area
Harvard University Medical School/Monsanto	$ 23.5	12	1974	Cancer angiogenesis
Leicester University/ICI	4.2	12	1978	Genetics
Massachusetts General Hospital/Hoechst	70.0	12	1981	Molecular biology
Scripps Institute/Johnson & Johnson	30.0	Open-ended	1981	Synthetic vaccine
Washington University/Mallink	3.8	5	1981	Hybridomas
Harvard University Medical School/Dupont	6.0	5	1981	Genetics
Yale University/Celanese	1.1	5	1981	Enzymes
Johns Hopkins University/Johnson & Johnson	1.0	Open-ended	1982	Biology
Rockefeller University/Monsanto	4.0	5	1982	Photosynthesis
Washington University/Monsanto	100.0	12	1982	Biomedical research
Yale University/Bristol Myers	3.0	5	1982	Anticancer drugs
Cold Spring Laboratory/Exxon	7.5	5	1982	Molecular genetic
Rochester University/Kodak (Sterling)	0.5	Open-ended	1983	DNA
Columbia University/Bristol-Myers	2.3	6	1983	Gene structure
Oxford University/Monsanto	20.0	5	1983	Glycoproteins
Georgetown University/Fidia	62.0	Open-ended	1985	Neuroscience
Harvard Medical School/Takeda	1.O[a]	Open-ended	1986	Angiogenesis factors
Oxford University/Squibb	32.0	7	1987	Pharmacology (central nervous system)
Johns Hopkins University/SmithKline Beckman	2.2	5	1988	Respiratory disease
Cambridge University/SmithKline French	4.0	5	1988	Molecular medicine
Oxford University/Beecham	8.0	10	1989	Neuropsychobiology
University of London P/Squibb	47.0	7	1989	Molecular biology: proteins
Massachusetts General Hospital/Shiseido	85.0	1	1989	Dermatology
University College London/Eisai	75.0	15	1990	Neuroscience
Harvard University Medical School/Hoffman-LaRoche	10.0	5	1990	Medicinal chemistry
Massachusetts General Hospital/Bristol-Myers Squibb	37.0	5	1990	Cardiovascular
University of California at San Diego/Ciba Ceigy	20.0	6	1990	Rheumatoid and osteoarthritis

a Harvard Medical School/Takeda contract is $1 million per annum (open-ended).

SOURCE: A.J. Webster and H. Etzkowitz, *Amdemic-industry Relations: The Second Academic Revolution: A Framework Paper for* a *Proposed Workshop on Academic-Industry Relations* (London, England, Science Policy Support Group, 1991).

Support for specific research projects by firms that use the techniques of biotechnology in their R&D totaled between $85 and $135 million in 1984, or between 8 and 24 percent of all funds available for biomedical research in academia (51),[8] Spending per project was less than the average size of NIH grants, and they were typically of a shorter duration suggesting industrially supported research can be more focused and applied in nature than that funded by government (51,483).

Life science faculty at major research-intensive universities also receive support through *consulting arrangements* with private firms. About 40 percent of such faculty had consulted with industry for money at least once over the 3-year period ending in 1984 (53).

Large-scale collaborations between pharmaceutical companies and academia are largely a phenomenon of biology and pharmacology (5 11). Although these agreements may represent extensive support and collaborative opportunities for the faculty involved, they are relatively infrequent. Table 9-2 lists the bulk of such relationships of direct or indirect relevance to the pharmaceutical industry. In some cases, the industrial partner may create an entire physical structure in which industrially-supported work

[8] Because biotechnology has applications beyond biology and medicine, some of this estimated industrial support of academic research went for work in fields such as agriculture.

takes place; in others the company may support research in an existing academic facility.

Among other potential benefits to the industrial partner, some collaborations allow the placement of company scientists in university laboratories. Table 9-2 shows the industrial commitment in these relationships is often for a longer period than is industrial project-specific support. Though some systematic research about the structure, workings, and scientific or commercial outcomes of these large collaborations is currently underway, little is known about them today (228,512).

Private industrial ventures begun by universities or their faculty have created controversy about the appropriate limits of commercial activities on campus. Such startup ventures come in two main varieties: 1) commercial ventures established directly by the university to commercialize academic research and to benefit the school financially; and 2) firms founded by individual faculty members to commercialize their own research, usually for the financial benefit of the founders and other stockholders.

One of the earliest universities to try to capture the commercial benefits of its faculty's research is the University of Wisconsin, whose Wisconsin Alumni Research Foundation (WARF) dates from the 1920s. All faculty at the University of Wisconsin are required to assign the rights to patents arising from their work to the independent WARF, which then attempts to license the technology. Proceeds are shared by the university and the inventing faculty member. The vast majority of all its income is attributable to a single early patent of importance to the dairy industry, which suggests that such enterprises may be unable to generate much patent income for the university **(50).**

Despite the mixed success of the WARF example, during the 1980s a number of other research-intensive universities created similar institutions to commercialize campus research. The growth of these arrangements is partly due to the increasing opportunities to commercialize academic life science research and partly to a 1980 change in law that gave universities sole ownership of patents arising from government-sponsored research (Public Law 96-517)[9] (228).

An important feature of almost all these enterprises is that they are organizationally independent of the universities that own them. The separation is intended to prevent commercial considerations from perverting the traditional academic values of the university.

Critics of these arrangements have questioned whether true organizational separation is possible given the frequent involvement of individuals with strong ties to the parent university in the decisions of the commercial enterprise (50,228). Indeed, Harvard University soundly rejected a 1980 proposal to establish a firm to commercialize research because it was considered incompatible with the university's central missions of learning and the pursuit of knowledge (54). By 1988, the attitude had changed; the university reversed itself by establishing Medical Science Partners, an enterprise designed to commercialize biomedical research findings in a manner similar to WARF. In doing so, the university faced little of the faculty questioning or media attention that accompanied the 1980 proposal (514). To date, no evidence is available on whether these enterprises have in fact stimulated commercialization of research findings or whether the earlier fears of the critics were justified.

In the 1980s, many faculty in the life sciences founded companies with products or services based on their own research (445,450). Some early products based on biotechnology (such as diagnostic tests using monoclinal antibody technology) had a relatively fast R&D period, thus

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[9] The Bach-Dole Patent and Trademark Act of 1980 (Public Law 96-517) gave universities, nonprofit organizations, and small businesses the rights to inventions resulting from research supported with Federal grants. It also required these institutions to share any royalty income from patents with the individuals responsible for the invention. Congress extended these patent rights in 1984 to Federal laboratories operated by universities and nonprofit corporations (Public Law 98-620).

generating early revenues and increasing interest in such enterprises among other faculty and the investment community (419).

Faculty-founded companies led universities to question how deeply involved in the commercial enterprise a faculty member should become while maintaining his or her university affiliations (228,415,5 11). In recent years, some universities have banned faculty equity holding in firms that support the faculty members' own research, while others have relied on faculty disclosure of such financial interests and a case-by-case consideration of their appropriateness (51,331).

Although individual cases have been controversial, the scanty evidence that exists suggests the phenomenon of faculty equity-holding in commercial enterprises is actually very infrequent. In 1985 only 8 percent of faculty involved in biotechnology at universities reported holding equity in a firm whose products or services were based on their research (53). In addition, only 0.5 percent held equity in firms from whom they also received support for their university research. Although responding faculty may have underreported these activities, the 8 percent no doubt includes equity ownership in nonstartup fins.

Issues in Current University-Industry Collaborations

During the early 1980s, as the frequency of industrial collaborations grew, so did questions about their ethical implications for the university and the appropriate balance between the potential risks and the benefits gained by the transfer of academic research to productive industrial applications (54,234). Among the most often-mentioned potential risks of university-industry collaboration are conflicts over faculty time commitments to the university, conflicts of interest for faculty who are in a position to benefit financially from their university laboratory research, and increased secrecy or other restrictions on the dissemination of industrial research results.

There is little evidence that the behaviors associated with these risks are at all widespread. Although one survey found that a minority of faculty has done some research in which the results could not be published without consent of the sponsor, the faculty who collaborate with industry tend to be among the most productive (53). They publish and teach more than their colleagues, so commitment to the academic institution appears not to be a big problem.[10] As indicated earlier, the potential for conflicts of interest arising from faculty involvement in startup firms appears to exist in only a very small minority of cases. Furthermore, in the last 2 years, the Federal Government and the research community itself have taken steps to prevent researchers from having any financial interest in the outcome of research they conduct.11

TARGETED FEDERAL PHARMACEUTICAL R&D PROGRAMS

In addition to the general research and training support that makes up the life science research infrastructure, NIH and other parts of the Federal Government have established 13 programs specifically targeted to fund pharmaceutical R&D.

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10 Data from the surveys conducted by Blumenthal and colleagues (52) suggest that while fins' expectations of their academic collaborators may vary, there is a general consensus about what constitutes acceptable behavior for academics who collaborate with fins. For example, patent rights arising from industrially supported research are expected to be owned by the university, although firms sometimes may have the right of first refusal for exclusive licensing for some period of time. Researchers have a right to publish and are usually not expected to protect trade secrets for a firm (52). A recent survey of graduate school deans suggests there has been increasing administrative attention to these ethical issues on campus as measured by the adoption and revision of university policies governing student and faculty communication of research results, teaching commitments, and interactions with industry (249).

11 For example, in 1989, the *New England Journal of Medicine* (NEJM) adopted a policy that required authors to Sign a Statement that they had no personal financial interest in a firm that could benefit from the outcome of research reported in articles submitted to the journal for review and possible publication (347). The American Medical Association House of Delegates has considered the issue, and the *Journal of the American Medicu/Association has* adopted policies similar to those of NEJM (10). NIH is spearheading an effort for the Public Health Service to develop similar guidelines for the recipients of Federal health research funds. In April 1989, NIH solicited comments on proposed regulations (54 FR 17828), but has not yet issued a revised set of guidelines.

There are also cases in which federally supported research projects incidentally, but directly, influence pharmaceutical R&D, even though the government is pursuing research goals far removed from the discovery and development of new therapies. Consider a hypothetical research project:

> in an effort to understand the physiology of a particular disease, researchers test the hypothesis that the absence of a substance naturally produced by the body (such as an enzyme or protein), but largely lacking in patients suffering from the condition, actually causes the disease. The research involves administering to people with the disease a pharmaceutical compound that is used to treat another disease but is known to stimulate the body's production of the missing substance. The researchers' main objective is to understand whether providing the substance alleviates the disease, However, the research may also benefit the makers of the drug or biological who now have a potential new indication for which they may seek Food and Drug Administration (FDA) approval.

This mixing of basic research with more applied efforts that directly advance the development of new drug therapies makes it difficult to sort out the exact nature of any implied subsidy of private pharmaceutical R&D. OTA's discussions with Public Health Service (PHS) officials and its reviews of federally supported biomedical research projects suggest the use of potential pharmaceutical compounds in projects aimed at increasing basic understanding of diseases can be a common form of such hybrid work. Thus, it is difficult to assess how much of a research project represents targeted drug R&D as the private sector would perform it, how much merely aids such private efforts but does not mimic it, and how much is clearly unrelated to the drug R&D process. Box 9-A provides several examples of the link between federally supported basic research and the development of new drugs.

OTA identified 13 programs within the Federal Government whose specific mission is to conduct R&D involving actual or potential pharmaceutical products. There is no ambiguity in these

Box 9-A–Examples of the Link Between Basic Federal Biomedical Research and the Development of New Drugs

All basic research supported through the disease-oriented institutes of NIH and ADAMHA contributes to the ability to research and develop new pharmaceuticals by increasing fundamental understanding of normal and diseased functioning of living organisms. The line where untargeted basic research ends and targeted drug discovery begins is hazy at best. About $4.4 billion of the $6.9 billion appropriated for R&D at the Public Health Service in 1989 was for basic research.[1] The results of this public funding for basic research provide a necessary foundation for subsequent pharmaceutical R&D. The following three examples show how basic research in the biological sciences ultimately affects the introduction of new pharmaceutical products.

. In the early 1960s, scientists at the National Eye Institute (NEI) showed that cataracts (an obstruction of the lens of the eye) in animals with diabetes were due to the formation and accumulation of polyols (sugar alcohols). They discovered that an enzyme, aldose reductase, converts blood sugars (which are found in high levels in diabetics) into polyols. The sugar alcohols accumulate in cells, weaken the cell membrane, and eventually leak out of the cell, causing the cataracts. The discovery of aldose

[1] According to National Science Foundation definitions, "in basic research, the objective of the sponsoring agency is to gain fuller knowledge or understanding of the fundamental aspects of phenomena and of observable facts without specific applications toward processes or products in mind. " Hence, this would exclude any research where the goal is to identify, characterize, or test an actual, potential pharmaceutical product.

(Continued on next page)

Box 9-A–Examples of the Link Between Basic Federal Biomedical Research and the Development of New Drugs--(Continued)

reductase and its role in diabetic cataracts led scientists to search for therapies that block the enzyme's action. The resulting class of drugs, aldose reductase inhibitors (ARIs), became the first therapies for diabetic complications that are unaffected by other treatments for diabetes itself (i.e., insulin used to lower blood sugar levels).[2] Current NEI research is intended to understand the role of aldose reductase and polyols in causing other complications of diabetes, including nerve and kidney damage.

- Since 1987, the National Institute of Allergies and Infectious Diseases (NIAID) has provided just under $3 million in grant support to three projects of research on the structure, functioning, and replication of rhinoviruses, which are estimated to cause 50 percent of common colds. The purpose of this support is to provide enough fundamental understanding of these viruses that pharmaceutical companies will be willing to invest in the development of preventive or therapeutic drugs. Laboratory analysis funded by NIAID has identified unique features of all rhinoviruses and has led to the development of drugs (called WIN compounds) that block viral replication in animals. Study of these drugs in animals (funded by NIAID) in turn increased fundamental scientific understanding of how the viruses behave in the body. At the same time, Sterling Winthrop pharmaceuticals has recently received investigational new drug (IND) status to test WIN compounds in humans.[3]
- Over the last 15 years, the National Institute on Drug Abuse (NIDA) provided sustained support for basic research to understand the specific mechanisms by which opiates affect brain cells and cause pain relief, addiction, and various side effects. In particular, NIDA-supported scientists have found that different opiate compounds attach themselves to brain cells at different places. This understanding has provided researchers with leads with which to seek medications to treat drug addictions. The NIDA-supported discovery of how opiates affect brain cells also provided scientists with a technique for rapidly screening potential pharmaceuticals that may act upon brain cells; researchers can determine if the pharmaceutical candidate 'binds' to a desired 'binding site' found on brain cells, and whether or not it also binds to undesired sites. This screening technique has been used by academic and industrial researchers in the development of new pain relievers and antipsychotic drugs among other types of pharmaceuticals.

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2 NEI also played a major role in clinical testing of these therapies by jointly designing, funding and conducting with Pfizer Pharmaceuticals a 5-year multicenter, randomized clinical trial of Pfizer's investigational ARI, Sorbinil™, in patients with diabetes. This Sorbinil Retinopathy Trial (SRT) showed that this particular ARI compound was not significantly effective and caused adverse reactions in some patients.

3 Neither NIAID Or any other research agency of the Federal Government has provided support for these clinical studies.

SOURCE: Office of Technology Assessment, 1993. Based on data from: Dvornik D., Simard-Duquesne N., Kraml M., et al., "Inhibition of Aldose Reductase in Vivo," Science 182:1146-1147, 1973; Groft, S., Acting Director, Office of Science Policy and Legislation National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Bethesda, MD, personal communication, February 8, 1991; Heinz, B.A., Ruechert, R., Shepard, D.A., et al., "Genetics and Molecular Analyses of Spontaneous Rahino Virus #14 Mutants of H- Cells that are Resistant to an Antiviral Compound," *Journal of Virology* 63:2476-2485, 1989; Kinoshita, J.H., *"Cataracts in* Galactosemia," *Investigative Ophthalmololgy and Visual Sciences* 5:786-789, 1965; Kinoshita, J.H., Dvornik, D., Draml, M., et al., "The Effect of an Aldose Reductase Inhibitor on the Galactose-Exposed Rabbit Lens," *Biochimica et Biophysica Acta* 158:472-475, *1968;* Kinoshita, J.H., "Mechanism Initiating Cataract Formation," *Investigative Ophthalmology and Visual Sciences* 13:713-724, *1974;* National Science Board, Science and *Engineering Indicators-1989*, NSB Pub. No. 89-1 (Washington, DC: Us. Government Printing Office, 1989); Pevear, D.C., Fancher, M.J., Felock, P.J. et al., "Confirmation and Change in the Floor of Human Rahino Virus Canyon Blocks Adsorption to HeLa Cell Receptor, "*Journal of Virology 63:20(X2-2(X17, 1989;* Rossman, M.G., "The Structure of Antiviral Agents that Inhibit Uncoating when Complexed with Viral Capsids," *Am#viral Research* 11(1):3-13, 1989; Sakamoto, N., Kinoshäita, J.H., Kador, Pi:, and Hotta N (eds.), *Polyol Pathway and its Role in Diabetic Complications: Proceedings of the International Symposium on Polyol Pathways and their Role in Diabetic Complications (New* York, *NY:* Excerpta Medica, *1988);* Science, "The Microchip Microbe Hunters," *Science* 247:804-806, 1990; Van Heyningen, R., "Formation of Polyols by the Lena of the Rat witb Sugar Cataract," *Nature* 184:194-196, 1959.

programs. They are intended to make new therapies available through public funding of R&D. Together, these 13 programs accounted for $387 million in spending in fiscal year 1989, about 55 percent of the total (preclinical and clinical) government-sponsored drug R&D estimated by OTA in the next two sections. It is impossible to estimate the proportion of these funds devoted to preclinical research, because most of the 13 programs support both clinical and laboratory research.

One program--National Cancer Institute's (NCI) Cancer Therapy Evaluation program, which accounts for 78 percent of the $387 million fiscal year 1989 funding-is devoted exclusively to clinical testing of cancer drugs. The NCI drug development programs together accounted for roughly 80 percent of all funds for Federal dedicated drug development programs in fiscal year 1989 (see table K-1 in appendix K). All but one of these programs, the Department of the Army's Antimalarial Program, are at NIH.[12]

The 13 programs vary in size, purpose, and methods of operation. Some have significant intramural laboratory programs; others are extramural grant and contract programs. Appendix K contains a summary of the 13 Federal dedicated pharmaceutical R&D programs.

What is the justification for direct public spending on targeted drug discovery? In certain cases, public health authorities have determined that national priorities necessitate public investment to speed the process of developing new therapies. Illnesses related to human immunodeficiency virus (HIV) is one example. There may also be barriers to private-sector involvement. The orphan drug programs exist because some conditions affect so few patients that the private sector might otherwise find investment in potential treatments financially unprofitable.

In another example, the National Institute on Drug Abuse suggested to OTA that private pharmaceutical firms have traditionally shown little interest in medications to treat substance abuse because of difficulties in getting clinical research subjects to comply with research protocols (343). It is also possible that firms perceive products for substance abuse treatment to represent relatively low potential returns, perhaps because of limited third-party coverage of such services.

Another reason the Federal Government conducts or supports targeted drug discovery is the difficulty of distinguishing basic from applied investigation. At least one long-time observer of science policy, Donald E. Stokes, has noted that most research projects have at once basic and applied qualities (410). Another observer has suggested that making such separations in the life sciences has become more difficult in the last 15 years as the development of new biotechnological techniques has ''collapsed" the amount of time traditionally needed to move from basic scientific understanding to potential products, including drugs (306).[13]

Federal Support for Preclinical Drug R&D

OTA asked NIH and the former Alcohol, Drug Abuse and Mental Health Administration (ADAMHA), which together makeup the bulk of Federal health-related R&D, to estimate all of their expenditures for preclinical drug discovery, whether or not such expenditures were made as part of one of the targeted drug development programs described above.

The results must be considered rough estimates, because the institutes did not uniformly follow OTA's guidelines for classifying research projects, and some institutes were unable to

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[12] One of the programs, the Drug Abuse Medication Development Program, is administered by the National Institute 011 Drug Abuse (NDA) which was part Of ADAMHA until 1992. Recent legislation has moved this institute to NIH (Public Law 102-321).

[13] T. make the division of labor between the Federal Government and private industry even less tidy, most industrial scientists interviewed by OTA during our visits to eight pharmaceutical firms stressed that while their primary mission is to bring new drugs to market, their work can also produce advances in basic scientific understanding. Such industrial contributions to the scientific literature are borne out by analyses of bibliographic and citation databases (286).

Table 9-3--Estimates of NIH and ADAMHA Research Support for Preclinical Pharmaceutical Screening, Synthesis, Evacuation and Development Activities, Fiscal Years 1988-90($ thousands)

	Fiscal year 1988	Fiscal year 1989	Fiscal year 1990
NIH			
NCI	$283,576	$308,851	$316,729
NHLBI[a]	28,324	31,983	28,350
NIAID[b]	46,603	52,358	64,897
NIDDK[c]	8,500	9,417	9,700
NICHD[d]			
NIA[a]	1,265	0	955
NINDS[e]	4,812	6,168	5,079
NIDR[f]	14,165	14,918	11,056
NCRR[g]	10,502	12,296	11,485
NIAMS[c]	284	275	618
NEI		6,420	8,557
ADAMHA[h]			
NIMH	N/A	N/A	N/A
NIDA	N/A	N/A	28,843
NIAAA	N/A	6,286	13,261
Total[i]	398,031	448,972	499,530

a NHLBI, NIA: Data are institutes' best estimates.
b NIAID: Based on narrow definition of drug development; may differ from earlier NIAID reports.
C NIDDK: Estimates include clinical research.
d NICHD: National drug development and clinical research cannot be separated; both included in clinical estimates (table 9-5).
e NINDS: Estimates prior to fiscal year 1990 with approximately 1o percent variance.
f NIDR: Fiscal year 1990 is the most accurate; others are likely overestimates.
g NCRR: Includes clinical research involving pharmaceutical development.
h ADAMHA: Data not available for following institutes and years: NIMH—fiscal years 1988 and 1989; NIDA—fiscal year 1988; NIAAA—fiscal years 1988, 1989, and 1990.
i Totals are only an approximation since data for several institutes are missing (counted as zero) and data for others indude clinical activities.

KEY: ADAM HA = Alcohol, Drug Abuse and Mental Health Administration. NCI = National Cancer Institute. NCRR = National Center for Research Resources. NEI = National Eye Institute. NHLBI = National Heart, Lung and Blood Institute. NIA - National Institutes on Aging. NIAAA. National Institute on Alcohol Abuse and Alcoholism. NIAID = National Institute of Allergy and Infectious Diseases. NIAMS = National Institute of Arthritis and Musculoskeletal and Skin Diseases. NICHD = National Institute of Child Health and Human Development. NIDA = National Institute on Drug Abuse. NIDDK = National institute of Diabetes and Digestive and Kidney Diseases, NIDR = National Institute of Dental Research. NIH - National Institutes of Health. NIMH = National Institute of Mental Health. NINDS = National Institute of Neurological Disorders and Stroke.

SOURCE: Office of Technology Assessment, 1993. Based on data provided by individual institutes of the Public Health Service, U.S. Department of Health and Human Services.

provide any estimates at all. Total estimated preclinical pharmaceutical R&D constituted approximately $450 million in 1988 (table 9-3), about 6 percent of the overall combined research budgets of NIH and ADAMHA. Such activity is highly concentrated at NIH, with a majority falling within the National Cancer Institute. OTA also estimated that NIH and ADAMHA's 1988 preclinical drug research spending of $400 million represented roughly 14 percent of the amount spent by private pharmaceutical firms for similar R&D functions (table 9-4).

Table 9-4-Estimates of NIH and ADAMHA Preclinical Pharmaceutical Research Support as a Percentage of PMA Firms' Expenditures for Preclinical R&D Activities, Fiscal Year 1988

	Estimate
A. PMA firms' R&D for human ethical pharmaceuticals	$6.31 billion
B. Percent preclinical[b]	44%.
C. PMA firms' preclinical R&D (A multiplied by B)	$2.77 billion
D. NIH/ADAMHA preclinical pharmaceutical R&D[c]	$ .40 billion
E. NIH/ADAMHA as a percent of PMA (D divided by C)	14%

a From Annual PMA Survey Reports, 1988-90.
b R&D functions included: '{biological screening and pharmacological testing," "synthesisand extraction, pharmaceutical dosage, formulation, and stability testing," and "toxicology and safety testing." Excluded functions: "process development for manufacturing and quality control," all "clinical evaluation," "regulatory, investigational new drug and new drug approval preparation, submission and processing," and "other."
c Assumption for middle estimate is a rough approximation based on data from individual institutes of the Public Health Service, U.S. Department of Health and Human Services (presented in table 9-3); assumption of high and low estimates are 50 percent higher and lower than middle estimate.

KEY: ADAM HA = Alcohol, Drug Abuse and Mental Health Administration; NIH = National Institutes of Health; PMA = Pharmaceutical Manufacturers Association.

SOURCE: Office of Technology Assessment, 1993.

Federal Support for Clinical Drug R&D

OTA also requested NIH and ADAMHA to provide estimates of clinical research involving pharmaceuticals. Table 9-5 presents estimates provided by NIH and ADAMHA. The participating institutes estimated that between $200 million and $250 million per year was spent on research involving clinical pharmaceutical investigation in the fiscal years 1987-90. Together NIH and ADAMHA clinical research in 1988 represented roughly 11 percent of clinical research conducted by Pharmaceutical Manufacturers Association (PMA) firms in that year (table 9-6).

These estimates by themselves divulge little about the nature of clinical pharmaceutical research directly supported by the Federal Government. OTA reviewed federally funded clinical research projects for four drugs approved for marketing in the United States by the FDA in 1987—lovastatin, fluoxetine, zuidovidine (AZT), and tissue plasmiogen activator (TPA). The results indicated that the clinical projects supported by NIH and ADAMHA institutes span the pre- and post-FDA-approval periods. Projects involving drugs already approved for marketing include attempts to better understand the efficacy or safety of the drug as well as investigations into potential new indications for its use. Pharmaceu-

Table 9-5—Estimates of NIH and ADAMHA Support for Clinical Research Involving Pharmaceuticals, Fiscal Years 1988-90 ($ thousands)

	Fiscal year 1988	Fiscal year 1989	Fiscal year 1990
NIH			
NCI	**$51,991**	**$55,072**	**$57,889**
NHLBI	22,555	**30,292**	**26,540**
NIAID [a]	61,394	**80,236**	**96,304**
NIDDK			
NICHD [b]	11,252	**12,512**	**11,107**
NIA [c]	2,686	**1,934**	**3,380**
NINDS [d]	23,324	**25,060**	
NIDR [e]	9,193	**8,127**	**5,246**
NCRR	6,502	**6,762**	**5,246**
NEI	6,523	**6,849**	**5,877**
ADAMHA [f]			
NIMH	7,782	**6,661**	**6,293**
NIDA		**16,500**	**17,500**
NIAAA			**1,227**
Total [g]	**203,202**	**250,005**	**237,977**

a NIAID: Fiscal year 1990 is rough estimate,

b NIDDK and NICHD: Clinical and drug development activities could not be separated. NIDDK estimates were reported as preclinical (table 9-3) NICHD figures were reported here (as clinical research)

c NIA: Data are best estimates; not based on CRISP search.

d NIDS: Fiscal year 1990 unavailable; fiscal year 1989 based on examination of abstracts from CRISP search; estimates for earlier years based on fiscal year 1989.

e NIDR: Figure for fiscal year 1990 is most accurate, based On review of abstracts; others are rough estimates.

f ADAMHA: Data not available for following institutes and years: NIDA—fiscal year 1988; NIAAA—fiscal years 1988 and 1989.

9 Totals are approximation since data for some institutes are missing (counted as zero) and data for others include nonclinical activities.

KEY: ADAM HA = Alcohol, Drug Abuse and Mental Health Administration. NCI = National Cancer Institute. NCRR = National Center for Research Resources. NEI = National Eye Institute. NHLBI = National Heart, Lung and Blood Institute. NIA = National Institute on Aging. NIAAA = National Institute on Alcohol Abuse and Alcoholism. NIAID = National Institute of Allergy and Infectious Diseases. NICHD = National Institute of Child Health and Human Development. NIDA = National Institute on Drug Abuse. NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases. NIDR = National Institute of Dental Research. NIH = National Institutes of Health. NIMH = National Institute of Mental Health, NINDS = National institute of Neurological Disorders and Stroke,

SOURCE: Office of Technology Assessment, 1993; based on data provided by individual institutes of the Public Health Service, U.S. Department of Health and Human Services.

Table 9-6-Estimates of NIH/ADAMHA Support for Clinical Pharmaceutical R&D as a Percentage of PMA Firms' Expenditures for Clinical R&D Activities, Fiscal Year 1988

	Estimate
A. PMA firms' R&D for human ethical pharmaceuticals	$6.31 billion
B. Percent clinical [b]	30°A
C. PMA firms' clinical R&D (A multiplied by B)	$1.89 billion
D. NIH/ADAMHA clinical pharmaceutical R&D [c]	$ .20 billion
E. NIH/ADAMHA as a percent of PMA (D divided by C)	11"A

a From Annual PMA Survey Reports, 1988-90.

b Clinical evaluation = phases 1, 11, III, and IV

c Estimate is based on data from individual institutes of the Public Health Service, U.S. Department of Health and Human Services (see table 9-5).

KEY: ADAM HA = Alcohol, Drug Abuse and Mental Health Administration; NIH = National Institute of Health; PMA = Pharmaceutical Manufacturers Association.

SOURCE: Office of Technology Assessment, 1993.

Box 9-B--NIH Clinical Trials Involving Cholesterol-Lowering Drugs

The class of cholesterol lowering drugs called HMG-CoA reductase inhibitors whose discovery and development is described in box 4-A has also been the subject of clinical research at NIH. In 1987, an advisory committee of the National Heart, Lung and Blood Institute (NHLBI) recommended that the institute fund a large-scale, multiyear trial to evaluate the long-term effectiveness and safety of this class of drug as a means of preventing fatal and nonfatal heart attacks among the elderly. Because the three drugs in this class currently on the U.S. market were approved on the basis of the short-term, 'surrogate' measure of effectiveness-whether or not they lowered levels of cholesterol in blood-there was no available empirical evidence as to whether these drugs actually prevented death, particularly among the elderly. Given that as many as 60 million people are estimated to have high cholesterol, but fewer than 1 million people currently receive drug therapy, the results of this investment by NIH could have inportant scientific and economic implications. On the one hand, the trial could reinforce the effectiveness of this drug, thus maintaining or brightening their market prospects. On the other hand, if the research suggests the drugs are not effective or carry unforeseen risks for patients, the market for these drugs could evaporate.

Although funds were not available to mount a full-scale trial, which was expected to cost at least $60 million and involve 5,500 research subjects at 16 **to 20** locations, NHLBI did fund a 2-year, $2.5-million pilot study to estimate the cost of the full-scale trial and to identify potential problems in carrying it out. The pilot study, called the Cholesterol Reduction in Seniors Program (CRISP), began in July 1990 at five sites (chosen by NHLBI through a competitive process) and involved 400 research subjects. In addition to measuring the rate at which potential subjects agree to participate in the trial and their compliance with the trial's protocol, the pilot study also collected data on side effects, the extent of cholesterol reduction observed, and a number of other measures of the drug's efficacy and long-term toxicity in elderly patients.

The three HMG-CoA reductase inhibitors currently available in the United States are manufactured by two firms: lovastatin and simvastatin by Merck, and pravastatin by Bristol-Myers Squibb. NHLBI invited each of the manufacturers to submit proposals to NIH for the use of their drugs in the trial. Because NHLBI considered the two companies' proposals to be equivalent, it suggested using both companies' products.

(Continued on next page)

tical firms typically provide the Federal Government with drugs used in federally supported trials at no cost; but the other costs of the trial are funded by the government.

The National Heart, Lung and Blood Institute's (NHLBI) potential support of a trial comparing the use of different HMG-CoA reductase inhibitors in treating high levels of serum cholesterol, described in greater detail in box 9-B, is an example of Federal support for clinical research on a drug--lovastatin--that is already marketed. Several other examples of federally supported investigations into new indications for drugs already marketed came from the National Institute of Mental Health (NIMH), which has supported trials testing new uses of a drug, fluoxetine, that is already marketed as a treatment for depression.

As in the case of AZT, a drug whose use in treating HIV was demonstrated in research at NCI during the 1980s, the Federal Government also supports trials whose results ultimately yield evidence of efficacy and safety necessary for an FDA marketing application. NCI's involvement with AZT was the result of an urgent, specific Federal initiative to find therapies for HIV and its related illnesses (276,493). Because of data limitations, OTA was unable to make any better estimate of how frequently the Federal Government funds clinical work that later becomes part of a fro's new drug application.

When NIH supports clinical research, part of the total health care expenses incurred by patients

When one of the companies rejected this proposal, NHLBI chose to use Merck's lovastatin because it had received FDA marketing approval first and had experienced a low rate of serious side effects during its, by then, 3 years on the market. The pilot study's protocol involved two different doses of the drug and a placebo.

Merck bore the costs providing both the drug and placebo, including its distribution. All remaining costs associated with establishing the trial, administering the drug, diagnostic tests, related patient care, data collection, and analysis ($2,5 million) were paid by the Federal Government through NHLBI. According to NHLBI, industry scientists were not directly involved in planning the clinical trial or developing its protocol. They have participated in a steering committee for the pilot study convened by NHLBI, although they had no access to the study's data until its completion.

The pilot study ended in June 1992, and investigators expect to publish results in the medical literature during 1993. Plans are currently underway to make the full cholesterol-lowering trial part of a large Antihypertensive and Lipid-Lowering Treatment for the Prevention of Heart Attack Trial, which will begin in the fall of 1993, Of the 30,000 research subjects that will participate in this trial, 12,000 will meet researchers' criteria to receive an HMG-CoA reductase inhibitor. The study will follow these patients for 5 to 7 1/z years, measuring heart attacks and long-term toxicity associated with the drugs. The researchers may also have sufficient statistical power to measure the potential effects of cholesterol reduction on overall mortality.

NHLBI has budgeted $78.3 million for the whole trial over 9 years, A protocol committee will convene in early 1993 to determine which drugs and what doses will be part of the trial. As of December 1992, NHLBI had entered into discussions with the relevant pharmaceutical manufacturers about their contributions to this effort. At a minimum, NHLBI hopes to receive drugs and placebos from the companies, but it may try to receive additional financial contribution as well in light of the importance of this research for the companies' markets. The role of pharmaceutical scientists (if any) in the design and administration of the trial is also yet to be determined.

SOURCE: Office of Technology Assessment, 1993. Based on information provided in personal communications from: S. Groft, NIH Office of Science Policy and Legislation, Feb. 8, 1991; C. Roth, Office of Policy and Legislation, National Heart Lung and Blood Institute, Dec. 22, 1992; J. Cutler, National Heart, Lung and Blood Institute, Dec. 22, 1992; David Gordon, National Heart, Lung and Blood Institute, Dec. 22, 1992; A. Garber, Assistant Professor of Internal Medicine, Stanford University, January 6, 1993.

enrolled in such trials is paid by the Federal Government. For those clinical trials conducted at the NIH clinical center, all services provided to patients are paid by the Federal Government (476). At other institutions, the cost of care associated with the research protocol is paid for by the Federal Government through research patient care rates established by the Department of Health and Human Services (DHHS). ''Usual patient care' (e.g., items and services furnished ordinarily to patients by providers under the supervision of a physician or other certified health professional) are typically paid by the patient or the patient's health insurer.

INDUSTRY COLLABORATION WITH FEDERAL RESEARCH LABORATORIES

The Federal investment in biomedical research includes a substantial amount of intramural research conducted in Federal Government laboratories. In 1990, about $2.6 billion was spent on intramural health research at laboratories operated by the Federal Government (483).[14]

Over the last 10 years, Congress and the Executive Branch have paid increasing attention

[14] In addition to in-house research, this includes program management and direct operations attributable to health R&D. A total of $1.4 billion of this amount is for R&D that was performed at NIH. The remainder was performed at ADAMHA, FDA, CDC, Department of Defense, the Department of Veterans Affairs, the Environmental Protection Agency, the Department of Energy, and the National Aeronautical and Space Administration.

to the role of these Federal research laboratories in fostering commercial innovation. Legislation was enacted to encourage the transfer of research results from Federal laboratories to private firms when commercial applications are feasible. This section reviews Federal. technology transfer activities within the Public Health Service, which contains NIH and other health research agencies.

Legislative History of Federal Technology Transfer Activities

Since 1950, the Federal Government has explicitly required Federal employees to report inventions created during the course of their work to the Federal Government (Executive Order 10096; 15 FR 389). Beyond this requirement, however, there was no uniform patent and licensing policy for ail Federal agencies until 1980 when Congress passed the Stevenson-Wydler Technology Innovation Act (Public Law 96-480).

The Stevenson-Wydler Act made the transfer of Federal technology to the private sector a national policy and duty of Federal laboratories. Among its provisions, the act required that Federal laboratories spend at least 0.5 percent of their research budgets on "Federal technology transfer activities." Additional legislation in 1984 directed the Department of Commerce to issue regulations governing licensing of technologies developed in Federal laboratories (Public Law 98-620; 50 FR 9801; 37 CFR 404).

These actions proved insufficient to bring about the intended level of formal interaction between government and industrial scientists (456), so Congress passed the Federal Technology Transfer (FIT) Act of 1986 (Public Law 99-502).

The FTT Act gives the Federal employee the right to his or her invention if the government determines the invention has no commercial value and does not intend to license it. The FTT Act also requires Federal agencies share at least 15 percent of royalties from any licensed inventions with the inventing scientists, and it directs agencies to establish cash awards for other personnel involved in productive Federal technology transfer activities.[15]

Most importantly, the legislation permits the establishment of formal cooperative research and development agreements (CRADAs) in which a Federal laboratory provides personnel, services, facilities, equipment or resources *(but not funds),* and a non-Federal party (e.g., a private company) provides finds, personnel, services, facilities, equipment or other resources for R&D.

The legislation does not provide any greater detail about the form or amount of resources each party must bring to a CRADA. It leaves implementation of a CRADA policy up to the relevant agency. As part of a CRADA, the Federal Government can agree in advance to grant licenses to the collaborating partner on *any* inventions resulting from research under the agreement. The use of CRADAs within the Public Health Service is discussed in greater detail later in this chapter.

Technology Transfer in the Public Health Service

NIH has taken the lead in implementing Federal technology transfer activities for PHS. Most of this responsibility has fallen to the Patent Policy Board (PPB), which recommends NIH policy, and to NIH's Office of Technology Transfer (OTT), which reports to the Board and carries on the administrative functions associated with technology transfer.[16] Federal technology transfer activities involving PHS laboratories and the private sector fall into three related areas: patenting policy, licensing policy, and CRADAs.

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15 The legislative history of the FTT Act stresses that it was not intended to alter any of the conflict-of-interest regulations that prevent current or former Federat employees from improperly benefiting from their government affiliation. At NIH, this includes limitations and prohibitions against renumeration from any outside source that has any formal agreement with an employee's laboratory or institute branch (478).

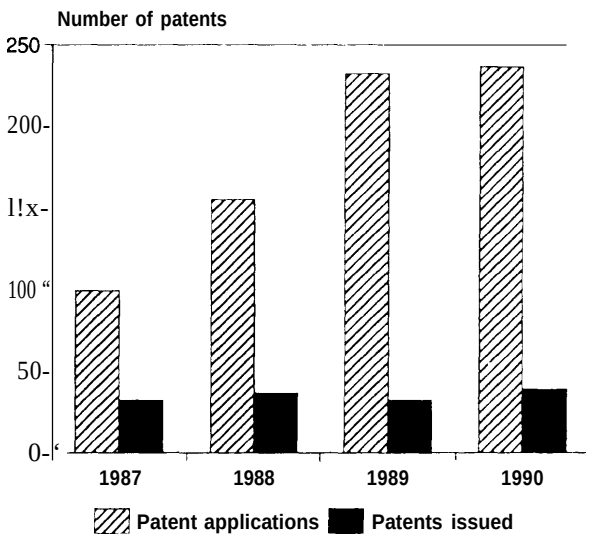
16 The bulk of PHS technology transfer activity occurs at NIH. Although the Patent Policy Board and OTT are located at NIH, they now also recommend policy and administer CRADAs, patents, and licenses for ADAMHA and the Centers for Disease Control (CDC), the other PHS agencies with technology transfer activities.

PATENTING INVENTIONS OF FEDERAL BIOMEDICAL RESEARCH LABORATORIES

When an invention is created in a PHS laboratory or under a CRADA the Federal employee involved must report it to a technology development coordinator located in his or her institute so that patent applications may be filed before the discovery is published or discussed at scientific meetings. The coordinator determines whether the invention is patentable.

The number of patents filed annually by PHS has grown dramatically since 1987, the frost year for which data on PHS patents are available. The number of applications more than doubled between 1987 and 1989 alone (figure 9-5). The number of patents awarded to PHS by the U.S. Patent and Trademark Office (PTO) in the same period did not increase, however, because of the substantial lag between application and award.[17] These trends indicate the financial incentives and organizational structure for patenting of inventions introduced in the FTT Act of 1986 had the desired effect.

Figure 9-5—Public Health Service Patent Applications and Patents Issued, 1987-90



SOURCE: The Office of Technology Assessment, 1993. Based on data from U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Office of Technology Transfer, 1991.

LICENSING INVENTIONS FROM FEDERAL BIOMEDICAL RESEARCH LABORATORIES

Outside parties who want to use patented PHS inventions must obtain a license from the Federal Government. Under all PHS licensure agreements, the licensee must agree to make all efforts to develop a commercial product with the licensed invention. PHS monitors progress toward commercialization and can revoke the license under certain circumstances.

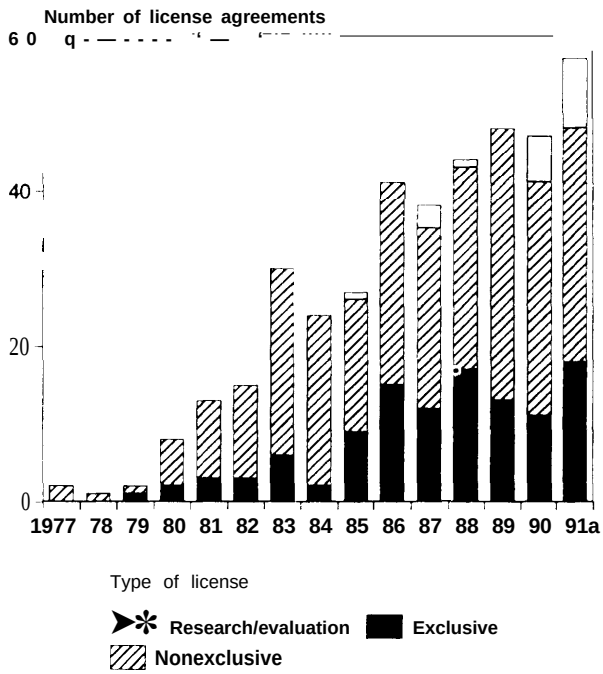
Royalties paid to the inventing PHS agency typically do not exceed 5 to 8 percent of the resulting product sales. The kinds of licenses available and the conditions under which they are given depend on the nature of the invention and whether or not it was developed as part of a CRADA (484,486). PHS grants exclusive *commercialization licenses* ‘ ‘*in* cases where substantial additional risks, time and costs must be undertaken by a licensee prior to commercialization” (484,486). Under CRADAs, collaborating firms may have the right to negotiate exclusive licenses to such inventions as part of the agreement itself.

Unless it receives a request for an exclusive license, PHS tries to negotiate *nonexclusive commercialization licenses* for inventions developed in its laboratories. Under such an agreement, PHS can license a single invention to more than one party. For both exclusive and nonexclusive licenses, PHS has developed a model agreement that is the basis for negotiations between it and the potential licensee.

PHS grants nonexclusive *research/evaluation licenses* to facilitate further research on the invention itself, but not for commercial production or as a substitute for commercially available research materials that the researcher could otherwise purchase. Research licenses are available even for inventions developed under a CRADA or

17 The General Accounting Office found that the average time between patent application and issuance in 1988 was 21.0 months for all patents and 29.4 months for those involving biotechnology (433).

Figure 9-6—Licenses Issued by the U.S. Department of Health and Human Services, Fiscal Years 1977-91



a Number in fiscal year 1991 annualized from the number of agreements reached during first 4 months of the year.

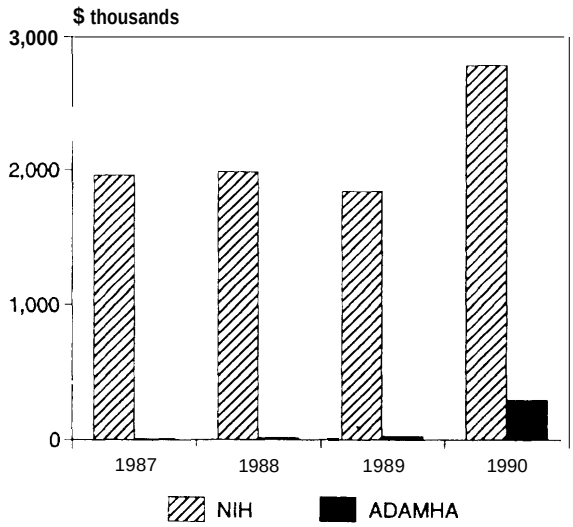
SOURCE: Office of Technology Assessment, 1993. Based on data from U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, office of Technology Transfer, 11991.

already the subject of an exclusive commercial license by another party.[18]

Figure 9-6 shows the number of licenses issued by the DHHS through 1991.[19] These data indicate a fairly steady growth in licensing that predates the implementation of the FTT Act and CRADAs. Given the lag between patent application and issuance, the licensing data displayed in this figure do not capture any additional growth that might result from PHS's efforts since 1986 to promote technology transfer.

Pharmaceutical firms that license inventions from PHS laboratories receive economic benefits when the inventions are commercialized and lead to product sales. Private firms pay royalties to PHS (and its employees) that offset these economic benefits somewhat. Data on royalty income to PHS agencies suggest the royalties obtained by PHS are a small fraction of the total PHS intramural budget. In 1988, the total NIH royalty income (figure 9-7) was just 0.03 percent of total NIH intramural spending (76). Furthermore, the vast majority of all NIH royalty income in 1988 is attributable to a single institute and a single technology: NCI's HIV-antibody test kit, for which 12 nonexclusive licenses have been negotiated since 1984 (3,143). The patents on this

Figure 9-7--NIH/ADAMHA License Royalty Income, Fiscal Years 1987-90



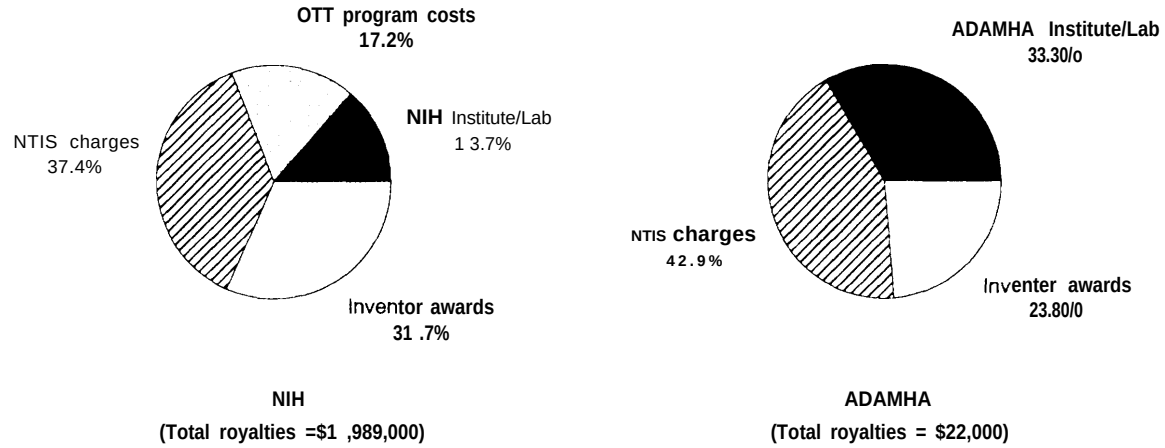
KEY: ADAM HA-Alcohol, Drug Abuse, and Mental Health Administration; NIH = National Institute of Health.

SOURCE: Office of Technology Assessment, 1993. Based on data from U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Office of Technology Transfer, 1991.

18 In addition t. licenses, the PHS also enters into materials transfer agreements, the most common formal relationships between PHS laboratory and a private firm (3). Under such agreements (479) PHS provides biological research materials (such as a type of cell) not covered by a patent in return for a fee (479). The agreement also limits the scope the materials use, requires an acknowledgement of the PHS contribution in reporting research results, and absolves the government of liability associated with its use (Model MTA Agreement). PHS laboratories use the same agreement to obtain research materials from outside paroles (3).

19 Most DHHS patentable inventions, and hence licenses, are from NIH, ADAMHA, and CDC (72).

Figure 9-8—Distribution of NIH/ADAMHA Royalty Collections for Fiscal Year 1988



a Net of $3.4 million in royalties from NCI's HIV antibody test kit licenses paid to private foundation as part of agreement with the French government. Inventor awards are calculated from gross revenue.

KEY: ADAMHA = Alcohol, Drug Abuse, and Mental Health Administration; NCI = National Cancer Institute; NIH = National Institute of Health; NTIS = National Technical Information Service; OTT = NIH Office of Technology Transfer; PHS = Public Health Service.

SOURCE: The Office of Technology Assessment, 1993, Based on data provided by the U.S. Department of Health and Human Services, Public Health Service, National institutes of Health, Office of Technology Transfer, 1991.

one technology brought $1.76 million to NIH in fiscal year 1988, which represents 89 percent of all NIH royalties for that year.[20]

NIH takes the position that the purpose of royalties is to stimulate technology transfer by ''offering an attractive incentive to encourage [PHS] scientists to participate in collaborations with industry . . .' rather than to augment or replace funds appropriated by Congress for research (75). The distribution of royalties received by NIH and ADAMHA is consistent with this policy (figure 9-8). Almost one-third of NIH royalty income in 1988 went to the scientists responsible for the invention.[21] About 55 percent of royalty income went to reimburse the government for the costs of negotiating and administering licenses themselves.[22] Only 14 percent (or $272,000) went back to the PHS division responsible for the invention.

The net returns to the licensee rise and fall directly with the ultimate cost to consumers of obtaining the product. The PHS policy governing exclusive licenses and licenses granted under CRADAs requires that prices of commercial products be commensurate with the extent of "public investment in the product, and the health and safety needs of the public' (486). The policy further states that licensees may be required to

20 Royalties from licenses on these NCI patents actually totaled $5.16 million. However, under an agreement with the French Government settling a dispute over the discovery of HIV, $3.40 million was paid in 1988 to the nonprofit French-American AIDS Foundation to fund future work. A similar percentage of royalties from these licenses was paid in each of the other years, and is not reflected in the data.

21 PHS policy directs inventing employees to get 25 percent of the first $50,000 of royalty income, 20 percent of the next $50,000, and 15 percent of the remainder up to $100,000 per employee per year from all patents for which they are inventors. NIH policy also allows some awards to go to noninventing employees that nonetheless contributed to the invention. After other expenses, the remainder is returned to the budget of the organizational unit responsible for the award (486).

In recent years (including 1988 as shown in figure 9-9), the amount of income to inventors for NCI's HIV-antibody test kit patents was calculated on the basis of gross revenues prior to the $3.4 million distribution to the French-American AIDS Foundation. Hence, final inventor awards in fiscal year 1988 totaled 32 percent of royalties actually turned over to the NIH.

22 Until recently, the National Technical Information Service (NTIS) was charged with this function and received more than one-third of NIH royalties. The Office of Invention Development (now OTT) received about 17 percent to cover its costs. OTT has taken over the responsibilities previously carried out by NTIS.

Photo credit: NATIONAL GAUCHER FOUNDATION

After several years of treatment, this girl shows few visible signs of the Gaucher disease that afflicts her. The drug used in her treatment--Ceredase ™--was originally discovered and developed by Federal scientists.

provide ''reasonable evidence' to support their pricing decisions.

To date, PHS has implemented this pricing clause in only one case-the antiviral drug ddI manufactured under exclusive license by Bristol-Myer Squibb.[23]

Health consumers and activists have publicly questioned pharmaceutical pricing decisions for other products that have been developed at least in part through public investment (337). As mentioned earlier, the role of Federal laboratories in the development of one such drug, AZT, an antiviral drug used to treat HIV, has been the subject of public controversy and litigation stemming, in part, from its price to consumers (276,493).

The case of Ceredase™, a treatment for the rare hereditary disorder Gaucher disease, also raises questions about the Federal Government's ability to protect the public's research investment in new drugs that come from our national laboratories. This drug, which is manufactured by Genzyme, Inc. of Massachusetts, was discovered in the early 1970s by NIH scientists and received FDA approval in 1991 on the basis of NIH designed, funded, and conducted clinical trials. An analysis by OTA[24] indicates that at Genzyme's current price and under accepted doses, this drug costs

[23] In a public hearing, representatives of patient groups at NIH in 1992 voiced no objections to Bristol-Myer Squibb's proposed price, which included a plan to give the drug free to those who could not otherwise afford it (3).

[24] OTA'S analysis of the R&D leading to the Ceredase™ and the implications of the drug's costs is contained in a separately published OTA background paper prepared as part of this assessment (141).

patients between $71,000 and $550,000 per year, thus threatening the lifetime maximum insurance benefit of those with private insurance within a few years (455). Gaucher patients require this therapy for life. Because Ceredase™ is also a federally-designated orphan drug (as discussed later in this chapter), Genzyme has the right to market it without competition for 7 years.

While the pivotal discoveries for this drug predate current NIH technology transfer policies and procedures, it does suggest that the current mechanism of enforcing NIH's fair pricing policy alone might not be sufficient to protect the public's interest and ensure adequate compensation for the government's research investment. Even though OTA was able to infer a great deal about Genzyme's production costs and its own R&D investment in Ceredase™ from data provialed by Genzyme, the company did not give sufficient information for OTA to determine independently the drug's ultimate profitability in the course of our year-long study of the drug (455). The Federal Government is likely to be faced with the same difficulties in gathering data upon which to make a confident judgment about the fair pricing of other drugs that come from its laboratories.

CRADAs

CRADAs give Federal laboratories the flexibility to accept industrial resources, including funds, and to provide Federal resources (except funds) for collaborative research. PHS encourages the use of CRADAs by Federal scientists who want to engage in collaborative R&D activities with outside parties (486). The disposition of intellectual property resulting from a CRADA follows the general PHS patenting and licensing guidelines described in previous sections of this chapter with the exception that the agreement may include a company's option to negotiate an exclusive license to any invention resulting from research under the CRADA.

Between fiscal years 1987 and 1990, 109 CRADAs were established within NIH and ADAMHA (table 9-7). An OTA analysis of CRADAs in effect in October 1990 in PHS (NIH, ADAMHA, CDC, and FDA) shows that CRADAs were heavily concentrated in the National Cancer Institute, which had 26 percent of all such agreements at that time (table 9-8).

Table 9-7--CRADAs Established by NIH and ADAMHA, Fiscal Years 1987-90

Year	Number of CRADAs established
1987	8
1988	21
1989	46
1990	34
Total CRADAs	109

KEY: ADAMHA = Alcohol Drug Abuse and Mental Health Administration; CRADAs = cooperative research and development agreements; NIH = National Institutes of Health.

SOURCE: Office of Technology Assessment, 1993. Based on data provided by U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Office of Technology Transfer, 1991.

Table 9-8—PHS CRADAs in Effect October 1990

CRADAs:	Percent[a]
in which the private collaborator is a PMA member	37%
in which NCI is the PHS collaborator	26
that are HIV- or AIDS-related	18
that involve the R&D of vaccines or other prophylactics	10
that involve the R&D of diagnostics	8
in which the private collaborator is a university or nonprofit institution	5

a Categories are not mutually exclusive or collectively exhaustive, and hence, do not add to 1.00.

KEY: AIDS = acquired immunodeficiency syndrome. CRADAs . cooperative research and development agreements; HIV - human immunodeficiency virus. NCI = National Cancer Institute. PHS = Public Health Service. PMA = Pharmaceutical Manufacturer Association.

SOURCE: Office of Technology Assessment, 1993. Based on data compiled from the U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Office of Technology Transfer, *PHS Technology Transfer Directory,* October 1990.

Box 9-C-Examples of Two CRADAs at NIH

Thomas Kindt of the National Institute of Allergy and Infectious Diseases has been working with the gene for CD4--the protein that regulates the entry of HIV (human immunodeficiency virus) into cells-and wanted a good animal model for studying CD4 gene expression in lymphoid tissue. After reading one of Kindt's early papers, people from a Massachusetts company that makes transgenic animals called to propose a collaboration. They would make rabbits with the human CD4 gene, using their expertise at creating transgenic animals. Kindt would have the animal model he needed.

Says Kindt, "This is a nice, focused collaboration and provides my lab with resources we needed. I don't have the facilities for making rabbits." It does not cost Kindt a thing-the company pays for the breeding and care of the animals. And what does it get in return? The possibility that the rabbit will, in fact, turn out to be a good model for studying AIDS. Then, the company could make money selling these genetically special animals to people studying AIDS or testing AIDS drugs.

What would Kindt have done 3 years ago, before CRADA fever? He would have gone "hat in hand" to colleagues in academia who do research with transgenic animals. "I would have been asking for a favor," Kindt says, "and even if someone agreed, making animals for me would not necessarily be atop priority. With a CRADA I have a true collaboration."

Richard Jed Wyatt of the National Institute of Mental Health is another investigator who has made use of a CRADA to get needed research rabbits. A neuroscientist interested in how the AIDS virus gets into the brain, Wyatt began collaborating with a colleague at NIH who had developed an animal model. But the colleague did not have facilities for breeding and keeping rabbits. Neither did Wyatt. The solution: find investors to form a company that make rabbits. Wyatt did and RRI of McLean, Virginia, was formed. Then Wyatt and his colleagues signed a CRADA with RRI. The researchers have their rabbits, the company has a possible product. Another good idea.

But traditionalists worry. If CRADAs become common, will they really be true collaborations with intellectual, scientific input from both sides? Or will they just be another form of cent.ract+e in which NIH benefits without having to pay?

Conversely, could CRADAs eventually turn NIH into little more than a giant contract lab if companies lure NIH scientists into cooperative agreements that serve the companies' need for NIH brain power at the expense of basic research?

SOURCE: Reprinted with permission from B.J. Cullition, "MH Inc: The CRADA Boom," *Science* 245:1034-1036, 1989.

Although the idea for a CRADA can come from a variety of sources,[25] the first stage in establishing the arrangement is a research plan that includes the goals and activities of the CRADA, the respective contributions of each party, an abstract for public release, and identification of relevant patents and other NIH technology transfer agreements related to the CRADA (484). After review by legal counsel within the agency, a CRADA subcommittee of the Patent Policy Board must approve the CRADA before it is signed by the institute director and the private collaborator. Preference is given to CRADAs involving small businesses arid firms that ''agree to manufacture substantially in the United States" any inventions developed through CRADAs. Box 9-C describes two recent CRADAs.

[25] The Office of Technology Transfer has taken steps to make the private sector more aware of opportunities for collaboration with PHS agencies by sponsoring an annual conference for the past 3 years highlighting PHS research with potential commercial value. More recently, PHS has established an electronic bulletin board providing outside parties with information about specific collaborative opportunities.

According to the PHS Policy Statement on CRADAs and intellectual property licensing, "In certain areas of research, e.g., where the Government has the intellectual lead or where both scientific and commercialization capabilities are deemed essential at the outset, NIH/ADAMHA may competitively seek a collaborator through Federal Register notification. The Patent Policy Board has left to each institute the decision of when to publish in the Federal Register" (486).

As shown in table 9-8, the bulk of all CRADAs in 1990 (82 percent) are related either directly or indirectly to R&D on new human therapies, with vaccine or other prophylaxis research accounting for another 10 percent, and R&D on diagnostic tests accounting for the remaining 8 percent. At least 18 percent of all CRADAs are related to acquired immunodeficiency syndrome (AIDS) and HIV therapies or vaccines. This statistic reflects both a general emphasis on HIV-related research at NIH and an urgent interest in transferring knowledge about HIV into treatments or other products.

To what extent do private firms participating in CRADAs provide funds to the collaborating Federal research agency? All but 1 of the 14 NIH and ADAMHA institutes, centers, and divisions with CRADAs in fiscal year 1989 received some financial resources from their collaborations (table 9-9). At NIH, CRADA collaborators provided $1.8 million, of which $1.2 million went to support the salaries of 47 personnel. Over one-half of all support was centered in NCI. At ADAMHA, total financial support in 1989 under CRADAs was $187,000 with all but $10,000 going to support salaries of nine scientists at the National Institute of Mental Health. Even though the money received was only 0.2 percent of overall institute budgets for research within NIH and ADAMHA laboratories,[26] such support may be a catalyst for successful research. Furthermore, the data in table 9-4 are based on one of the earliest years of the CRADA program. Data for subsequent years may show more extensive financial support to Federal laboratories that have CRADAs.

Table 9-9—Financial Resources Provided to NIH and ADAMHA Through CRADAs, Fiscal Year 1989

Institute	Personnel[a]		Program support[b]
NIH			
CC	$ 0		$ 5,000
DRS	0		0
NCI	623,288	(24)	325,635
NEI	0		0
NHLBI	0		2,625
NIA			25,000
NIAID	34,327	(1)	74,000
NIAMS	30,000	(1)	0
NICHD	127,028	(5)	20,000
NIDDK	57,000	(2)	0
NIDR	174,000	(7)	103,050
NINDS	177,500	(7)	20,000
Total	$1,223,143	(47)	$575,310
ADAMHA			
NIAAA	$		$ 10,000
NIMH	177,250	(9)	0
Total	$ 177,250	(9)	$ 10,000

a Support for personnel; numbers in parentheses are numbers of persons supported.
b Travel, equipment, or supplies, used in conducting any part of the research effort.

KEY: ADAMHA = Alcohol, Drug Abuse and Mental Health Administration. CC = Warren Grant Magnuson Clinical Center. CRADA = Cooperative Research and Development Agreements Collaborators. DRS = Division of Research Services. NCI = National Cancer Institute. NEI = National Eye Institute. NHLBI = National Heart, Lung and Blood Institute. NIA = National Institute on Aging. NIAAA = National Institute on Alcohol Abuse and Alcoholism. NIAID = National Institute of Allergy and Infectious Diseases. NIAMS = National Institute of Arthritis and Musculoskeletal and Skin Diseases. NICHD = National Institute of Child Health and Human Development. NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases. NIDR = National Institute of Dental Research. NIH = National Institutes of Health. NIMH = National Institute of Mental Health. NINDS = National Institute of Neurological Disorders and Stroke.

SOURCE: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Office of Technology Transfer, 1989.

ORPHAN DRUGS

Congress passed the Orphan Drug Act (Public Law 97-414) in 1983, providing strong incentives for private firms to discover and develop treatments for rare diseases and conditions. Amended three times since its initial enactment (Public Law 98-551, Public Law 99-91, Public Law 100-290), the law has three provisions (in addition to a tax credit described in chapter 8) designed to subsidize R&D costs or to remove other disincentives to developing drugs of limited commercial value:[27]

26 Intramural (i.e., taking place on the PHS laboratories campus) research support totaled $782 million in fiscal year 1989 (482) and $103 million at ADAMHA in the same year (485).

27 The Orphan Drug Act as first adopted excluded antibiotics from eligibility for orphan designation. Congress eliminated this restriction in August 1985 (Public Law 99-9 1).

- Food and Drug Administration assistance to orphan drug developers in protocol design for new drug approval (NDA) or product license approval (PLA) applications;[28]
- Research grants for clinical and preclinical studies of orphan products; and
- A grant of 7 years of exclusive U.S. marketing rights to the first firm that receives NDA approval for an orphan drug.

The FDA first published proposed regulations to implement the law in January 1991 (FR 1/29/91) (56 FR 3334). Prior to these proposed regulations, the FDA relied on interim guidelines that differed from the proposed regulations in important ways described later. Though the proposed regulations have not been adopted officially as final, the FDA has operated under these rules since they were published.

Designation of Orphan Drugs

The first step in a request for orphan drug subsidies is to apply for official orphan drug status from the FDA's Office of Orphan Products Development (OPD) (468). Drug sponsors may seek this designation at any time between the granting of an investigational new drug (IND) exemption and the submission of an NDA.[29] In making such a request, the applicant must show the disease or condition that the drug is intended to treat:

. "Affects less than 200,000 persons in the United States; or
. Affects more than 200,000 persons in the United States and. . . there is no reasonable expectation that the cost of developing and making [the drug] available in the United States will be recovered from sales in the United States of such drug" (468).

Since 1985, virtually all orphan designations have met the frost criterion. The exact interpretation of this provision has been subject to dispute. For example, the number of AIDS patients in this country has climbed above 200,000, but several AIDS drugs were designated as orphans early in the epidemic, when the prevalence of the disease was much lower (21).

In its recent proposed regulations (adopted as final in December 1992, the FDA makes clear that "the 200,000 prevalence figure means 200,000 affected persons in the United States at the time that the orphan-drug designation request is made (not 200,000 new cases annually)" and that a "drug would remain an orphan drug even if the disease or condition ceases to an orphan disease or condition because of increased prevalence' in order to ''protect a sponsor's good-faith investment" (56 FR 3339);

More than one sponsor can receive orphan designation for the same drug for a single indication. For example, by December 1989, Biogen, Genentech, and SmithKline Beecham had all received orphan drug status for a single drug undergoing clinical research, human recombinant soluble CD4 for the treatment of AIDS (470). At most, only one of the three companies will ultimately be granted approval to market the drug for its orphan use.

Between January 1984 and the end of September 1992, the FDA granted orphan status to 494 drugs and biological (table 9-10). Of all the orphan designations ever given, 16 percent were granted during 1991 alone. Almost two-thirds of orphan designations (63 percent) went to sponsors who were not members of the U.S. Pharmaceutical Manufacturers Association. Because PMA membership is available only to companies marketing an FDA-approved pharmaceutical in the United States, this statistic suggests that a high

28 NDAs and PLAs are formal applications made to the FDA by pharmaceutical sponsors to manufacture and market therapeutic drugs in the United States. NDAs are for synthetic chemical drugs and PLAs are for biological products. This chapter uses the term "NDA" to refer to both types of applications. See chapter 6 for additionat discussion of the drug approval process in the United States.

29 Prior to 1988, the orphan drug law did not specify exactly at what stage in the regulatory process the sponsor of an investigational drug fora rare disease or condition could seek an orphan designation from the FDA. Public Law 10029O, adopted April 18, 1988, clarified that this designation could be granted only prior to the submission of an NDA or PLA.

Table 9-10-Orphan Designations[a] Granted January 1984 Through September 1992

	Number of designations	Percent of total
Total	494	100
Given in 1991only	81	16
Given to PMA members	183	37
Given to Non-PMA members	311	63

a As provided under section 526 of the Federal Food, Drugs and Cosmetic Act (21 U. S.C 30 et seq.) and amended by the Orphan Drug Act (Public Law 97-41 4).
b Includesboth drugs and biological.

SOURCE: Office of Technology Assessment, 1993. Based on data supplied by the U.S. Department of Health and Human Services, Food and Drug Administration, Office of Orphan Product Development, 1992.

percentage of all orphan drug research is being sponsored by new (and probably small) firms or other organizations with little previous experience in researching and marketing drugs in the United States.[30]

An analysis of all orphan designations granted through November 1990 revealed that about 23 percent of all compounds granted orphan status by that date had more than one designation (table 9-1 1). Different sponsors can receive orphan designations for the same indication when they are simultaneously developing the same drug. As of November 1990, 66 compounds had orphan designations by at least two competing fins. A single sponsor may also receive multiple designators for a single drug, but for different potential uses of the compound. As of November 1990, 59 compounds had multiple designations by same sponsor.

Table 9-1 l—Multiple Orphan Designations" for the Same Generic Compound, January 1984 Through November 1990

A. Number of distinct generic compounds with orphan status: 227

Percent of orphan compounds with multiple designations: 23%

B. Multiple orphan designations for a given generic compound

Number of designations given	Number of compounds receiving that number of designations
2	45
3	8
4	4
5	4
6	2
7	1
9	1
10	1
	Total 66

C. Multiple orphan designations for a given generic compound received by a single sponsor

Number of designations given	Number of compounds receiving that number of designations
2	44
3	8
4	4
5	1
7	1
10	1
	Total 59

a As provided under section *526* of the Federal Food, Dregs and Cosmetic Act (21 U. S.C 30 et seq.) and amended by the Orphan Drug Act (Public Law 97-41 4).

SOURCE: Office of Technology Assessment, 1993. Based on data supplied by the U.S. Department of Health and Human Services, Food and Drug Administration, Office of Orphan Product Development, 1992.

Protocol Assistance

The FDA is required by law to provide written assistance upon request about the design of studies to support an NDA for an orphan drug. So far, the total number of such requests has been small compared with the total number of orphan drug designations issued (227). In 1985, FDA received nine such requests; they have virtually disappeared in recent years.

The sponsor of any drug or biological has the option of requesting protocol advice directly from the FDA's Center for Drug Evaluation and Research (CDER) or the Center for Biological

30 This statistic may underestimate the percentage of orphan drugs being researched at the initiative of PMA members since some academic or nonprofit 'sponsors' may receive research funding from PMA firms. As discussed earlier in this chapter, the firm that supports such research may have the rights to market the drug if its succeeds.

Evaluation and Research (CBER). Because such meetings need not be requested formally and can involve iterative questioning and discussion, sponsors probably perceive this type of assistance as more flexible and useful than the formal interchanges mandated under the Orphan Drug Act (227). Some observers have suggested the FDA may actually discourage written requests for assistance (270).

Grants for Clinical Research

The Orphan Drug Act authorized grants for clinical research on potential orphan products, and one of its more recent amendments (Public Law 100-290) extended this authority to preclinical studies. These grants represent a direct subsidy for orphan drug R&D.[31] The Office of Orphan Products Development administers the program in a manner parallel to other Public Health Service grants.

Grants are given for single, discrete studies and are available to for-profit, nonprofit, and government organizations. In almost all cases, the grants have been limited to a maximum of $100,000 in direct costs per year for up to 3 years. Although recipients are not required to possess official orphan drug status for the drug or biological under study, the grants are designed for treatment of conditions affecting less than 200,000 patients in the United States.[32]

The orphan products grants program has grown steadily since 1983. In 1990, the Office of Orphan Products Development allocated a total of $7.6 million among 65 recipients (table 9-12).[33] For-profit organizations represent a very small part of the total grant program (table 9-12). The average size of each award each year (annual direct plus indirect costs for new and continuing grants) has increased from $79,000 in 1987 to $111,000 in 1990. This represents an increase of 6.5 percent per year in constant dollars.

Market Exclusivity

The first drug sponsor to receive NDA approval for a drug and indication with orphan status may market it exclusively for a 7-year period beginning on the day the FDA approves the drug .34 This exclusivity prevents the FDA from approving an NDA for a drug for which another sponsor has already received marketing approval for the same indication.[35] Any patent protection covering the drug runs contemporaneously with the market exclusivity. Two or more sponsors may receive FDA approval for a single orphan drug if their approvals are for different indications and if they do not violate any patent protections.

ORPHAN EXCLUSIVITY VERSUS PATENT PROTECTION

In practice, the exclusivity clause is the strongest incentive in the orphan drug law, and for some drugs it may be more important than patent protection in effecting market exclusivity[36]:

- For some drugs orphan market exclusivity may extend beyond the expiration of the

31 Because the Orphan Drug Act's grant authority has never received funding from Congress, the FDA has funded this program using money appropriated for orphan drug research under a general grants program of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 30 et seq.).

32 Grants under this program are actually not limited to drugs and biological but are also available for medical devices and medical foods for rare diseases and conditions. In practice, almost all grants are for drugs and biological. For example, none of the new awards given in fiscal year 1989 were for medical devices or foods.

33 These 65 recipients do not include 10 supplemental awards given to recipients of full grants in 1990 or earlier years who requested additional funds to cover unanticipated costs. In 1990, supplemental awards represented $388,332 of the total $7.6 million program.

34 As first enacted in 1983, the Orphan Drug Act (Public Law 97-414) permitted market exclusivity only for orphan pharmaceuticals that were ineligible for a U.S. patent at the time of marketing approval. In August 1985, Congress removed this limitation making all orphan drugs eligible for the 7-year exclusive marketing period if no other sponsor has received approval for that therapy for that indication (Public Law 99-91).

35 Because orphan drug status is given for a particular indication, market exclusivity is also limited to particular indications.

36 In addition to patents and orphan drug market exclusivity for a specific indication, another potential barrier to Competition fOr an orphan drug is FDA's regulatory approval process itself. A potential competitor must conduct R&D and receive FDA approval of an NDA or PLA for *each* indication for which it would like to market the drug (21).

Table 9-12—Orphan Products Development Grants for Clinical Research: Selected Statistics

	1983[f]	1984[f]	1985[f]	1986[f]	1987	1988	1989	1990
Number of awards								
First year awards[a]	8	11	21	21	27	18	19	30
Continuing (year 2 or >) awards[b]	—	—	—	—	21	32	31	35
Supplemental awards[c]	—	—	—	—	6	13	11	10
Total	8	11	21	21	53	63	61	75
Program outlays (in current dollars)								
Direct costs	—	—	—	—	$ 2,840,190	$ 3,473,561	$ 4,106,211	$ 5,470,428
Indirect costs	—	—	—	—	1,076,129	1,286,262	1,447,035	2,165,281
Total	$ 500,000	$ 1,030,000	$ 2,420,000[e]	$ 2,885,000	$ 3,916,319	$ 4,759,823	$ 5,553,546	$ 7,635,709
First year awards[a]	—	—	—	—	$ 2,110,008	$ 1,754,008	$ 2,093,254	$ 3,441,175
Continuing awards[b]	—	—	—	—	1,600,573	2,655,793	3,149,415	3,806,202
Supplemental awards[c]	—	—	—	—	205,738	350,022	310,577	388,332
Total	$ 500,000	$ 1,030,000	$ 2,420,000[e]	$ 2,885,000	$ 3,916,319	$ 4,759,283	$ 5,553,546	$ 7,635,709
Awards to for-profit organizations								
Number of first year or continuing awards	—	—	—	—	2	3	4	3
Number of supplemental awards	—	—	—	—	1	3	1	1
Total program outlays (in current dollars)	—	—	—	—	$ 53,735	$ 281,614	$ 393,082	$ 346,542
Mean award size[d]								
Mean direct cost per award	—	—	—	—	$ 57,356	$ 64,266	$ 77,586	$ 79,930
Mean indirect costs per award	—	—	—	—	21,592	23,931	27,267	31,569
Mean total costs per award	—	—	—	—	$ 78,948	$ 88,197	$ 104,853	$ 111,499
Mean total costs per award in 1987 dollars[g]	—	—	—	—	78,948	85,361	97,464	99,668

[a]Grants for 1-year awards or the first year of multiple-year awards.
[b]Grants for second, third, or fourth year of multiple-year awards.
[c]Supplemental awards given for existing grants upon application by investigators.
[d]Mean awards calculated net of supplemental awards; given in current dollars unless otherwise noted.
[e]1985 funds include $1 million provided by the National Institute of Maternal and Child Health, U.S. Department of Health and Human Services under interagency agreement.
[f]U.S. Food and Drug Administration, Office of Orphan Products Development, data systems can provide only limited information for years 1983-86.
[g]1987 dollars calculated using the GNP implicit price deflator.

SOURCE: Office of Technology Assessment, 1993. Based on data provided by U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Office of Orphan Products Development, 1992.

relevant patents. Because manufacturers usually receive their 17-year patents on potential new drugs early in the development process (220), the amount of time remaining on the patent at the time of FDA approval may be less than the 7 years guaranteed by the orphan drug exclusivity (21).

. Some drugs duplicate substances that naturally occur in the body (e.g., ''biological' '), For these, the state of patent law is currently so murky that the 7-year market exclusivity is a more certain means of protecting the product from competition (45 1).

Problems in Awarding Orphan Market Exclusivity Rights--Controversy has arisen over how different the molecular structure of two drugs must be in order for both to receive market exclusivity. Because biological pharmaceuticals tend to have relatively large and complex molecular structures, scientists can alter their makeup slightly without changing their clinical effects. If the Federal Government interprets any small clinically insignificant change as the creation of a "different" orphan drug eligible for its own market exclusivity, it effectively eliminates the incentives of the exclusivity clause for many biotechnology drugs. Since the orphan drug law was enacted, competitors have challenged the exclusivity of two approved orphan drugs by seeking approval of slightly different versions of the same pharmaceuticals.

Human Growth Hormone-In 1985, Genentech received FDA approval and exclusive marketing as an orphan drug for a human growth hormone (HGH) product to treat children whose bodies do not naturally produce enough of the hormone to ensure normal growth. Genentech's HGH product, Protropin™, contains one more amino acid than is found in the version usually produced by the body's pituitary gland, but this particular amino acid does not appear to alter the hormone's activity in the body.

Eli Lilly independently developed its own HGH product Humantrope™, with a molecular structure that is *identical* **to the** HGH produced by the human body. Eli Lilly applied for orphan drug status and marketing approval for Humantrope, arguing that because of the additional amino acid on Protropin, the Eli Lilly drug was ''different' from Protropin. In 1986 the FDA agreed, giving orphan status to Humantrope.

Genentech subsequently challenged the FDA's decisions in court by arguing the FDA did not have the authority to grant orphan status to Eli Lilly. The courts ruled against Genentech. Currently, each manufacturer has orphan status for its version of HGH, and each drug is sold on the market .37

The results of the HGH case established that the FDA has the authority to determine when two therapies are sufficiently different from one another that each can receive its own orphan designation (240).

Recombinant Erythropoietin[38]*--In June 1989,* Amgen received approval to market its version of recombinant erythropoietin (rEPO) for the treatment of anemia in patients with chronic renal failure. EPO is a protein usually produced by the kidneys and necessary for the production of red blood cells. Amgen had first produced the drug in 1983 and had received orphan status for it in 1986. In September 1988, Chugai Pharmaceuticals of Japan, in a joint venture with Upjohn Pharmaceuticals, filed a PLA with the FDA to market its own version of rEPO in competition with Amgen.

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37 The orphan protection prohibits each manufacturer from marketing a version of HGH that is molecularly identical to the version produced by the other firm. For example, Genentech developed a new HGH that was identical to the HGH produced naturally by the body. However, because this new Genentech HGH was also identical to Lilly's Humantrope™, the FDA prohibited Genentech from marketing it (240).

38 For a more complete discussion see chapter 3 of OTA's study on recombinant erythropoietin (45 1).

39 Because amino acids are the building blocks of proteins, and because rEPO is designed to fulfill the function of the missing natural EPO, the drug's amino-acid sequence can be important in the effectiveness of the rEPO.

Although the Chugai/Upjohn drug has an amino-acid structure[39] identical to that found in the Amgen version, Chugai/Upjohn argued that the two drugs differed in glycosylation, the linkages of carbohydrates to the molecule, and that their version was therefore eligible for its own orphan designation and marketing approval. Although the FDA had not yet acted on the Chugai/Upjohn application for orphan drug designation at the time of the Amgen approval, then-FDA commissioner Frank Young stated publicly that the Chugai/Upjohn version appeared ''different' from the Amgen drug (240). In October 1989, Amgen requested that the FDA develop regulations to determine the circumstances under which two molecularly similar orphans are eligible for shared exclusivity .40

Proposed Regulations—The FDA recently attempted to set forth general criteria for determining when two drugs are sufficiently different to warrant orphan status and exclusivity for both. In proposed regulations published on January 29, 1991 (56 FR 3338) and adopted as final in December 1992, the FDA would presume two orphan drugs to be the same ''if the principal, but not necessarily all, structural features of the two drugs were the same, unless the subsequent drug were shown to be clinically superior. According to these guidelines, different glycosylation patterns in two protein drugs, the difference suggested to have been found in the two versions of rEPO, would not be sufficient to find the Upjohn/Chugai drug different from the Amgen drug. The proposed regulations identify three circumstances under which a subsequent drug could be deemed ''clinically superior' to an already approved orphan, and hence, approvable:

- The subsequent drug is more effective than the first drug as shown in comparative clinical trials.
- The subsequent drug is safer than the first for a ''substantial portion of the target population, ' including the case where the two drugs have about the same therapeutic effect, the frost drug has significant side effects, and the subsequent drug achieves its effect at a lower dose.
- The subsequent drug ''makes a major contribution to health" as in the development of an oral dose form where the drug had only been available by parenteral administration.

While awaiting approval from the White House Office of Management and Budget to adopt a final version of the regulations, the FDA operated according to the draft regulations (227).

Impact of orphan Drug Subsidies

The clinical research tax credit (discussed in chapter 8), protocol assistance, and clinical research grants theoretically lower the cost of orphan drug R&D; the market exclusivity provision increases the expected revenues to such R&D. In practice, the protocol assistance has had little effect, especially in recent years, and the tax credit and grants program represent, overall, a relatively small commitment of Federal funds to orphan products. This commitment may be critical for certain drugs, however, so it should not be discounted.

The 79 biological and drug applications approved for marketing by the FDA with orphan status as of September 1992 represent broad and extensive R&D efforts for rare diseases. The test of the Orphan Drug Act's effectiveness, however, is whether it has led to the approval and marketing of drugs for orphan conditions that would otherwise have been unavailable to patients. If pharmaceutical companies would have developed and marketed orphan drugs even without these subsidies, then their true effectiveness would be nil.

It is impossible to estimate how many of the new orphan drugs would have been made available since 1983 in the absence of these subsidies. Simple comparison of the number of such drugs approved and marketed before the passage of the act with those made available since its passage is

[40] Appendix E describes a controversy over patent rights for rEPO that took place at the same time as this dispute over orphan designation.

inappropriate because, many other factors, especially the state of scientific knowledge, may affect pharmaceutical innovation.

A recent analysis of the Orphan Drug Law's first 8 years concluded that while most orphan incentives have gone to the type of drugs Congress intended to subsidize, there is evidence that some drugs with orphan status would have been commercially viable without Federal help. Furthermore, the authors concluded there might have been sufficient information for the FDA to determine the drug's commercial viability in granting orphan status had the Orphan Drug Law permitted such consideration in awarding orphan drug incentives (389).

Concerns that the Orphan Drug Law has subsidized the development of commercially successful drugs which did not really need help from the Federal Government led to legislation in the 102d Congress that would have removed an orphan drug's exclusivity once cumulative net sales in the United States surpassed $200 million (S. 102-2060). Another piece of legislation (H.R. 102-1713) would tax ' 'profits" on orphan drugs that exceed certain levels.[41]

Another measure of the law's effectiveness may be the extent to which orphan drugs have been sponsored by relatively small startup fins. As drug R&D costs go up, smaller firms may have a harder time mustering enough resources to bring new products to the market. By lowering barriers for such fins, the orphan drug subsidies may encourage competition in the industry and provide a new mechanism to realize the commercial benefits of biotechnological and other scientific discoveries, especially those originating in academia. As shown earlier, almost two-thirds of orphan designations have gone to drug sponsors that are not PMA members, a characteristic commonly found among startup fins.

MEDICARE AND MEDICAID SUPPORT FOR CLINICAL DRUG R&D

The Medicare and Medicaid programs are the sources of the vast majority of Federal spending for health services. Medicare and Medicaid payment for patient care rendered in association with clinical research on a pharmaceutical agent therefore constitutes a potential subsidy of pharmaceutical R&D. Nevertheless, there are no good estimates of clinical-trial-related health care costs paid for by Medicare and Medicaid (395).

By law, Medicare does not cover any drugs administered outside of the hospital or a physician's office, and the program does not pay for clinical research (487). Furthermore, to be covered by Medicare, drugs must be 'reasonable and necessary, ' a criterion that the Health Care Financing Administration (HCFA) "has interpreted . . . to exclude . . . those medical and health care services that are not demonstrated to be safe and effective by clinical evidence' (487). HCFA has taken this to mean that "experimental" and ''investigational' drugs are not covered.

"Group C" cancer drugs[42] represent the one exception to the statutory and regulatory exclusion of unapproved drug therapies from Medicare payment. Because Medicare does pay the costs associated with the administration of Group C drugs,[43] some patients have requested that Medi-

41 There have been other congressional attempts t. limit retroactively the use of orphan subsidies. In legislation passed by Congress in 1990, but later pocket-vetoed by the President, manufacturers would lose their exclusivity if disease prevalence grew more that 200,000. In addition, the legislation would have allowed more than one manufacturer to share an orphan market exclusivity if each reached certain regulatory hurdles contemporaneously (H.R. 101-4638).

42 ''Group C' cancer drugs are pharmaceuticals for which significant data on safety and efficacy are already available. These drugs are usually in phase III trials. NCI and the FDA jointly developed the concept of Group C drugs in 1976, although DHHS has never formalized the definition in regulations (NCI, 1990). Only physicians registered with NCI as clinical investigations can administer the drugs. Some of the drugs in the Group C category may never receive final FDA approval to market because firms consider them to be commercially unviable.

43 NCI provides the Group C drugs free of charge.

care cover all drugs with Treatment INDs as well (69).[44]

In practice, there are other exclusions from Medicare coverage, particularly for drugs administered as part of a clinical research protocol. Prior to 1983 Medicare paid hospitals for the individual services they provided to patients. Anecdotal evidence suggests that Medicare's payment for clinical research was common in that period (446),

Since 1983, Medicare has paid hospitals a fixed amount per admission for a package of services based on a patient's primary diagnosis and major treatments. Medicare will now cover attendant hospital costs for patients receiving an experimental drug if the admission was not solely for the experiment. Some observers have suggested that adjustments to hospital payments allowed by Medicare to cover costs associated with medical education also underwrite some of the patient and faculty costs associated with clinical research. Medicare contractors, the companies that administer the Medicare program under contract with HCFA, interpret these policies differently in different parts of the country (395).

Although Medicare contractors screen claims submitted by hospitals to determine whether they are appropriate, and utilization and quality control peer review organizations (PROS) may screen and refuse payment for inappropriate services given Medicare beneficiaries by hospitals, it is likely that a great deal of patient care associated with pharmaceutical trials is paid for by Medicare because of the difficulty of screening claims to detect such services.

Because the Medicaid program, which pays for health services for individuals who are low-income, is administered by the States, decisions about coverage of pharmaceuticals (whether investigational or approved) are up to each State. Medicaid is one of the biggest payers for prescription drugs in the United States, accounting for 10 to 15 percent of total spending.[45]

A recent informal DHHS survey of Medicaid drug program administrators found that while many States do not cover investigational drugs under any circumstances, some are willing to provide payment for investigational therapies under specific circumstances (487). Policy varies by State: a few States pay for investigational pharmaceuticals on a case-by-case basis; one State covered treatment IND drugs for treatment of AIDS, and the State legislature was considering codifying this practice. Another State requires prior approval for use of an investigational drug.

The results of this survey suggest it is possible (perhaps likely) that Medicaid is paying for some investigational pharmaceuticals and the attendant medical care costs of persons enrolled in clinical trials. However, the tremendous variation in Medicaid policies among States makes such subsidies impossible to estimate.

CONCLUSIONS

The Federal Government is the mainstay of support for the scientific infrastructure upon which advances in medical technology depend. The pharmaceutical industry makes use of this infrastructure through its hiring of scientists, its formal and informal interactions with federally-supported scientists in universities and in Federal laboratories, and informational resources that document research and its results. In addition, the government provides even more direct support to industry R&D through drug development programs in Federal laboratories, orphan drug policies, and Medicare and Medicaid reimbursements.

The public sector has been the major source of funds for training scientific personnel. Over the

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44 The Treatment IND program, established in 1987 and administered by the FDA, allows the release of investigational drugs to medical practitioners on a case-by-case basis for use in the treatment of immediately life-threatening diseases for which no satisfactory alternative treatment exists. Under this program, described in greater detail in chapter 6, the drug must be under investigation in controlled clinical trials and the sponsor must be actively pursuing marketing approval. With the permission of the FDA, sponsors may charge patients for Treatment IND drugs in order to recover production and R&D costs (21 CRF 312.34.(a)).

45 See table 10-1 in chapter 10.

past decade, industrial demands for biomedical scientists have grown much faster than demands for biomedical scientists as a whole (12 to 13 percent per year versus 5 percent).

Collaborations with academic scientists have historically been an important component of the drug industry's R&D efforts and continue to be so today. Of all U.S. industries, innovation within the pharmaceutical industry is the most dependent on academic research and the Federal funds that support it. In recent years, advances in biotechnology that occurred within academic research laboratories added to the task of transferring basic scientific knowledge from academia and government to industrial applications.

The pharmaceutical industry's support for university scientists include consulting arrangements, funds for specific research projects, and to a lesser extent long-term support for entire laboratories or university research programs. The bulk of shorter-term research support from industry goes to laboratories that receive most of their support from the Federal Government.

A more direct form of Federal support for pharmaceutical R&D comes through the Federal Government's funding of research targeted to drug discovery and development. The Federal Government has 11 research programs devoted solely to the encouragement, finding, and coordination of nonclinical pharmaceutical R&D. At three institutes, these programs include the screening and characterization of potential medications submitted by outside researchers including pharmaceutical fins.

OTA's ability to measure the precise extent of different types of federally supported drug R&D is limited both by problems with defining relevant R&D and a lack of adequate data. But, a conservative estimate of research involving nonclinical drug discovery functions funded just by NIH and ADAMHA in 1988 is $400 million; this estimate represents 14 percent of the amount spent by firms in the PMA for the same R&D functions.

A conservative, likely underestimate of NIH- and ADAMHA-funded research in 1988 specifically involving clinical R&D is $200 million, which represents 11 percent of industry's expenditures for phases I, II, III, and IV clinical research. The Federal Government also indirectly supports clinical research by paying a portion of the health care bills of Medicare and Medicaid beneficiaries who are also enrolled in clinical trials. No data exist to measure the exact extent of this support.

In recent years, the innovation of the CRADA has allowed companies and Federal laboratories greater latitude for productive interactions. Although a comprehensive assessment of the benefits and risks of such arrangements for both parties is yet to be taken, the terms of such collaborations offer some preliminary indications. Through 109 CRADAs signed between 1987 and 1990, PHS gave pharmaceutical industry collaborators access to Federal research laboratories and potentially exclusive property rights for patentable commercial applications arising from the research. In return for such rights, PHS received just under $2 million in research resources from industrial and other CRADA partners in 1989.

In another form of technology transfer, DHHS issued 44 licenses (17 exclusive) for Federal patents in 1988. Income from licenses in 1988 netted NIH and ADAMHA research laboratories just $272,000 after expenses (.004 percent of NIH budget), the majority of which is attributable to a single technology (the HIV antibody test).

In the Orphan Drug Act, the Federal Government has created several potentially strong incentives for firms to pursue the R&D and marketing of pharmaceuticals for relatively rare conditions. In particular, designated orphan drugs are eligible for a 7-year exclusivity covering their approved indications and a 50-percent tax credit for clinical R&D that lowers the cost of qualifying clinical trial expenses by 76 percent. Researchers also received $7.6 million in grants from the Federal Government for 75 phase I and II clinical trials studying potential orphan drugs.

The policies and programs laid out in this chapter (and the one that precedes it) suggest that

Federal involvement can substantially lower the private sector's costs of bringing some new drug products to market. Furthermore, because this report does not examine any incentives provided by State and local governments to pharmaceutical firms located in their jurisdictions, actual public-sector involvement may be greater than that implied here.

Industry provides some compensation for its access to these resources, although such compensation is relatively limited. The true cost of pharmaceutical R&D is greater than just the private funds invested in this enterprise, and the Federal Government's support of the country's research infrastructure is critical to industry's ability to bring forth new drugs.

In the case of orphan drugs, some of the pharmaceuticals receiving help from the Federal Government might have been commercially viable anyway. Various proposals debated by Congress have attempted to target orphan drug subsidies more precisely on only those drugs that would not otherwise be available to patients.

When the fruits of Federal pharmaceutical research are transferred to the private sector for development and marketing, the Federal Government currently has neither sufficient incentive nor expertise to negotiate compensation or limits on prices that reflect the Federal investment in dollars or the technical risk of failure absorbed by the government during the R&D process. As the case of the drug Ceredase™ illustrates, this failure, along with extensive insurance coverage of pharmaceuticals described in the next chapter, creates the potential for the Federal Government to pay for such drugs twice--once through support of the R&D process and once again as a health insurer.