

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**TECHNOLOGY TRANSFER
AND THE PUBLIC INTEREST:**

**COOPERATIVE RESEARCH AND
DEVELOPMENT AGREEMENTS
AT NIH**



NOVEMBER 1993

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NOVEMBER 1993 OEI-01-92-01100

EXECUTIVE SUMMARY

PURPOSE

The purpose of this study is to assess the extent to which the National Institutes of Health protects the public interest in its establishment and oversight of Cooperative Research and Development Agreements.

BACKGROUND

The National Institutes of Health (NIH) is one of the world's premier biomedical research institutions. Its mission encompasses both the pursuit of basic scientific knowledge and the application of that knowledge to the provision of health care. In fulfilling this mission, NIH intramural scientists have long collaborated with outside organizations in the research and development of biomedical discoveries and inventions and in the transfer of Federal technologies to industry. This collaboration ranges from undocumented exchanges of research materials, to informal compound-screening efforts, to clinical trials conducted by NIH with private organizations.

In 1986 Congress passed the Federal Technology Transfer Act (FTTA), which established the Cooperative Research and Development Agreement (CRADA) as a new collaborative mechanism intended to foster the private commercialization of Federal technology. Of the 125 CRADAs administered by the U.S. Department of Health and Human Services in 1992, 93 were at NIH. Sixty-nine percent of these were concentrated within three institutes: the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Our report examines the usefulness of the CRADA as a collaborative mechanism and identifies important challenges to the future success of the NIH CRADA program. We conducted this study in response to a request from the Chairman of the United States Senate Special Committee on Aging.

Our findings are based primarily on a review of documents for the 61 CRADAs established at NCI, NIAID, and NIDDK in 1990, 1991, and 1992; and on interviews with NIH principal investigators and administrators, and industry representatives involved in the 24 CRADAs established in those 3 institutes in 1992.

FINDINGS

Government and industry participants in NIH CRADAs reported that the CRADA is a useful mechanism for collaboration.

- The CRADA can facilitate the pooling of NIH and private-sector intellectual and financial resources, equipment, facilities, and research materials.

- The CRADA can protect the intellectual property rights of the government in inventions that result from collaborative efforts.
- The CRADA can facilitate the transfer of technology from NIH laboratories to the private sector for development and commercialization.

Nonetheless, several challenges to the effective management of the NIH CRADA program could jeopardize its future success.

- Many CRADA projects may not be well-suited for the CRADA mechanism because they do not focus on the transfer of Federal technology to the private sector for commercialization, which is the central intent of the FTTA.
- The process of establishing a CRADA is lengthy and complex. This may discourage participation in CRADAs, and may undermine the intent of the FTTA, which calls for an expeditious review and approval process.
- The NIH does not have guidance that adequately addresses the complexities of providing fair access to CRADA opportunities. Failure to ensure fair access--and the appearance thereof--could deter industry participation in CRADAs, impede market competition, and undermine public support for the CRADA program.
- Limited NIH oversight of CRADA projects may inhibit the ability of NIH to ensure that CRADA work is consistent with the intent of the FTTA and NIH policy.
- The pricing of CRADA products is a matter of considerable controversy that reflects NIH's difficulty in achieving a balance between protecting the public investment in CRADAs and maintaining industry's incentive to participate in them. This controversy threatens to undermine support for the NIH CRADA program.

RECOMMENDATIONS

The NIH has already identified and begun to address several of these challenges. In each area, a successful response requires that a careful balance be achieved between enhancing the protection of the public investment in CRADAs and preserving interest in CRADA participation among NIH scientists and in industry. Such a response must also be consistent with the decentralized and expeditious CRADA management called for by the FTTA. With these considerations in mind, we offer the following recommendations to strengthen the management of the NIH CRADA program:

The NIH should implement guidelines that clearly indicate the types of research projects that are appropriate for the CRADA mechanism.

The NIH should build upon its current efforts to clarify and streamline the CRADA review and approval process.

The NIH should further develop the fair access guidelines to reflect the full range of issues involved.

The NIH should develop and maintain a central database system to track all ongoing CRADA work.

The NIH, working with the Office of the Secretary and the Office of the Assistant Secretary for Health, should seek a consensus on how to resolve the reasonable pricing controversy.

COMMENTS ON THE DRAFT REPORT

We solicited and received formal comments on our draft report from the Public Health Service (PHS). The complete text of these comments appears in appendix C.

The PHS concurred with four of our five recommendations and indicated steps it has taken and plans to take to implement them. The PHS did not concur with our recommendation that NIH should implement guidelines that clearly indicate the types of research projects that are appropriate for the CRADA mechanism.

The agency believes that restrictions on the use of the CRADA are already explicitly addressed in current CRADA guidelines, that there is no legal requirement for further restrictions, that there is no inconsistency between the intended and current uses of the CRADA, and that NIH laboratories and public access to CRADA inventions are adequately safeguarded by current NIH policy and procedures.

We continue to believe that it is important for NIH to provide further guidance regarding the types of research projects that are appropriate for the CRADA mechanism. Our concern focuses on fulfilling the intent of the FTTA rather than on a narrowly defined compliance with the letter of the law. We are particularly concerned that basic-science research projects and NIH routine testing of industry-patented inventions may not be well-suited for the CRADA mechanism.

The PHS can best protect the public investment in NIH and its scientists by providing clear guidance now, before CRADA activity becomes more prevalent, before more public resources are expended, and before more CRADA products reach the market.

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INTRODUCTION

PURPOSE

The purpose of this study is to assess the extent to which the National Institutes of Health (NIH) protects the public interest in its establishment and oversight of Cooperative Research and Development Agreements (CRADAs).

BACKGROUND

Collaboration between the NIH and Non-Federal Organizations

The NIH is one of the world's premier biomedical research institutions. It has as its mission "science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability."¹ The NIH fiscal year 1993 budget of \$10.3 billion supports research through 16 institutes, 6 centers, 1 division, and the National Library of Medicine. Approximately 85 percent of this budget is spent in support of extramural research conducted by scientists who are not Federal employees, working in laboratories that are not owned or operated by the Federal government. The remaining 15 percent of the budget supports intramural research conducted by federally employed scientists working primarily on the NIH campus.²

Intramural researchers have long collaborated with organizations outside of the Federal government in the research and development of biomedical discoveries and inventions and in the transfer of Federal technologies to industry for commercialization. Intramural scientists publish their research findings, present their work in lectures and at meetings, act as unpaid advisors to external organizations, and, on their own time, perform paid consultancies. In addition, they exchange chemical compounds for research purposes with outside laboratories, screen chemical compounds for such organizations, and conduct clinical trials with such organizations. Some collaboration is undocumented; other cooperative work is formalized in written agreements.

Historically, however, Federal scientists have not been encouraged to pursue research with potential commercial applications. In addition, because exclusive licenses were difficult to obtain, industry had little incentive to develop Federal inventions.³ Of the more than 28,000 patents that the Federal laboratories accumulated over the years, only approximately 5 percent had ever been licensed as of the mid-1980s.⁴

Legislation in Support of Technology Transfer

Growing concern about U.S. competitiveness in the world economy has motivated the passage of several technology transfer laws since 1980. These laws are intended to

increase U.S. productivity by fostering collaboration between academic institutions, Federal laboratories, and private industry in the development of new technology. The Stevenson-Wydler Technology Innovation Act of 1980 (P.L. 96-480) was intended "(1) to build links between generators of knowledge (universities and Federal laboratories) and users of knowledge (industry and State and local governments); and (2) to build into the Federal Government a positive concern for the welfare of industry."⁵ The Federal Technology Transfer Act (FTTA) of 1986 (P.L. 99-502) amended the Stevenson-Wydler Act with provisions specifically designed to "improve the transfer of commercially useful technologies from the Federal laboratories and into the private sector."⁶

The CRADA

The FTFA established the CRADA as a new mechanism for collaboration between Federal researchers and State and local governments, private businesses, foundations, nonprofit organizations, and others. Through CRADAs, Federal agencies can provide personnel, services, facilities, equipment, and other resources, but not funds, to nonfederal organizations for the conduct of specific collaborative research and development efforts that are consistent with the Federal laboratories' missions. The nonfederal organizations can contribute all of the above and funds. The NIH stipulates that all collaborative partners must make significant intellectual contributions to CRADA projects.⁷ The FTFA requires that Federal agencies give preference to small and domestic businesses when choosing CRADA partners.

The CRADA provides incentives for both industry and government to cooperate in the development and commercialization of Federal inventions. It allows industry to invest funds directly in specific government research projects and to negotiate in advance for exclusive rights to cooperatively developed inventions.⁸ The FTFA makes technology transfer the responsibility of each Federal laboratory and provides for compensation of Federal employees with royalties and cash awards programs.⁹ It allows agency heads to delegate to their laboratory directors the authority to enter into CRADAs and calls for expedited central-agency consideration of proposed CRADAs.¹⁰

According to the Department of Commerce, Federal laboratories administered a total of 731 active CRADAs in 1991.¹¹ The Department of Health and Human Services administered 125 active CRADAs in 1992. Of the 93 managed by NIH in 1992, 69 percent were concentrated within three institutes: the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).¹²

The number of CRADAs established annually at these 3 institutes has increased from 16 in 1990 to 24 in 1992. The number of companies and NIH investigators entering new CRADAs has also increased. The total number of industry partners entering new CRADAs at the three institutes increased from 14 in 1990 to 23 in 1992. The number

of NIH principal investigators entering new CRADAs increased from 13 in 1990 to 20 in 1992. (See table 2 in appendix B for more information.)

Concerns about NIH CRADAs

Policy and procedures on CRADAs continue to evolve as NIH experience with this relatively new collaborative mechanism grows. Several recent studies have found, however, that problems persist in the choice of CRADA research topics, the identification of CRADA partners, the specifics of CRADA documents, and the oversight of CRADA work. The Office of Inspector General, through the Office of Audit Services, issued a report in March 1992 that identified problems in the management of NIH technology transfer efforts and in the management of NIH patents and royalty income.¹³ Several NIH administrators have themselves indicated concern over the need for improved CRADA management.¹⁴

As the Federal investment of resources and personnel in CRADAs increases, it is imperative that NIH protect the public interest with practices that adequately guard against potential vulnerabilities. In order to satisfy the intent of the FTTA, however, these practices cannot be so cumbersome as to discourage either industry or NIH researchers from collaborating through CRADAs.

Our report examines the usefulness of the CRADA as a collaborative mechanism and identifies important challenges to the future success of the NIH CRADA program. We conducted this study in response to a request from the Chairman of the United States Senate Special Committee on Aging.

METHODOLOGY

Our findings are based primarily on a review of documents for the 61 CRADAs established at NCI, NIAID, and NIDDK in calendar years 1990, 1991, and 1992; and on interviews with NIH principal investigators, NIH administrators, and industry representatives involved in the 24 CRADAs established at these three institutes in 1992. We gathered supplemental information from a review of relevant legislation, Congressional testimony, literature, NIH memoranda and training materials on CRADAs, and minutes from the meetings of the NIH Technology Transfer Board and its CRADA Subcommittee. (See appendix A for more detail on our methodology.)

We conducted our review in accordance with the *Quality Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

FINDINGS

GOVERNMENT AND INDUSTRY PARTICIPANTS IN NIH CRADAS REPORTED THAT THE CRADA IS A USEFUL MECHANISM FOR COLLABORATION.

The CRADA can facilitate the pooling of NIH and private-sector intellectual and financial resources, equipment, facilities, and research materials.

Investigators at NIH reported that the CRADA is a useful means by which they can enter into formal collaborative relationships with their peers in the private sector in order to share intellectual property, research materials, skills, and expertise. The need for collaboration among scientists in government, industry, and academia has increased in recent years as the questions addressed in the life sciences have become increasingly complex. The legal protection provided by the CRADA allows the NIH and private sector partners to work together and to share proprietary information freely in the pursuit of common research goals.

Most of the NIH investigators with whom we spoke stressed that their industry partners made substantial contributions to their CRADA projects. As one NIH investigator explained, "most CRADAs don't arise out of a single brilliant idea from an NIH lab; both sides have some good ideas and some limitations, and both bring something to the table. It's a real merger of talents." Several NIH investigators informed us that, in fact, the research they were conducting through their CRADAs would not have been possible without the option of formal collaboration. In some instances the industry partner held the patent to an invention whose use was necessary for the research. In other cases, the industry partner possessed expertise not readily available at NIH.

The industry representatives with whom we spoke--including scientific, management, and legal staff--described the CRADA as a valuable means of expediting the development and commercialization of new products. One industry investigator summed up a common industry comment, noting that "if these sorts of relationships were not possible, it would be a serious blow to the field and to the nation." Representatives of small companies consider working with NIH to be a particularly great benefit.

Many NIH investigators with whom we spoke also described the CRADA as a useful means of expediting research projects through the addition of funds and staff. The median industry financial contribution to the 61 CRADAs established at NCI, NIAID, and NIDDK during the 1990-92 period was \$40,000--ranging from \$0 to more than \$5 million each.¹⁵ One-third of these CRADAs involved no contribution of funds; one-quarter involved total contributions of more than \$100,000 each. (See tables 4 and 5 in appendix B for more information.)

The CRADA can protect the intellectual property rights of the government in inventions that result from collaborative efforts.

Investigators at NIH noted that the legal protections of the CRADA serve well to safeguard the government's interest in the potential outcomes of their collaborative efforts. These protections give the scientists a sense of security, allowing them to share materials and work freely. The CRADA serves as what one investigator described as a "seal of approval" on their collaborative arrangements, allowing them to demonstrate that they have covered all the bases in their dealings with an industry partner.

While scientists continue to conduct tests and to share information and materials outside of the CRADA framework, NIH policy requires that investigators establish "a formal CRADA upon determination that interactions with outside collaborators might result in an invention or commercial product."¹⁶ As one institute scientific director described it, the CRADA is "a tool to use when your research has brought you to the point where it looks as though you have something that might work." One investigator described another commonly noted advantage: Although scientists can no longer share information and materials with their peers outside NIH as quickly or as readily as they could before the CRADA mechanism was introduced, they can actually share such things more widely and freely once the paperwork is done. They can be confident that the government's interests are protected.

The CRADA can facilitate the transfer of technology from NIH laboratories to the private sector for development and commercialization.

In 10 of the 32 CRADAs established at NIAID and NIDDK during the 1990-92 period, the government held a preexisting dominant patent necessary for the research project (this information was unavailable from NCI). The CRADA mechanism allows NIH investigators to share these technologies with their industry collaborators, both as components of larger research projects and, in some instances, as potentially marketable products. A number of industry representatives reported that, as one described it, the CRADA is "a substantial inducement to the development of new technologies."¹⁷

The CRADA program itself has served to heighten awareness among NIH researchers of the potential for the practical applications of research. One NIH investigator summed up this effect, describing CRADAs as having made NIH scientists "think more about the implications of their research for health." He commented of his research that he "never would have thought that this stuff was marketable." Many of our contacts remarked on the significance of this heightened awareness. As another scientist explained, "the bench is getting closer to the patient. Working with industry means that you are closer to the bedside, which is ultimately what NIH is all about." He added that it is "gratifying" for NIH investigators to see their work put to practical use.

NONETHELESS, SEVERAL CHALLENGES TO THE EFFECTIVE MANAGEMENT OF THE NIH CRADA PROGRAM COULD JEOPARDIZE ITS FUTURE SUCCESS.

Many CRADA projects may not be well-suited for the CRADA mechanism because they do not focus on the transfer of Federal technology to the private sector for commercialization, which is the central intent of the FTTA.

According to Congress, "the primary purpose of the [CRADA] agreements is to take technologies that originate in the [Federal] laboratories and to stimulate or support their development and commercialization."¹⁸ The NIH policy further states that the CRADA is designed to "facilitate the transfer of technology from Federal labs into the private sector for further development and commercialization."¹⁹

Many of the 61 CRADA projects established at NCI, NIAID, and NIDDK between 1990 and 1992, however, do not adhere to the central intent of Congress and NIH. In particular, this is true of those CRADA projects that center on either basic research or NIH routine testing of industry-patented inventions.²⁰ (See tables 8 and 9 in appendix B for more information.)

Thirteen of the 61 CRADA projects focused exclusively on basic research. Such research involves the investigation of fundamental biological structures and mechanisms. The purpose of one basic-research CRADA was to determine the tumor-producing mechanism of an industrial chemical. The goal of another was to discern the structure of a chemical found in the body. While some basic-research CRADAs may yield results which provide a foundation for future endeavors with clear commercial relevance, this kind of research is not intended to transfer commercially useful technology to the private sector. Accordingly, while it is not prohibited by law, it is inconsistent with the central intent of the FTTA and with NIH CRADA policy.

None of the scientists with whom we spoke cited this inconsistency as a source of worry. Several, however, made a point of noting that industry funding of basic research through CRADAs could bias the choice and direction of NIH research. These scientists were concerned that future NIH research budgets might be reduced by an anticipated amount of CRADA funding and that their laboratories might, as a result, become dependent on "soft" industry funding.²¹

Of the 12 preclinical and clinical CRADAs for which we were provided patent information, 2 focused on NIH performing routine testing of industry-patented inventions.²² In one such CRADA project, NIH coordinated clinical trials for regulatory approval of a new therapeutic agent that is patented by industry. In another, NIH conducted clinical trials to evaluate a new use for an already-marketed, industry-patented drug. Here again, even though the CRADA might result in expedited drug development and approval, and even though the CRADA might allow NIH to obtain unique resources or important data, no transfer of technology from the

Federal laboratories to the private sector is intended. Thus, these CRADAs are inconsistent with the central intent of the FTTA and NIH CRADA policy.²³

Five of the 26 NIH CRADA scientists with whom we spoke made a point of expressing concern about this type of CRADA. The scientists' apprehensions were summarized by one, who explained that "it seems less a scientific collaboration than a service." A few CRADA administrators also expressed unease about such routine-testing CRADAs. They did not want to sacrifice scientific advancement by committing the finite intellectual and financial resources of NIH to clinical trials that would otherwise be conducted by industry.

Why, then, do NIH scientists collaborate with their industry counterparts in CRADAs if they do not focus on technology transfer as envisioned by Congress and NIH? The most basic explanation we were able to derive from our interviews is that, amidst concerns about conflict of interest and intellectual property rights, the CRADA mechanism provides unique and valuable formal protection for both governmental and industry partners. Thus, some collaborations that might well have been undertaken informally in prior years are now more likely to be formalized through CRADA agreements, even if they do not involve the transfer of Federal technology to the private sector.

The process of establishing a CRADA is lengthy and complex. This may discourage participation in CRADAs, and may undermine the intent of the FTTA, which calls for an expeditious review and approval process.

- *For the 24 CRADAs established at NCI, NIAID, and NIDDK in 1992, the median length of time from initial contact between the NIH and industry partners to final approval was 330 days. This was an increase from a median of 259 days in 1990.*

The NIH CRADA approval process requires several levels of review, and a CRADA can be reviewed more than once at each level for revisions.²⁴ The final stage of this process entails a central review by the CRADA Subcommittee of the NIH Technology Transfer Board. This step allows the central NIH administration an opportunity to disapprove or require modification of proposed CRADAs; the FTTA allows a maximum of 30 days for such review. Of the 24 CRADAs approved at NCI, NIAID, and NIDDK in 1992, however, only 2 received this central review within 30 days. The median time required for this step was 69 days.²⁵ (See tables 6 and 7 in appendix B for more information.)

Despite ongoing efforts to improve the process,²⁶ it continues to be complex and confusing. The institute technology development coordinators recently noted their "frustration and concern with the number of individuals and organizations which review the CRADA, the often repetitive nature of the review, ... [and] the excessive time from submission to final approval of a negotiated CRADA."²⁷

Private-sector collaborators also contribute to the length of the process. Several industry contacts with whom we spoke noted that their organizations often require considerable time to make both scientific decisions about the content of projects and business decisions about the legal obligations of the agreement.

- *Many NIH and industry partners describe the process as inefficient and view it as a disincentive to their continued participation in the NIH CRADA program.*

Twelve of the 24 NIH investigators and 11 of the 15 industry partners with whom we spoke made a point of noting that the process was not time-efficient. One NIH investigator summed up the frustrations of many, noting that "things take a very long time; if you're not really interested in a project, forget it." Several NIH investigators noted that it is easy for the "science to get stale" after a lengthy wait for approval. One investigator described his project as a "hot topic," and expressed great disappointment that the research had been delayed 14 months because of CRADA paperwork.

Several of the NIH investigators with whom we spoke reported that they would avoid doing collaborative research through the CRADA mechanism again because of the delays involved. One investigator noted that, on seeing what "a hassle" the process had been for him, his colleague in an adjacent lab decided never to do a CRADA. Another NIH investigator pointed out that "some good projects don't happen because the process is too long;" the process may actually discourage collaboration that might otherwise be undertaken informally.

At the time of the passage of the FTTA, Congress noted that "lengthy headquarters approval delays can cause businesses to lose interest. . . ."²⁸ Indeed, several of the industry partners with whom we spoke suggested that, although they were currently involved in CRADAs, they regarded the length of the process as a great disincentive to participation. The technology development coordinator at one institute told us of three major drug firms that will not participate because of the time required by the process.

The NIH does not have guidance that adequately addresses the complexities of providing fair access to CRADA opportunities. Failure to ensure fair access--and the appearance thereof--could deter industry participation in CRADAs, impede market competition, and undermine public support for the CRADA program.

Ensuring fair access to NIH CRADAs is a complex matter that raises many difficult questions. Under what circumstances should the institutes advertise specific CRADA opportunities? How should they take into account prior collaboration between NIH scientists and potential CRADA partners? How broad should they allow the scope of a CRADA research plan to become? How many CRADAs should they allow any one company to enter in a specific field of research at NIH? How should they provide

preference to small and domestic businesses as potential CRADA partners, as called for by the FTTA?

Congress, in the FTTA, gives little guidance on how to answer these questions, except to indicate that conflict of interest guidelines should be established for Federal employee conduct and that normal procurement contract procedures do not apply to CRADAs. The PHS goes somewhat further. In a February 1989 policy statement, PHS stresses the importance of both ensuring fairness in access and adhering to congressional preferences; it then offers some guidelines for NIH and other PHS components to use in fulfilling these goals.²⁹ The NIH has not elaborated upon these guidelines to provide further guidance for its scientists and CRADA administrators.

As a result, NIH scientists and CRADA administrators in the institutes are handicapped in their attempts to answer the myriad difficult questions concerning fair access. While the FTTA indicates that the institutes should retain considerable independence and flexibility in establishing CRADAs, central operational guidance is necessary to address such a sensitive and complicated matter as fair access. At present, the institutes lack such guidance regarding at least four central dimensions of providing fair access:

(1) They lack sufficient guidance regarding the circumstances in which they should advertise specific CRADA opportunities. The 1989 PHS fair access guidelines call for specific announcements when it is anticipated that a "substantial number of private sector organizations are likely to be interested in the opportunity."³⁰ Neither the PHS fair access guidelines nor NIH, however, identify the types of CRADAs that might elicit interest from multiple organizations. As a result, individual institutes address the need for special announcements according to their own policies or on a case-by-case basis. Many of the scientists with whom we spoke were uncertain of their responsibilities regarding the provision of fair access. Of the 61 CRADAs established at NCI, NIAID, and NIDDK between 1990 and 1992, 8 were advertised as specific CRADA opportunities.³¹ For 33 of these 61 CRADAs, we were provided information on which CRADA partner had initiated the collaboration; in 8 of these, the industry partner had done so.³² It might be inappropriate for NIH to advertise such CRADAs.

(2) They lack sufficient guidance regarding what relationships may exist between NIH scientists and their CRADA partners prior to the establishment of a CRADA. The PHS fair access guidelines do not address this issue. The NIH requires all NIH CRADA participants to submit a "Conflict of Interest and Fair Access Survey" as part of the CRADA approval process, but the individual institutes have different procedures to manage conflict of interest concerns. At least one institute requires a six-month "cooling-off" period between the termination of a consulting relationship between an NIH scientist

and a company and the establishment of a CRADA between the two; other institutes have no such requirement.³³

Many of the scientists with whom we spoke expressed confusion as to what preexisting relationships between themselves and their CRADA partners were acceptable. Of the 61 CRADAs established at NCI, NIAID, and NIDDK in 1990, 1991, and 1992, 20 grew out of prior working relationships between the partners.³⁴

(3) They lack sufficient guidance regarding the fair access implications of the breadth of CRADA research plans or the number of CRADAs that a company is allowed in a specific area of research. Narrowly defined work plans allow greater competition and are less likely to enable any single company to monopolize a given field of NIH research. Similarly, controlling the circumstances in which a company is allowed multiple CRADAs in a given field is a means of both promoting competition and limiting opportunities to monopolize NIH research. Neither the PHS fair access guidelines nor NIH, however, explicitly address these issues.

(4) They lack clear, operational definitions of the terms "small business" and "domestic business" to assist them in their compliance with the FTTA. In December 1992, the Office of the Secretary, Office of the General Counsel provided the CRADA Subcommittee with an opinion about the meaning of these terms. From the perspective of many in the institutes, however, much ambiguity remains.³⁵ In addition, because neither the PHS fair access guidelines nor NIH offer guidance regarding the means by which this preference is to be provided, the individual institutes have inconsistent practices. One institute advertises each CRADA for which a foreign industry partner is being considered; others do not.

Unfair access to CRADA opportunities--or even the appearance of it--could have serious detrimental effects. It could result in certain companies gaining advantaged access to patentable new technologies and expedited product development, while others lose interest in what they regard to be a closed process. It could discourage competition in emerging markets and therefore contribute to higher prices and/or reduced access to products. Furthermore, it could undermine public support for a collaborative mechanism intended by Congress to promote the public interest.

Limited NIH oversight of CRADA projects may inhibit the ability of NIH to ensure that CRADA work is consistent with the intent of the FTTA and NIH policy.

The FTTA indicates that CRADAs should be managed largely at the institute level. Nevertheless, some central-NIH oversight is necessary to protect both the government and its industry partners by providing coordination and consistency in the

administration of CRADAs among the many NIH institutes. Indeed, the FTTA clearly states that each agency is to maintain a record of all CRADA agreements.

The NIH has established a central structure to coordinate CRADA activities among the institutes. Central-NIH oversight of CRADAs is handicapped, however, because NIH has not implemented a central system to track approved CRADAs, the involvement of industry partners in CRADAs at more than one institute, or the NIH investment of funds, resources, and personnel in CRADA projects.³⁶

The central-NIH administration is not apprised of the status of ongoing CRADA projects. Some CRADAs expire and are terminated without the knowledge of the central-NIH administration. Companies fund multiple CRADAs with different institutes, and no central-NIH record documents the extent of their full involvement with NIH. It has been the practice to allow significant amendments to previously approved CRADAs without the knowledge of the central-NIH administration. For example, one CRADA, which was originally approved in 1987 as a one-year project, has been renewed annually without central NIH review. Other CRADAs, which began as preclinical research projects, have progressed to clinical trials without central-NIH oversight.³⁷

This lack of information at the central-NIH level limits NIH's ability to make prudent decisions about the allocation of its resources and the commitment of its intellectual property in newly proposed CRADAs. This information gap also limits NIH's ability to ensure that approved CRADA projects are being conducted in a manner that is consistent with NIH policy and the intent of the FTTA.

The pricing of CRADA products is a matter of considerable controversy that reflects NIH's difficulty in achieving a balance between protecting the public investment in CRADAs and maintaining industry's incentive to participate in them. This controversy threatens to undermine support for the NIH CRADA program.

Congress, in the FTTA, did not address the pricing of products emerging from CRADAs. The NIH has done so, however, with the inclusion of a "reasonable pricing" clause in the "NIH Policy Statement on Cooperative Research and Development Agreements and Intellectual Property Licensing."³⁸ This clause is also incorporated into the model CRADA. It expresses NIH's interest that there be a "reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public." It further states that NIH may require CRADA partners to support this relationship with "reasonable evidence." While the clause has served as an important reference point in the crafting of CRADAs, it is widely regarded as inadequate.

As industry representatives, Congressional representatives, academics, and NIH administrators have noted, NIH is ill-equipped to implement its policy for the pricing of CRADA products. It lacks explicit legislative authority to obtain necessary cost

information from industry partners and the requisite expertise to analyze such data. The NIH director reported to Congress that "NIH is not equipped, either by expertise, or programmatic or legislative mission, to undertake an analysis of the 'reasonableness' of private-sector product pricing decisions."³⁹

Consumer advocates have pointed out that, as a result, NIH is unable to protect the public's investment in products which result from CRADAs. Such advocates have argued that the public is left in a position in which it might be forced to pay inappropriately high prices for drugs whose research and development they have financed as taxpayers.

Industry views the clause as being too broad and too threatening to companies' proprietary interests in a highly competitive marketplace.⁴⁰ Industry partners argue that they must agree to the clause without knowing how NIH will attempt to implement its intent when it comes time to market a product. Some companies have cited it as the basis for their refusal to participate in CRADAs.⁴¹ Many who have participated have done so on the condition that specific limitations or assurances be reflected; the clause has been modified in 13 of the 61 CRADAs established at NCI, NIAID, and NIDDK between 1990 and 1992.⁴²

To date, only one CRADA product has reached the marketplace and been priced--an anti-cancer agent, Taxol.⁴³ In this instance, however, the model "reasonable pricing" clause was modified and NIH did not attempt to ascertain that there was a reasonable relationship between the price of the product and the public investment in its development.⁴⁴ Instead, to promote the establishment of a "fair market price," NIH asked its industry CRADA partner to set the price of the drug below the median for other recently approved anticancer drugs. In addition, NIH entered into a CRADA with another company to develop a product that will provide market competition for Taxol.⁴⁵

In the months following the pricing of Taxol, controversy regarding the NIH approach has resulted in three Congressional hearings.⁴⁶ While NCI and its CRADA industry partner are apparently satisfied with the approach taken to ensure a fair price for the drug, Congressional representatives, consumer advocates, and academics have raised strong objections.⁴⁷ They contend that the method employed was inappropriate, that the data used were seriously flawed, and that NCI had insufficient information to ascertain that the price set was, indeed, fair.⁴⁸

During the next few years additional CRADA products are likely to come to market. Left unresolved, the controversy concerning the pricing of these products could escalate to such a point that it jeopardizes the entire NIH CRADA program.

RECOMMENDATIONS

Government scientists and their industry partners consider the CRADA to be a useful mechanism that can facilitate the transfer of technology from the NIH laboratories to the private sector for development and commercialization. Thus, NIH CRADAs can accelerate the development of healthcare inventions and stimulate the U.S. economy, as Congress intended.

We have identified several important challenges to the effective management of the program, however, that could undermine its future success. In a recent report, the Office of the Assistant Secretary for Health noted some of the same challenges. The NIH has also identified and begun to address several of these challenges.⁴⁹

In each area, a successful response requires that a careful balance be achieved between enhancing the protection of the public investment in CRADAs and preserving interest in CRADA participation among NIH scientists and in industry. Such a response must also be consistent with the decentralized and expeditious CRADA management called for by the FTTA. With these considerations in mind, we offer the following recommendations to strengthen the management of the NIH CRADA program:

The NIH should implement guidelines that clearly indicate the types of research projects that are appropriate for the CRADA mechanism.

To address the apparent inconsistency between the intended and current uses of the CRADA, NIH should build upon its current efforts to develop and implement clear criteria for determining if proposed collaborative research projects are appropriate for the CRADA mechanism. The NIH should clarify under what circumstances, if any, projects that are not intended to transfer technology to the private sector for commercialization--such as those that primarily involve either basic research or NIH performing routine research on industry-patented compounds--are appropriate for the CRADA.

In order to facilitate the CRADA management process and to reduce confusion among potential CRADA participants, it is important that NIH inform its scientists and potential industry CRADA partners about the appropriate uses of the CRADA mechanism. With this clarification, NIH could better ensure that its CRADA projects are consistent with the central intent of the FTTA and with NIH CRADA policy.

Because collaborative basic-research efforts and projects in which NIH performs routine testing of industry-patented compounds can be of benefit to the public and are consistent with the NIH mission, NIH could pursue the development of alternative mechanisms to formalize these collaborations. The NIH might consider whether or

not legislative amendments are necessary to support the development of these alternative mechanisms.

The NIH should build upon its current efforts to clarify and streamline the CRADA review and approval process.

To reduce the length and complexity of the CRADA review and approval process, NIH should build upon its current efforts to better define this process. The NIH should determine which reviews are necessary and the exact purpose of each. The NIH might clarify the circumstances in which particular classes of CRADAs--perhaps those in which options to negotiate exclusive licenses have been waived--might be exempted from particular stages of review. The NIH should determine the appropriate participants in each stage of review. In defining this process, it is important that NIH pay particular attention to avoiding possible redundancies.

As an additional step to increase the timeliness of the CRADA review and approval process, NIH could establish timeframes for completing each stage of the approval process. Review teams that currently meet on a monthly basis could meet more frequently or on an as-needed basis to complete their work within the established timeframes.

Providing greater definition to the CRADA review and approval process would both expedite that process and reduce confusion--and resulting frustration--among CRADA participants and administrators.

The NIH should further develop the fair access guidelines to reflect the full range of issues involved.

To better ensure the consistent provision of fair access to NIH CRADA opportunities in all institutes, NIH should build upon the current PHS guidelines regarding announcements of specific CRADA opportunities. In particular, NIH should clearly define the circumstances in which a substantial number of companies are likely to be interested in a CRADA opportunity. For example, NIH might determine that there is likely to be wide interest in CRADAs that include clinical trials which are not primarily dependent on industry-patented inventions. The NIH could indicate other circumstances that warrant announcements of specific CRADA opportunities. For instance, NIH might determine that special announcements are called for whenever a foreign partner is being considered for a CRADA project that is not primarily dependent upon industry-patented inventions.

The NIH should build upon the "Technology Transfer Act Interagency Conflict of Interest Guidelines" now being developed by the Interagency Task Force on Technology Transfer. With this as a basis, NIH could clarify appropriate procedures for managing prior relationships between NIH scientists and their CRADA partners.

It is also important that NIH provide guidance to its scientists and CRADA administrators regarding the fair access implications of the breadth of CRADA research plans and the circumstances in which a company might be allowed to enter into multiple CRADAs in a given field of NIH research. To assist its scientists in their efforts to ensure fair access, NIH might provide examples of overly broad research plans and amended, more narrowly focused research plans.

Finally, the NIH should seek to establish clear, operational definitions of the terms "small business" and "domestic business" so that Federal scientists and CRADA administrators will be better able to comply with the intent of the FTTA.

A detailed compendium of rules and regulations would be counterproductive in an organization such as NIH, in which flexibility is central to the nature of the work. More fully developed guidance, however, would ensure a greater degree of consistency among institutes in the provision of fair access. It would also ease confusion and frustration on the part of CRADA participants, and diminish misunderstandings on the part of both industry and the public.

The NIH should develop and maintain a central database system to track all ongoing CRADA work.

To assist central and institute administrators in their efforts to ensure that CRADA projects are appropriate and acceptable, NIH should develop a central CRADA database that is frequently updated and readily accessible by Technology Transfer Board members, CRADA Subcommittee members, and the TDCs in all institutes. In developing this system, NIH could build upon its experience with CRADA databases in the individual institutes and the OTT.

The database might include information on several different dimensions of CRADA research, perhaps including the name of the principal investigator; the name of the nonfederal CRADA partner; the subject of the research; a classification of the research as basic, preclinical, clinical, involving the development of laboratory techniques or equipment, or other; the original approval date and intended term of the CRADA; CRADA renewal dates and renewed terms; any other amendments to the originally approved CRADA and their dates; CRADA expiration or termination dates; the funds that have been approved for transfer from industry; the funds that have actually been transferred; the NIH investment of funds, personnel, and resources in CRADA projects; who holds the patents necessary for the CRADA research; a listing of all patents, licenses, and products that have resulted from the CRADA; and a listing of any unresolved problems with the CRADA.

Such a database would support NIH in its efforts to ensure both that CRADA work is consistent with the intent of the FTTA and NIH policy, and that newly proposed CRADAs are appropriate in the context of the NIH-wide CRADA portfolio.

The NIH, working with the Office of the Secretary and the Office of the Assistant Secretary for Health, should seek a consensus on how to resolve the reasonable pricing controversy.

The pricing of CRADA products is an extremely complex and volatile matter--one that involves issues extending well beyond NIH's own domain. It is intricately related to the current deliberations on national health care reform. It involves basic considerations about the prices of all pharmaceuticals, whether or not they are produced through the CRADA mechanism. It raises questions about what, if any, access government should have to private-sector cost data and the criteria it should use in determining what is fair. It triggers still other questions about the expertise necessary to determine what is a fair price and about where such expertise should reside.

These are questions and considerations which NIH can not resolve itself. Nonetheless, NIH has an important role in helping the broader policy community recognize that the entire CRADA effort is dependent on resolving them in a manner that lowers the level of controversy and allows the Department to achieve a balance between the competing objectives of protecting public investment in NIH CRADAs and preserving industry's incentive to participate in them.

Obtaining such resolution is urgent. In the next few years many of the CRADA projects now underway are likely to result in marketable products. Some of these may raise pricing controversies every bit as intense as the one surrounding Taxol. At present there is a window of opportunity that could be used to help ensure the future success of NIH's CRADA efforts.

COMMENTS ON THE DRAFT REPORT

We solicited and received formal comments on our draft report from PHS. We respond here to the major themes contained in the comments. We first summarize the comments, and then provide our response in italics. We include the complete text of the agency's comments in appendix C.

The PHS concurred with four of our five recommendations. The agency did not concur with our recommendation that NIH should implement guidelines that clearly indicate the types of research projects that are appropriate for the CRADA mechanism.

The PHS believes that restrictions on the use of the CRADA are already explicitly addressed in current CRADA guidelines, that there is no legal requirement for further restrictions, that there is no inconsistency between the intended and current uses of the CRADA, and that NIH laboratories and public access to CRADA inventions are adequately safeguarded by current NIH policy and procedures.

In our report findings, we note that many NIH CRADA projects may not be well-suited for the CRADA mechanism because they are inconsistent with the central intent of the FTTA. This intent is articulated on page one of the Legislative History of the Act (Senate Report No. 99-283), where it is stated "the purpose of this bill [the FTTA] is to improve the transfer of commercially useful technologies from the Federal laboratories and into the private sector." This purpose is reiterated throughout the legislative history of the Act.

We are particularly concerned that basic-science research projects and NIH routine testing of industry-patented inventions may not be intended to transfer commercially useful technologies from the Federal laboratories to the private sector. We recognize that none of the NIH CRADA projects we reviewed is prohibited by the FTTA. Our concern focuses on fulfilling the intent of the Act, rather than on a narrowly defined compliance with the letter of the law.

In our recommendation, we urge NIH to implement guidelines that clearly indicate the types of research projects that are appropriate for the CRADA mechanism. We suggest that NIH clarify under what circumstances, if any, projects that are not intended to transfer technology to the private sector for commercialization are appropriate for the CRADA.

We continue to believe that it is important for NIH to implement such guidelines. As the draft NIH CRADA Manual Policies and Procedures acknowledges, "only a segment of the broad spectrum of all NIH research activities may be appropriate for consideration for CRADAs." We urge NIH to elaborate on this statement by providing further guidance to potential CRADA participants and CRADA administrators as to the definition of the segment of NIH research that may be appropriate for conduct as a CRADA. The NIH can best protect the public investment in NIH and its scientists by providing clear

guidance now, before CRADA activity becomes more prevalent, before more public resources are expended, and before more CRADA products reach the market.

The PHS concurred with our recommendation that NIH build upon its current efforts to clarify and streamline the CRADA review and approval process. The PHS referred to a committee that has been formed to address this task and to a policy document that it is developing to fulfill this recommendation.

The PHS concurred with our recommendation that NIH further develop the fair access guidelines to reflect the full range of issues involved. To fulfill this recommendation, NIH has established an ad hoc committee to evaluate fair access issues and to develop a revised PHS policy for fair access to CRADAs.

The PHS concurred with our recommendation that NIH develop and maintain a central database system to track all ongoing CRADA work. The PHS outlined steps it will take to develop a plan for such a database system and noted that there is not yet a date for completion of either the plan or the database system. In addition, PHS noted that it is difficult to quantify the value of personnel and resources that NIH devotes to CRADA projects.

We recognize that it is difficult to quantify the value of the NIH investment in CRADAs. We suggest, however, that the importance of being able to do so outweighs the burden of the work involved. The NIH responsibility for public accountability necessitates that the agency be prepared to provide a full report on the allocation of public funds. In addition, an understanding of the NIH investment in the development of commercial products to be sold for profit by industry is critical to any consideration of pricing for those products.

The PHS concurred with our recommendation that NIH, working with the Office of the Secretary and the Office of the Assistant Secretary for Health, seek a consensus on how to resolve the reasonable pricing controversy. The PHS noted the steps it has taken and plans to take in response to our recommendation.

In addition, PHS provided three technical comments on our report. *We have revised our report to reflect these comments.*

APPENDIX A

METHODOLOGY

Our findings and recommendations are based on five main sources of information:

1. A review of NIH documentation for the 61 CRADAs established at NCI, NIAID, and NIDDK in calendar years 1990, 1991, and 1992. These three institutes accounted for approximately 69 percent of all NIH CRADAs in 1992. Each file included the legal CRADA document, correspondence, and various patent and licensing records. From each file, we collected information on the length of the CRADA term, the amount of money to be transferred to NIH by the CRADA partner; and whether or not a clinical trial was being conducted, the collaborative opportunity was advertised, the industry partner was categorized by NIH as a small or foreign business, the reasonable-pricing clause was modified or deleted, and an option for a nonexclusive or exclusive license to CRADA inventions was provided.

In addition, we asked the technology development coordinators in each of the three institutes we reviewed to provide us with additional information for their respective 1990-92 CRADAs, including the type of research involved, and whether patents were held by NIH or the industry partners.

2. Interviews with NIH scientists and industry contacts involved in the 24 CRADAs established at NCI, NIAID, and NIDDK in 1992. We gathered information from each contact on his or her experience with the CRADA program. Most of these interviews were conducted by telephone.

3. Other interviews. We interviewed NIH administrators, including institute scientific directors, technology development coordinators, members of the Patent Policy Board (which was renamed the Technology Transfer Board in the Spring of 1993) and its CRADA Subcommittee, and staff in the Office of Technology Transfer and the Office of the Secretary, Office of the General Counsel. We also held discussions with academics concerned with technology transfer, and with representatives from the Department of Commerce, the General Accounting Office, and the Office of the Assistant Secretary for Health.

4. Review of the literature. We reviewed relevant legislation and literature, NIH memoranda and training materials, minutes from the meetings of the NIH Patent Policy Board and its CRADA Subcommittee, and CRADA files and database information from the Office of Technology Transfer.

5. Conference and meeting attendance. We attended the October 1992 PHS Technology Transfer Forum, two meetings of the CRADA Subcommittee, and a public meeting of the Advisory Committee to the Director of NIH.

APPENDIX B

A STATISTICAL PROFILE OF CRADAs ESTABLISHED AT NCI, NIAID, AND NIDDK

1990-92

Tables

- 1 Number of CRADAs approved, by institute and year; NCI, NIAID, and NIDDK; 1990-92
- 2 Number of NIH scientists and industry partners entering into at least one CRADA; NCI, NIAID, and NIDDK; 1990-92
- 3 Mean approved duration of CRADAs, in years; NCI, NIAID, and NIDDK; 1990-92
- 4 Mean funds approved to be provided by industry CRADA partners, in thousands of dollars; NCI, NIAID, and NIDDK; 1990-92
- 5 Median funds approved to be provided by industry CRADA partners, in thousands of dollars; NCI, NIAID, and NIDDK; 1990-92
- 6 Median elapsed time from initial contact between CRADA partners to final CRADA approval, in days; NCI, NIAID, and NIDDK; 1990-92
- 7 Median elapsed time from institute submission of a CRADA to completion of review by the CRADA Subcommittee of the NIH Technology Transfer Board, in days; NCI, NIAID, and NIDDK; 1992 only
- 8 Number and percentage of CRADAs involving each type of research, by year; NCI, NIAID, and NIDDK; 1990-92
- 9 Number and percentage of CRADAs involving each type of research, by institute; NCI, NIAID, and NIDDK; 1990-92
- 10 Number of CRADAs for which NIH held a preexisting patent necessary for the research; NIAID and NIDDK only; 1990-92
- 11 Number of CRADAs for which the industry partner held a preexisting patent necessary for the research; NIAID and NIDDK only; 1990-92

Tables

- 12 Number of CRADAs in which the reasonable pricing clause was modified; NCI, NIAID, and NIDDK; 1990-92
- 13 Number and percentage of CRADAs in which the industry partner was categorized by NIH as a small or foreign business; NCI, NIAID, and NIDDK; 1990-92
- 14 Number and percentage of CRADAs that were advertised as specific opportunities or that grew out of prior working relationships between the partners; NCI, NIAID, and NIDDK; 1990-92

Table 1

Number of CRADAs approved, by institute and year

**NCI, NIAID, and NIDDK
1990-92**

	1990	1991	1992	Total for all 3 years
NCI	9	12	8	29
NIAID	4	4	11	19
NIDDK	3	5	5	13
Total for all 3 institutes	16	21	24	61

SOURCE: OIG review of CRADA files at NCI, NIAID, and NIDDK

Table 2

Number of NIH scientists and industry partners entering into at least one CRADA

**NCI, NIAID, and NIDDK
1990-92**

	1990	1991	1992	Total for all 3 years
NIH scientists	13	18	20	42
Industry partners	14	21	23	51

SOURCE: OIG review of CRADA files at NCI, NIAID, and NIDDK

NOTE: Totals are not cumulative; partners who began multiple CRADAs in different years are counted only once.

Table 3

Mean approved duration of CRADAs, in years

**NCI, NIAID, and NIDDK
1990-92**

	1990	1991	1992	Mean for all 3 years
NCI	1.9	2.3	3.8	2.6
NIAID	2.8	3.3	3.5	3.3
NIDDK	1.5	1.8	2.2	1.9
Mean for all 3 institutes	2.0	2.4	3.3	2.7

N=61

SOURCE: OIG review of CRADA files
at NCI, NIAID, and NIDDK

NOTE: The actual duration of these CRADAs may
differ from the approved duration.

Table 4

**MEAN funds approved to be provided by industry CRADA partners,
in thousands of dollars**

**NCI, NIAID, and NIDDK
1990-92**

	1990	1991	1992	Mean for all 3 years
NCI	\$58	\$131	\$326	\$162
NIAID	51	350	1,230	837
NIDDK	17	22	94	48
Mean for all 3 institutes	49	146	724	\$348

N=61

SOURCE: OIG review of CRADA files at NCI, NIAID, and NIDDK

NOTE: The actual contribution from the industry partner
may differ from the approved amount.

Table 5

MEDIAN funds approved to be provided by industry CRADA partners,
in thousands of dollars

NCI, NIAID, and NIDDK
1990-92

	1990	1991	1992	Median for all 3 years
NCI	\$38	\$15	\$68	\$45
NIAID	55	0	132	54
NIDDK	6	25	6	6
Median for all 3 institutes	39	0	68	\$40

N=61

SOURCE: OIG review of CRADA files at NCI, NIAID, and NIDDK

NOTE: The actual contribution from the industry partner
may differ from the approved amount.

Table 6

**Median elapsed time from initial contact
between CRADA partners to final CRADA approval, in days**

**NCI, NIAID, and NIDDK
1990-92**

	1990	1991	1992	Median for all 3 years
NCI	381	368	411	368
NIAID	156	587	314	314
NIDDK	120	227	299	213
Median for all 3 institutes	259	333	330	299

N=61

SOURCE: OIG review of CRADA files
at NCI, NIAID, and NIDDK

Table 7

Median elapsed time from institute submission of a CRADA to completion of review by the CRADA Subcommittee of the NIH Technology Transfer Board, in days

**NCI, NIAID, and NIDDK
1992 Only**

	Central Review
NCI	48
NIAID	90
NIDDK	88
Median for all three institutes	69

N=24

SOURCE: OIG review of CRADA files
at NCI, NIAID, and NIDDK

Table 8

**Number and percentage of CRADAs for each type of research,
by year**

**NCI, NIAID, and NIDDK
1990-92**

	1990	1991	1992	Total for all 3 years
Basic	6 (38%)	4 (19%)	3 (13%)	13 (21%)
Preclinical	6 (38%)	10 (48%)	6 (25%)	22 (36%)
Clinical	1 (6%)	2 (9%)	4 (17%)	7 (11%)
Lab technique, machine, etc.	1 (6%)	0 (0%)	3 (12%)	4 (7%)
Combinations of the above topics	2 (12%)	5 (24%)	8 (33%)	15 (25%)
Total for all types of research	16 (100%)	21 (100%)	24 (100%)	61 (100%)

SOURCE: Reports to the OIG from the Technology Development Coordinators
at NCI, NIAID, and NIDDK

Table 9

**Number and percentage of CRADAs for each type of research,
by institute**

**NCI, NIAID, and NIDDK
1990-92**

	NCI	NIAID	NIDDK	Total for all 3 institutes
Basic	5 (17%)	6 (32%)	2 (15.5%)	13 (21%)
Preclinical	15 (52%)	4 (21%)	3 (23%)	22 (36%)
Clinical	3 (10%)	4 (21%)	0 (0%)	7 (11%)
Lab technique, machine, etc.	2 (7%)	0 (0%)	2 (15.5%)	4 (7%)
Combinations of the above topics	4 (14%)	5 (26%)	6 (46%)	15 (25%)
Total for all types of research	29 (100%)	19 (100%)	13 (100%)	61 (100%)

SOURCE: Reports to the OIG from the Technology Development Coordinators
at NCI, NIAID, and NIDDK

Table 10

**Number of CRADAs for which NIH held a
preexisting patent necessary for the research
NIAID and NIDDK Only
1990-92**

	1990	1991	1992	Total for all 3 years
NIAID	2	1	4	7
NIDDK	0	0	3	3
Total for both institutes	2	1	7	10

N=32

SOURCE: Reports to the OIG from the Technology Development Coordinators
at NIAID and NIDDK.

NOTE: This information was unavailable from NCI.

Table 11

**Number of CRADAs for which the industry partner held a
preexisting patent necessary to the research
NIAID and NIDDK Only
1990-92**

	1990	1991	1992	Total for all 3 years
NIAID	0	0	1	0
NIDDK	1	2	1	4
Total for both institutes	1	2	2	5

N=32

SOURCE: Reports to the OIG from the Technology Development Coordinators
at NIAID and NIDDK.

NOTE: This information was unavailable from NCI.

Table 12

Number of CRADAs in which the reasonable pricing clause was modified

**NCI, NIAID, and NIDDK
1990-92**

	1990	1991	1992	Total for all 3 years
NCI	1	2	2	5
NIAID	1	2	4	7
NIDDK	0	0	1	1
Total for all 3 institutes	2	4	7	13

N=61

SOURCE: OIG review of CRADA files at NCI, NIAID, and NIDDK

Table 13

Number and percentage of CRADAs in which the industry partner was categorized by NIH as a small or foreign business

**NCI, NIAID, and NIDDK
1990-92**

Small Business	24 (39%)
Foreign Business	8 (13%)

N=61

SOURCE: OIG review of CRADA files at NCI, NIAID, and NIDDK

Table 14

Number and percentage of CRADAs that were advertised as specific opportunities or that grew out of prior informal working relationships between the partners

**NCI, NIAID, and NIDDK
1990-1992**

CRADAs that were advertised as specific opportunities	8 (13%)
CRADAs that grew out of prior working relationships between the partners	20 (33%)

N=61

SOURCE: OIG review of CRADA files at NCI, NIAID, and NIDDK

APPENDIX C

COMPLETE COMMENTS ON THE DRAFT REPORT FROM THE PUBLIC HEALTH SERVICE



OCT - 8 1993

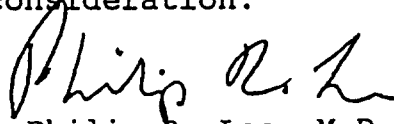
MEMORANDUM

From: Assistant Secretary for Health

Subject: Office of Inspector General (OIG) Draft Report
"Technology Transfer and the Public Interest:
Cooperative Research and Development Agreements at
the National Institutes of Health," OEI-01-92-01100

To: Acting Inspector General, OS

Attached are the Public Health Service comments on the subject
OIG draft report. In addition to our comments on the specific
recommendations in the report, we offer several technical
comments for your consideration.


Philip R. Lee, M.D.

Attachment

PUBLIC HEALTH SERVICE (PHS) COMMENTS ON THE OFFICE OF INSPECTOR
GENERAL (OIG) DRAFT REPORT "TECHNOLOGY TRANSFER AND THE PUBLIC
INTEREST: COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS AT
THE NATIONAL INSTITUTES OF HEALTH (NIH)," OEI-01-92-01100

OIG Recommendation

1. The NIH should implement guidelines that clearly indicate the types of research projects that are appropriate for the Cooperative Research and Development Agreements (CRADA) mechanism.

PHS Comment

We do not concur. There is no inconsistency between the intended and current uses of the CRADA. Also, there is no legal authority or compelling policy rationale for the proposition that the CRADA mechanism should be limited to any particular category of research.

Pursuant to Section 310(a) of the PHS Act, agencies of PHS, such as NIH, are authorized to:

"...conduct...and encourage, cooperate with, and render assistance to other appropriate public authorities, scientific institutions and scientists in the conduct of, and promote the coordination of, research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man..."

The Federal Technology Transfer Act of 1986 (FTTA) was enacted to promote technology transfer by authorizing Government laboratories to enter into CRADAs and conduct other relevant activities, such as the patenting and licensing of inventions. CRADAs are defined as "any agreement between one or more Federal laboratories and...non-Federal parties...toward the conduct of specified research or development efforts which are consistent with the missions of the laboratory."

The legislative history and implementation of the FTTA by various agencies show no indication that it was the intention of Congress to limit CRADAs only to research that reflects "practical technology" rather than to generally encourage mission-appropriate research. The FTTA broadly defined the categories of collaboration (e.g., research or development) that are acceptable, rather than any particular kinds of projects (e.g., basic or applied). The NIH Technology Transfer Manual, cited in the OIG report at footnote 19, is consistent with the foregoing interpretation as it merely paraphrases the FTTA's preamble.

We are unaware of any statutory basis for concluding that Congress intended to exclude any category of research or development within the mission of the agency from the possibility of joint efforts with outside entities. Moreover, given that the FTTA explicitly encompasses both research and development, it would be problematic to define basic and non-basic research in the context of NIH's research mission. For example, although clinical trials designed to answer fundamental questions about the pathophysiology of a particular disease might be considered basic or routine by some people, validly they could be considered to be developmental or commercial from the perspective of a corporate research partner.

By way of example, the statutory mission of the National Cancer Institute (NCI) includes research, experiments and studies related to the treatment of cancer, as well as programs for the application of NCI research to clinical practice. Therefore, clinical trials with company products that expedite drug development and Food and Drug Administration (FDA) approval fall squarely within the mandate of the PHS Act and the FTTA.

Complicating this picture is the pragmatic concern that the CRADA is the only statutory mechanism by which research agencies can make licensing commitments in advance to research partners for inventions yet to be made. Companies increasingly request CRADAs in order to secure patent rights for a wide variety of research projects. Some companies will not provide materials for clinical trials conducted at NIH without a promise of patent rights related to new methods of using their proprietary compound that may be discovered in the course of the study. Additionally, the CRADA mechanism is the primary statutory mechanism by which company contributions, such as funds, can be accepted and applied to designated intramural research laboratories.

The PHS is concerned that research laboratories not be "acquired" by various pharmaceutical or biotechnology companies. Thus, appropriate limits should be placed on the amount of time that any one investigator should contribute to any single CRADA, or on the number of CRADAs that any company might have with a PHS agency or its institutes, centers or divisions (ICD). The Technology Transfer Policy Board (TTPB) at NIH, which includes representatives from the Centers for Disease Control and Prevention, FDA, and the Office of the Assistant Secretary for Health (OASH), is developing recommendations to address these concerns.

To the extent that a fundamental invention is made under a CRADA and licensed to a CRADA partner, the NIH patent licensing agreement already contains several safeguards to ensure that (1) public access to the underlying technology is permitted, and (2) the commercial development rights are available to other

companies when necessary in the public interest. For example, NIH generally reserves the right to grant sub-licenses when the licensee cannot demonstrate a capability to respond to public health needs when additional uses for the product are identified.

In conclusion, we believe that the OIG report restricts its focus to the direct transfer of practical technology, rather than looking at joint research and development efforts that may transfer technology as a result of collaborations. We agree that interactions with companies involving only routine, conventional testing with no collaborative or intellectual contribution are not appropriate for CRADAs. For that reason restrictions on the use of CRADAs are set forth explicitly in current guidelines. We also agree that, in approving any CRADA, due consideration must be given to the possibility that the level of confidentiality associated with that CRADA project might inappropriately impair the degree of openness necessary to serve the public interest in the success of that research.

OIG Recommendation

2. The NIH should build upon its current efforts to clarify and streamline the CRADA review and approval process.

PHS Comment

We concur. An ad hoc CRADA Process Committee, comprised of technology transfer staff, began meeting in January 1993 to evaluate the CRADA review and approval process. This committee (now called the CRADA Committee) was reauthorized formally at the first meeting of the new TTPB in May 1993. A draft policy document was presented to the Board in June 1993.

Their assignment is to develop procedures and policies to simplify and facilitate the review and approval of CRADAs. In performing this function, they will identify specific review criteria as well as delineate the roles and responsibilities of reviewers at each level to alleviate duplication of effort and expedite processing. Among other charges, the CRADA Committee will also analyze the composition of the CRADA review committee in order to ensure the objective review of each CRADA.

In addition to this formal process, regular consultations take place on an on-going bases among the ICD Technology Development Coordinators on various aspects of policy and procedural development. Also, the Office of Technology Transfer (OTT) expects to recruit for and fill key CRADA management positions in Fiscal Year 1994. Filling these positions will facilitate the processing and review of CRADAs.

OIG Recommendation

3. The NIH should further develop the fair access guidelines to reflect the full range of issues involved.

PHS Comment

We concur. The TTPB, in August 1993, established an ad hoc committee to evaluate issues of fair access to CRADA opportunities. This committee is charged with evaluating and developing a reissuance of the February 1989 policy document entitled "PHS Policy for Ensuring Fairness of Access in CRADAs." In the course of its deliberations, the committee will consider related access procedures from other Federal laboratories. The issue of fair access in this context was a featured topic at the second annual summer meeting of the Association of Federal Technology Transfer Executives at their meeting last July.

OIG Recommendation

4. The NIH should develop and maintain a central database system to track all on-going CRADA work.

PHS Comment

We concur. Effective data management is a vitally important tool for oversight of the CRADA process and CRADA-related activities. The OIG report suggests several appropriate data fields. However, we note that it is difficult to quantify the value of personnel and resources contributed to a given CRADA by the participating research laboratory.

In connection with corrective action plans prepared in response to a 1992 OIG review of the technology transfer function (A-01-90-01502), and the organizational and internal controls study performed in 1993 by NIH's Division of Management Policy, an information systems assessment and users' requirements analysis is being developed. OTT has developed a prototype for an interim data system for monitoring CRADA activity and is comparing this system with existing systems developed by NCI and the National Institute on Allergy and Infectious Diseases. All three systems will be presented to the ICD Technology Development Coordinators, the TTPB, and the CRADA Committee to solicit their views as to the preferred interim system pending more comprehensive users' requirements analysis. A firm date for completion of the overall information systems management plan for OTT is not yet available.

OIG Recommendation

5. The NIH, working with the Office of the Secretary and OASH, should seek a consensus on how to resolve the reasonable pricing controversy.

PHS Comment

We concur. The issue of reasonable pricing is a complex matter in which the interests of the Government in facilitating collaboration and the transfer of technology sometimes appear to conflict with its interest in containing health care costs. The OIG report correctly notes that the issues raise questions about the role of research agencies in regulating or influencing private sector pricing decisions as well as the appropriate scope of access by the Government to cost and other price-related corporate data. NIH notes that it has no legislative mandate, programmatic mission, or expertise in the evaluation or regulation of drug prices.

On December 2, 1992, the Advisory Committee to the Director, NIH, assisted by a group of outside experts, discussed the policy implication of the "reasonable pricing" clause in considering the general issue of how the public investment in biomedical research should be reflected in the cost of products. The topic has also been considered at several House and Senate hearings earlier this year.

As a follow-up to the Advisory Committee meeting and the Congressional hearings, OTT is preparing an options paper for consideration by the TTPB and the Director, NIH, regarding the question of how the public investment in Federally-sponsored biomedical research should be reflected in products brought to market through joint NIH-private sector efforts. Appropriate roles for the Department and its research agencies must be considered in the context of the Administration's health care reform efforts.

Technical Comments

Page i under "Findings": CRADAs can also facilitate the pooling of NIH and private-sector equipment, facilities, research materials, as well as intellectual and financial resources. CRADAs can include academic institutions as research and development partners.

Page 6: The discussion focusses on CRADAs which are inconsistent with the "central intent" of the FTTA and NIH CRADA policy. The statement "although inconsistent with the central intent of the FTTA and with NIH CRADA policy, this type of research is allowed

by both" should be stated in the body of the report rather than in Appendix C. This would clarify that the focus of the finding is on the words "central intent."

Page 9: The report states that NIH advertised as CRADA opportunities only eight of the 61 CRADAs which were part of this study. The report should clarify whether all 61 CRADAs were initiated by NIH. Any CRADAs initiated by the private-sector counterpart cannot be included correctly in this statistical population because NIH may not advertise them.

APPENDIX D

NOTES

1. "National Institutes of Health Strategic Plan," April 1993.
2. The President's Fiscal Year (FY) 1994 Budget for the Department of Health and Human Services, pp. 25-28.

In FY 1993, NIH allocated \$5.7 billion (55 percent of its total budget) directly to 23,582 extramural research project grants. It allocated \$1.2 billion (11 percent of the budget) directly to intramural research. The remainder of the budget was allocated to the centers, research training, R&D contracts, research support, the National Library of Medicine, the Office of the Director, the Women's Health Study, the Minority Health Study, other research, and NIH facilities repairs.

3. Department of Commerce, "Technology Transfer under the Stevenson-Wydler Technology Innovation Act: The Second Biennial Report," January 1993, p. 1.
4. Senate Report No. 99-283 on Public Law 99-502, pp. 1-2.
5. House Report No. 96-1199 on Public Law 96-480, p. 3.
6. Senate Report No. 99-283 on Public Law 99-502, p. 1.

Other legislation supporting technology transfer includes the Bayh-Dole Act of 1980 (P.L. 96-517); the Small Business Innovation Development Act of 1982 (P.L. 97-219); the Cooperative Research Act of 1984 (P.L. 98-462); the Trademark Clarification Act of 1984 (P.L. 98-620); the Japanese Technical Literature Act of 1986 (P.L. 99-382); the Malcolm Baldrige National Quality Improvement Act of 1987 (P.L. 100-107); the Omnibus Trade and Competitiveness Act of 1988 (P.L. 100-418); the National Institute of Standards and Technology Authorization Act for Fiscal Year 1989 (P.L. 100-519); the Water Resources Development Act of 1988 (P.L. 100-676); the National Competitiveness Technology Transfer Act of 1989 (P.L. 101-189); and the Defense Authorization Act for Fiscal Year 1991 (P.L. 101-510). Executive Orders 12591 and 12618 in 1987 also supported technology transfer efforts.

7. According to the NIH/ADAMHA "Policy Statement on Cooperative Research and Development Agreements and Intellectual Property Licensing," "NIH/ADAMHA may permit their investigators to enter into CRADAs with collaborators who will make a significant intellectual contribution to the research project undertaken or who will contribute essential research materials

or technical resources not otherwise reasonably available. While NIH/ADAMHA welcome contributions to their gift funds for research purposes, they do not view CRADAs as a general funding source or mechanism for sponsored research."

8. The Federal government retains a nonexclusive, royalty-free license to use NIH- or collaboratively developed CRADA inventions throughout the world by or on behalf of the U.S. government. Additionally, NIH reserves the right to grant nonexclusive licenses to make and use any CRADA invention (even those developed solely by the collaborator) for purposes of research involving that invention.
9. The FTTA requires that Federal employees receive at least 15 percent of any royalties generated by a CRADA invention for which they are responsible. In addition, agencies with internal research and development budgets of more than \$50 million are required to implement cash awards programs for outstanding technical inventions or exemplary activities that promote domestic technology transfer.
10. Senate Report 99-283 states that "lengthy headquarters approval delays can cause businesses to lose interest in developing new technologies." (p. 4)

P.L. 99-502, Section 2. An agency head is allowed 30 days to either disapprove, or require modifications to, any CRADA presented by a director of a federally operated laboratory.
11. Department of Commerce, "Technology Transfer under the Stevenson-Wydler Technology Innovation Act: The Second Biennial Report," January 1993. Appendix B, Table 1.
12. National Institutes of Health, Office of Technology Transfer, "1992 PHS Technology Transfer Directory," 1992, pp. 25-33. This information was reported as of July 27, 1992.

The 93 CRADAs managed by NIH in 1992 included 25 with the National Cancer Institute; 21 with the National Institute of Allergy and Infectious Diseases; 18 with the National Institute of Diabetes and Digestive and Kidney Diseases; 6 with the National Institute on Neurological Disorders and Stroke; 5 with the National Heart, Lung and Blood Institute; 4 with each the National Institute of Child Health and Human Development, the National Institute of Dental Research, and the National Institute of Mental Health; 3 with the National Eye Institute; 2 with the National Institute on Drug Abuse and one with the Division of Computer Research and Training. Additional CRADAs are also being administered by the Centers for Disease Control and the Food and Drug Administration.

13. "Review of Public Health Service Controls over Technology Transfer and Royalty Income" (A-01-90-01502), Office of Inspector General, March 1992.

Relevant reports from the General Accounting Office include "Technology Transfer: Constraints Perceived by Federal Laboratory and Agency Officials," March 1988; "Technology Transfer: U.S. and Foreign Participation in Research and Development at Federal Laboratories," August 1988; "Technology Transfer: Implementation Status of the Federal Technology Transfer Act of 1986," May 1989; "Implementation of the Technology Transfer Act: A Preliminary Assessment," May 1990; "Technology Transfer: Copyright Law Constrains Commercialization of Some Federal Software," June 1990; "Technology Transfer: Federal Agencies' Patent Licensing Activities," April 1991; "Diffusing Innovations: Implementing the Technology Transfer Act of 1986," May 1991; "Technology Transfer: Federal Efforts to Enhance the Competitiveness of Small Manufacturers," November 1991; "Technology Transfer: Barriers Limit Royalty Sharing's Effectiveness," draft, 1992.

Other reports include "The Federal Technology Transfer Act of 1986: The First 2 Years," Department of Commerce, July 1989; "Technology Transfer under the Stevenson-Wydler Technology Innovation Act: The Second Biennial Report," Department of Commerce, January 1993; and "Report on the Administration of Cooperative Research and Development Agreements (CRADAs) within PHS," Office of the Assistant Secretary for Health, December 1992.

The NIH recently completed a review of its Office of Technology Transfer and is expected to release a report summarizing its findings.

14. In 1989, one CRADA administrator cited "a need to strengthen the management structure of our internal organizations responsible for training, patenting, industry liaison, licensing, and overall technology management." (Testimony of Dr. Philip S. Chen, Jr., Associate Director for Intramural Affairs and Chairman of the Patent Policy Board, National Institutes of Health, before the U.S. House of Representatives Small Business Subcommittee on Regulation, Business Opportunities, and Energy; October 5, 1989.)

In 1991, another administrator emphasized that collaboration between government laboratories and nongovernment entities "must develop under carefully crafted guidelines to ensure that the fundamental mission of NIH is preserved and that industry, academia and government work together honorably to ensure the public's trust." (Testimony of Reid G. Adler, J.D., Director, Office of Technology Transfer, National Institutes of Health, before the U.S. House of Representatives Science, Space and Technology, Subcommittee on Technology and Competitiveness; May 30, 1991.)

In 1992, the chairman of the CRADA Subcommittee noted that, "In attempting to formulate CRADA policies and procedures, three topics must be considered: (1) What is the definition of a CRADA? In other words, what are appropriate research activities for a CRADA and what are not? (2) What policies need to be formulated to preserve the intellectual and scientific integrity of the NIH, while fostering technology transfer?... (3) What are the actual mechanics required for the initiation, consideration, and approval of a CRADA?" (Dr. Dinah Singer, Chairman of the CRADA Subcommittee of the NIH Technology Transfer Board, "Policy Statement on Cooperative Research and Development Agreements (CRADAs)," draft, October 20, 1992, pp. 1-2.)

15. The mean approved industry financial contribution to a CRADA project during the 1990-92 period ranged from \$48,000 at NIDDK, to \$162,000 at NCI, to \$837,000 at NIAID. The median approved contribution ranged from \$6,000 at NIDDK, to \$45,000 at NCI, to \$54,000 at NIAID. The actual contributions may have differed from the approved amounts.

These figures refer only to the cash contribution to be transferred from the industry partner to NIH. The total value of the industry partner's contribution of materials, personnel, etc., may have been higher.

16. NIH/ADAMHA/CDC Technology Transfer Manual, February 1992, p. 16.
17. Nonetheless, only one marketed product has been developed through the CRADA mechanism to date. The NIH has not yet earned any royalty income from CRADA inventions.
18. Senate Report 99-283 on Public Law 99-502, p. 11.
19. The 1992 NIH/ADAMHA/CDC Technology Transfer manual, p. 1.
20. In consultation with the NIH Technology Development Coordinators (TDCs), the Office of Inspector General developed the following definitions to be used by the TDCs in their categorization of the nature of CRADA research:

Basic research: The partners are exploring a basic research question with no expectation of a near-term commercial application.

Pre-clinical research: The partners are conducting laboratory and animal testing aimed at developing a commercial product.

Clinical, pre-approval research: The partners are conducting clinical research aimed at securing FDA approval for a new compound that is anticipated to have commercial applications.

Clinical, post-approval research: The partners are conducting clinical research aimed at establishing a new use for an FDA-approved compound.

Laboratory technique, machine, etc.: The partners are developing a laboratory process, technique, procedure, or machine.

21. Nine of the 13 basic-research CRADAs entailed a transfer of funds from industry. Of the 26 NIH scientists involved in the CRADAs established at NCI, NIAID, and NIDDK in 1992, 9 made a point of expressing concern about industry funding of basic-research CRADAs.

The chairman of the CRADA Subcommittee of the NIH Technology Transfer Board has suggested that "research activities whose only immediate purpose is to broaden our base of fundamental knowledge and understanding" are inappropriate for CRADAs. She proposes that, to protect NIH scientists from unnecessarily committing NIH's intellectual property rights or restricting their own research programs, basic-research CRADAs should be allowed only in instances in which there is no funding from industry for the research and no provision for intellectual property rights for the industry partner. (Dr. Dinah Singer, "Policy Statement on Cooperative Research and Development Agreements (CRADAs)," draft, October 20, 1992, pp. 2-3.)

The NIH administrators who oversee the CRADA approval process have become increasingly critical of basic-research CRADAs, and the percentage of CRADAs that focus exclusively on basic science has dropped over the past three years from 48 percent to 13 percent (see table 8 in appendix B for more information).

22. Twenty-nine of the 61 CRADAs established at NCI, NIAID, and NIDDK between 1990 and 1992 focused exclusively on either preclinical or clinical testing. For 12 of these, NIH reported to us whether industry or NIH held the patents necessary for the CRADA research. For the remaining 17, patent information was unavailable.
23. Although inconsistent with the central intent of the FTTA and NIH CRADA policy, this type of research is allowed by both.
24. These levels usually include the laboratory chief, the institute director/scientific director, the institute technology development office, the NIH Office of Technology Development, the Office of the General Counsel, and the CRADA Subcommittee of the NIH Technology Transfer Board.
25. The CRADA Subcommittee of the NIH Technology Transfer Board, which conducts the NIH central review of CRADAs and serves as the advisor to the NIH Director, does not approve proposed CRADAs, but rather recommends "nondisapproval" or modifications to such proposals; authority for final approval resides at the institute level. After the Subcommittee makes a decision of nondisapproval, the CRADA must be signed by the NIH Director or a

designee. We found that in almost all cases we reviewed, this occurred within 5 days of the Subcommittee decision.

26. The institute technology development coordinators and the CRADA Subcommittee are currently exploring ways of further streamlining the process. In particular, they are focusing on bringing better definition to the roles and responsibilities of the various players.

The Office of the Assistant Secretary for Health has noted that NIH has made "substantial progress . . . in bringing structure to the CRADA process." "Report on the Administration of Cooperative Research and Development Agreements (CRADAs) within PHS," December 1992.

27. Memorandum from the Chair, Ad Hoc Technology Development Coordinators' Committee on CRADA Policy, to the Chair, Patent Policy Board, September 11, 1992. (The Patent Policy Board was renamed the Technology Transfer Board in the Spring of 1993.)
28. Senate Report No. 99-283 on Public Law 99-502, p. 4.
29. Memorandum from Robert E. Windom, MD, Assistant Secretary for Health, "PHS Policy for Ensuring Fairness of Access in Cooperative Research and Development Agreements," February 1, 1989.
30. Memorandum from Robert E. Windom, MD, Assistant Secretary for Health; pp. 1-2.

According to the memorandum, NIH should make routine periodic announcements of the general subject areas in which NIH offers collaborative opportunities. Suggested media for these routine announcements include the *Federal Register*, the *Commerce Business Daily*, industry collaboration forums, and directory listings. The NIH does make routine periodic announcements of general collaborative opportunities using these media.

Specific announcements are also indicated when a laboratory does not know of a suitable CRADA partner and when a laboratory has not yet made a routine announcement of the CRADA opportunity.

The NIH/ADAMHA/CDC Technology Transfer Manual states that "a competitive process is generally not required in choosing a CRADA partner, although it is required by PHS fair access guidelines under limited circumstances." (p. 114)

31. Of these eight, one was advertised in the Federal Register.
32. We were not provided with initial contact information for the other 28 CRADAs.

33. The NIH does not allow a scientist to consult for a company while participating in a CRADA with that company.

General guidelines from the Office of Government Ethics have directed NIH considerations of conflict-of-interest issues and the relationships that NIH scientists may have with a CRADA partner, either prior to the establishment of a CRADA, or concurrent with participation in a CRADA.

The Interagency Task Force on Technology Transfer is now developing "Technology Transfer Act Interagency Conflict Of Interest Guidelines" which will offer guidelines about permissible activities for government employees involved in CRADAs.

34. To many of these scientists, "fair access" seemed beside the point: They reported that their CRADAs developed as a result of ongoing discussions or informal collaborations with industry scientists, and that their industry partners' expertise or proprietary materials qualified them as appropriate CRADA partners. Some NIH scientists told us that they preferred to conduct research with partners with whom they knew from experience they could work well.
35. When asked how to differentiate between a small business and a big business, one CRADA administrator acknowledged the absence of clear definitions and suggested that, "if the company president is involved in the CRADA negotiations, then it's a small business."

The CRADA administrators expressed further concern about the FTTA stipulation that, for a company to be given preference in consideration as a domestic CRADA partner, it must manufacture CRADA products substantially in this country. They noted that, in an age of multinational businesses, it is sometimes not possible to ascertain where CRADA products will be manufactured.

36. The Technology Transfer Board, its CRADA Subcommittee, and the Office of Technology Transfer all develop policy and procedures for NIH CRADAs. The CRADA Subcommittee, the Office of the General Counsel, and the Office of Technology Transfer review proposed CRADAs to assure their acceptability, appropriateness, and legality. According to the NIH/ADAMHA/CDC Technology Transfer manual, the Office of Technology Transfer also has the responsibility to coordinate a comprehensive CRADA database to serve as a central information repository.
37. The Office of Technology Transfer keeps a record of those CRADAs that provide for intellectual property rights. This record, however, is not often updated. Further, there are inconsistencies between this record and those kept by the individual institutes. The OTT intends to develop a more comprehensive database.

Technology Development Coordinators (TDCs) in the individual institutes follow the progress of approved CRADAs. Both NCI and NIAID have developed computer tracking systems to assist their monitoring efforts. The TDC offices also document amendments to approved CRADAs.

In February 1993, the CRADA Subcommittee of the Technology Transfer Board set out to determine the types of amendments that it should review. Until new policy is set, the Subcommittee has asked that the TDCs in the individual institutes bring forward for Subcommittee review all proposed amendments that the TDCs consider to be significant.

38. The NIH model CRADA agreement, Section 8.3, states:

... NIH/ADAMHA have a concern that there be a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public. Accordingly, exclusive commercialization licenses granted for NIH/ADAMHA intellectual property rights may require that this relationship be supported by reasonable evidence.

The NIH model exclusive patent license agreement, Section 4.02, states:

... PHS may require LICENSEE to submit documentation in confidence showing a reasonable relationship between the pricing of a Licensed Product, the public investment in that product and the health and safety needs of the public. This paragraph shall not restrict the right of LICENSEE to price a Licensed Product or Licensed Process so as to obtain a reasonable profit for its sale or use. This Paragraph 4.02 does not permit PHS or any other government agency to set or dictate prices for Licensed Products or Licensed Processes.

39. Testimony of Bernadine Healy, MD, before the U.S. Senate Special Committee on Aging, February 24, 1993.

Others who have addressed the limited capacity of NIH to implement the "reasonable pricing" clause include Senator David Pryor, Congressman Ron Wyden, Associate Professor Peter Arno of the Albert Einstein College of Medicine, Professor Steven Schondelmeyer of the University of Minnesota College of Pharmacy, and several of the NIH CRADA administrators with whom we spoke.

40. Twelve of the 15 industry representatives with whom we spoke reported serious concerns about the clause.

Industry partners noted that, were the clause to be implemented, it would be necessary to take into account the following: the cost of the specific product,

the average development costs for the company's products, the company's opportunity costs, the average industry margins, the relative contributions of the partners, the marketing and distribution costs, presence and prices of similar competing therapies, likelihood and timing of market entry for additional competing products, projected time to recover development costs, and special discount/access programs.

Industry partners further suggested that various other factors serve to keep prices "reasonable," including anti-trust laws, market forces, and competition created by the granting of nonexclusive licenses for products with large potential markets.

41. Testimony of Bruce Chabner, MD, Director, Division of Cancer Treatment, NCI, before the House Small Business Subcommittee on Regulation, Business Opportunities, and Energy, January 25, 1993.

In interviews with the OIG, several NIH CRADA administrators also observed that some pharmaceutical companies refused to participate in CRADAs because of the "reasonable pricing" clause.

42. Examples of the specific modifications to the CRADA documents we reviewed include the following:
 - Addition of the phrase: "nothing in this article . . . shall be construed to restrict the right of the collaborator to price a licensed product so as to obtain a reasonable profit for its sale or use."
 - Addition of the phrase: "This CRADA shall not affect the collaborator's right to recover its research, development, and marketing costs."
 - Replacement of the phrase "require evidence" with "request evidence;" and addition of the following: "[the company] may decline to provide such evidence in which event NIH . . . may convert the license to a nonexclusive one . . ."
 - Addition of the following: "The reasonable evidence to be submitted in support of the relationship shall include but not be limited to evidence on (i) the cost of the collaborator's development of the product; (ii) the cost of the collaborator's overall research and development efforts and the need to fund past and future efforts through commercialization of the successful research, and (iii) the potential liability to which collaborator is subjected by commercialization of the licensed product."
 - Explicit clarification that the clause does not give NIH or the Government the "right to set or dictate price."

43. The first marketed product to be subject to the NIH "reasonable pricing" clause was the Bristol-Myers Squibb AIDS drug, Videx (ddI). In this instance, the clause was invoked as part of a licensing agreement, not a CRADA.

The NCI entered into a CRADA with Bristol Myers Squibb (BMS) to develop Taxol as a therapeutic to treat ovarian and possibly other types of cancer. Through the CRADA, BMS received exclusive rights to clinical and preclinical data necessary for FDA approval; the drug itself could not be patented. The pricing clause was modified to reflect the unique circumstances of this product.

44. The modified clause contained no mention of NIH requesting access to "evidence," and read: "Bristol Myers Squibb acknowledges [NIH's] concern, and agrees that these factors will be taken into account in establishing a fair market price for Taxol;" and NIH "acknowledges BMS's concerns, and agrees that these factors may be taken into account in establishing a fair market price for Taxol."
45. Testimony of Bruce Chabner, MD, Director, Division of Cancer Treatment, NCI, before the U.S. House of Representatives Small Business Subcommittee on Regulation, Business Opportunities, and Energy, January 25, 1993.

According to Dr. Chabner, "a number of intangible and unqualifiable factors contribute to a 'fair' price, including the market life of the product, the period of market exclusivity, potential competition or related products, and anticipated market size, all of which defy precise delineation. Furthermore, the CRADA did not require the company to disclose proprietary information regarding total costs of production development and marketing, and the company exercised its right not to disclose such information."

The industry partner did agree to provide various discounts and expanded access programs for patients who could not afford the drug and for research purposes.

46. These three Congressional hearings were: "The Pricing of Taxol and Enforcement of Fair and Reasonable Provisions in Cooperative Research and Development Agreements (CRADAs)," on January 25, 1993, and "Private-Sector Agreements to Market Federally Funded Research," on March 11, 1993, both held by the U.S. House of Representatives Small Business Subcommittee on Regulation, Business Opportunities, and Energy; and "The Federal Government's Investment in New Drug Research and Development: Are We Getting Our Money's Worth?" held by the U.S. Senate Special Committee on Aging on February 24, 1993.
47. Opening Statement of U.S. Representative Ron Wyden, Chairman of the U.S. House of Representatives Small Business Subcommittee on Regulation, Business Opportunities, and Energy; January 25, 1993.

Testimonies of Abbey S. Meyers, Executive Director, National Organization for Rare Disorders, and Stephen Schondelmeyer, Ph.D., Professor, College of Pharmacy, University of Minnesota, before the U.S. House of Representatives Small Business Subcommittee on Regulation, Business Opportunities, and Energy; January 25, 1993.

Opening Statement of U.S. Senator David Pryor, Chairman of the U.S. Senate Special Committee on Aging; February 24, 1993.

Testimony of Ralph Nader before the U.S. House of Representatives Small Business Subcommittee on Regulation, Business Opportunities, and Energy; March 11, 1993.

48. According to a March 12, 1993 letter from Genentech, Inc., to Representative Ron Wyden, NCI inappropriately included a Genentech product, Human Growth Hormone, on the list of reference oncology drugs for the pricing of Taxol. Human Growth Hormone was the most expensive drug listed, and the price cited is 168 percent higher than the company's own estimate. The inappropriate inclusion of this product on the reference list and the inflated price significantly increased the median price below which Taxol was to be priced.
49. Office of the Assistant Secretary for Health, "Report on the Administration of Cooperative Research and Development Agreements (CRADAs) within PHS," December 1992.

The NIH Division of Management Policy, "Office of Technology Transfer: Internal Control Review," draft, March 26, 1993.