

June 2003

TECHNOLOGY  
TRANSFER

NIH-Private Sector  
Partnership in the  
Development of Taxol



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## Abbreviations

AWP	average wholesale price
BMS	Bristol-Myers Squibb Company
CRADA	cooperative research and development agreement
FDA	Food and Drug Administration
FSU	Florida State University
FSS	Federal Supply Schedule
IND	investigational new drug application
NCI	National Cancer Institute
NDA	new drug application
NIH	National Institutes of Health
OFM	Office of Financial Management
OTT	Office of Technology Transfer
PHS	Public Health Service

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United States General Accounting Office  
Washington, DC 20548

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June 4, 2003

The Honorable Ron Wyden  
United States Senate

Dear Senator Wyden:

The transfer of technology resulting from federally funded research to the private sector is intended to bring pharmaceuticals to the marketplace much sooner and more efficiently than would have been possible for a federal agency acting alone. Much of the pharmaceutical-related technology transfer between the public and the private sectors originates with research conducted or funded by the National Institutes of Health (NIH). NIH uses mechanisms such as cooperative research and development agreements (CRADA) with industry partners and the licensing of patented inventions arising from research it funds to provide incentives for businesses to develop pharmaceuticals. However, the financial success of certain drugs that have benefited from government-funded research has raised concerns about whether the federal government is getting a fair return on its investment in the research leading to these products.

An example of pharmaceutical technology transfer is Taxol (paclitaxel), which by 2001 had become the best-selling cancer drug in history.<sup>1</sup> Taxol was commercialized by the Bristol-Myers Squibb Company (BMS). Through a collaboration with NIH, BMS benefited from substantial investments in research conducted or funded by NIH. In this instance, the NIH research examined the safety and effectiveness of this naturally occurring compound for the treatment of cancer and resulted in techniques for administering the drug. NIH transferred its research results and discoveries to BMS for its use in seeking approval from the Food and Drug Administration (FDA) to market the drug.

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<sup>1</sup>Paclitaxel is the name of the generic equivalent of Taxol. The drug was known as taxol from its discovery in the 1960s until 1992, when BMS trademarked the name Taxol. At that time, BMS objected to researchers using taxol as the generic name, and so it was changed to paclitaxel. In this report, we use the name Taxol to refer to the brand-name drug sold by BMS, and we use paclitaxel to refer to the drug in other contexts.

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You asked us to examine the legal and financial issues involved in technology transfer as illustrated by the case of the research, development, and commercialization of Taxol. Specifically, you asked us to examine the following questions: (1) How did the NIH-BMS technology transfer collaboration affect the research and development of Taxol? (2) What was NIH's financial investment in Taxol-related research, and what were the financial outcomes of the technology transfer process related to Taxol? (3) What factors influenced how NIH exercised its authority in Taxol-related technology transfer activities?

To address these questions, we reviewed published and unpublished documents describing NIH and BMS's partnership and their efforts to research and develop Taxol. Using the U.S. Patent and Trademark Office's database, we reviewed the patent history of Taxol. We reviewed the primary Taxol-related CRADA between NIH and BMS, which was signed in 1991. We also reviewed an additional Taxol-related CRADA and the license agreement between NIH and BMS.<sup>2</sup> We interviewed the principal investigators associated with those CRADAs to understand the research involved. To assess NIH's investments and financial outcomes resulting from Taxol-related research, we obtained and reviewed data from NIH's National Cancer Institute (NCI), Office of Financial Management (OFM), and BMS's Annual Reports.<sup>3</sup> We also reviewed Medicare drug purchase data from the Medicare part-B Extract Summary System and pricing data from the Federal Supply Schedule (FSS). We interviewed officials from BMS and from NIH's OFM, Office of Technology Transfer (OTT), and NCI about spending estimates and the use of royalty payments. To assess the factors that influence how NIH exercises its legal authority, we reviewed the relevant statutes and regulations pertaining to the technology transfer process and interviewed pertinent officials involved in the process at NIH and BMS. We also interviewed officials from one of NIH's key partners in paclitaxel-related research, Florida State University (FSU), where much of the early research on a semisynthetic method of producing paclitaxel was performed. The scope of our report was restricted to NIH's investment in paclitaxel, and we did not evaluate the effectiveness of commercializing Taxol in comparison to other drugs. For this reason, we consider the implications of the development of Taxol as a case study, not necessarily

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<sup>2</sup>BMS voluntarily agreed to the disclosure of its commercial information in the CRADAs and the license agreement so that our study could be completed and the results of our review could be made publicly available.

<sup>3</sup>Throughout the report, dollars are reported as actual dollars, not adjusted for inflation.

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as representative of the way NIH performs technology transfer activities. We conducted our work from October 2002 to June 2003 in accordance with generally accepted government auditing standards.

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## Results in Brief

NIH's collaboration with BMS provided the company with research results that enabled paclitaxel to be quickly commercialized as the brand-name drug Taxol and made available as a treatment—initially for ovarian cancer patients, and later for other cancer patients. Prior to the signing of the 1991 CRADA between NIH and BMS, and during the first 2 years of the CRADA, NIH conducted most of the clinical trials associated with paclitaxel. The results of NIH's clinical trials were critical for BMS to secure FDA's initial approval in 1992 to market Taxol for the treatment of advanced ovarian cancer. Five of the six studies submitted to FDA by BMS in support of its marketing application were either conducted or funded by NIH. As agreed in the CRADA, BMS supplied paclitaxel to NIH researchers to overcome previous shortages that had limited NIH's research. The additional paclitaxel supplied by BMS allowed NIH researchers to increase the number of patients enrolled in NIH clinical trials for paclitaxel from less than 500 patients in 1989 to 28,882 through the end of the CRADA term. Three inventions—which were methods for administering paclitaxel and treating side effects—resulted from the 1991 CRADA and were later patented by NIH. In 1996 NIH signed an agreement to license these inventions to BMS, but BMS officials told us that they were not used in any of BMS's applications to FDA to expand the approved uses of Taxol. In addition, an NIH grant to FSU led to the important discovery of a method for producing paclitaxel, which was licensed to BMS by FSU in 1990 and later used to produce Taxol.

NIH made substantial investments in research related to Taxol, but its financial benefits from the collaboration with BMS have not been great in comparison to BMS's revenue from the drug. NIH estimates that it invested \$183 million in research related to paclitaxel from 1977 through 1997, the end of the CRADA's term, although not all of this was for research supporting the 1991 CRADA. For one portion of its investment in Taxol, NIH estimates that its net cost for conducting clinical trials that supported the development of Taxol through the 1991 CRADA was \$80 million—NIH estimates that it spent \$96 million on the studies, and this expense was offset by \$16 million in financial support from BMS. We estimate that the paclitaxel BMS supplied NIH through the CRADA had a value of \$92 million. NIH spent an additional \$301 million on paclitaxel-related research from 1998 through 2002, some of which supported cancer research, bringing NIH's total investment in paclitaxel-related research

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from 1977 to 2002 to \$484 million. Overall, BMS officials told us that the company spent \$1 billion to develop Taxol. BMS's worldwide sales of Taxol totaled over \$9 billion from 1993 through 2002. In its 1996 license agreement with NIH, BMS agreed to pay NIH royalties at a rate of 0.5 percent of worldwide sales of Taxol, and NIH received royalty payments totaling \$35 million through 2002. The CRADA noted NIH's concern that Taxol be fairly priced given the public investment in Taxol research and the health needs of the public, but it did not require that reasonable evidence be presented to show that this would occur. The federal government has been a major payer for Taxol, primarily through Medicare. Medicare payments for Taxol totaled \$687 million from 1994 through 1999, the last full year before a generic version of Taxol was approved for marketing.

Several factors affected NIH's exercise of its authority in technology transfer activities related to the development of paclitaxel. First, in negotiations regarding a CRADA for paclitaxel, NIH's ability to exercise its authority was limited because, even though its research findings could be valuable in securing FDA approval for marketing the drug, NIH did not have a patent on paclitaxel, and thus could not grant a possible CRADA partner an exclusive patent license to market the drug upon FDA approval. Second, NIH's evaluation suggests that there was a shortage of available, qualified alternative CRADA partners. According to NIH's records, BMS's CRADA application scored significantly higher than others. Finally, the negotiation of royalties for NIH's later Taxol-related inventions was affected by multiple considerations, including the priorities that both NIH and BMS assigned to different factors in the setting of royalties. While nothing in applicable law restricts the amount of royalties NIH can negotiate, a number of considerations bear on the negotiations. These include the stage of product development, the potential market value of the invention, and the contribution to public health of making the product available. In this case, BMS officials told us that NIH's inventions did not contribute to BMS's successful marketing of Taxol.

In commenting on a draft of this report, NIH provided additional information about its expenditures and the contributions of BMS, which we incorporated, and also discussed its efforts to evaluate the pricing of Taxol. In its comments on a draft of this report, BMS expressed concern about our estimates of NIH's expenditures; we have revised our presentation based on information contained in NIH's comments. BMS also expressed concerns that our analysis overstated the cost of Taxol to Medicare. Our analysis did not overstate the cost, and we have clarified our discussion.

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## Background

Taxol is currently used to treat several types of cancer, including advanced ovarian and breast cancer, certain lung cancers (non-small cell) in patients who cannot have surgery or radiation therapy, and AIDS-related Kaposi's sarcoma. The bioactive compound in Taxol was first extracted from the bark of the slow-growing Pacific yew tree *Taxus brevifolia* in the 1960s. Following this discovery, the drug was developed primarily through research funded by NIH, and then transferred to the private sector and successfully commercialized by BMS.

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## Public-Private Technology Transfer

The 1991 NIH-BMS CRADA was one of the first CRADAs to result in a breakthrough drug. The groundwork for the public-private partnership that fostered the success of Taxol was laid in 1980. Prior to that time, the government generally retained title to any inventions created under federal research grants and contracts. This situation became a source of dissatisfaction because of a general belief that the results of government-owned research were not being made widely available for the public's benefit. For example, there were concerns that biomedical and other technological advances resulting from federally funded research at universities were not leading to new products because the universities had little incentive to seek uses for inventions to which the government held title. In 1980, the Congress passed two landmark pieces of legislation—the Stevenson-Wydler Technology Innovation Act of 1980<sup>4</sup> and the Bayh-Dole Act<sup>5</sup>—with the intent of promoting economic development, enhancing U.S. competitiveness, and benefiting the public by encouraging the commercialization of technologies developed with federal funding.

Although the acts have common objectives, the Stevenson-Wydler Act focuses on inventions owned by the federal government, while the Bayh-Dole Act focuses on inventions created under federal contracts, grants, and cooperative research and development agreements. Under the Stevenson-Wydler Act, inventions owned by the government remain the property of the agencies that produce them. However, the act as amended sets out guidelines and priorities that encourage commercialization of these inventions through the licensing of technology to U.S. business. In 1986 the Federal Technology Transfer Act<sup>6</sup> amended the Stevenson-Wydler

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<sup>4</sup>Pub. L. No. 96-480, 94 Stat. 2311.

<sup>5</sup>Pub. L. No. 96-517, § 6(a), 94 Stat. 3019.

<sup>6</sup>Pub. L. No. 99-502, 100 Stat. 1785.



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Act and enhanced the authority of federal agencies in this area, authorizing them to enter into CRADAs with nonfederal partners to conduct research.

The Bayh-Dole Act authorizes federal agencies to execute license agreements with commercial entities to promote the development of federally owned inventions, and to collect royalties for such licenses. The act also gives small businesses, universities, and other nonprofit organizations the right to retain title to and profit from the inventions arising from their federally funded research, provided they adhere to certain requirements. In 1983, a presidential memorandum extended this patent policy to large businesses. The act also contains several provisions to protect the public's interest in commercializing federally funded inventions, such as a requirement that a contractor or grantee that retains title to a federally funded invention file for patent protection and attempt commercialization. In return, the government retains the right to use the inventions without paying royalties. In general, most biomedical inventions are not a final end product; therefore the government rights would not extend to a final product.

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## NIH's Role in Technology Transfer

NIH, with a budget of over \$23 billion in fiscal year 2002, is the principal federal agency that conducts and funds biomedical research, including research on drugs. Within NIH, OTT is responsible for licensing the inventions of NIH employees to the private sector for development to benefit the public health. OTT oversees patent prosecution, negotiates and monitors licensing agreements, and provides oversight and central policy review of CRADAs.<sup>7</sup> NIH's stated goals with regard to the technology transfer process are, in order of priority, to foster scientific discoveries, to facilitate the rapid transfer of discoveries to the bedside, to make resulting products accessible to patients, and to earn income. NIH has broad authority under the statutes described above to negotiate agreements with outside partners in pursuit of its technology transfer goals.

NIH scientists and laboratories, scientists and laboratories in academia or other research institutions that receive public funding, and industry researchers are often all involved in the development of pharmaceuticals.

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<sup>7</sup>OTT also manages the patent and licensing activities for FDA and is responsible for the central development and implementation of technology transfer policies for NIH, FDA, the Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Quality.

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Usually, government and academic scientists conduct basic research on the biology of a disease and identify compounds, methods, and chemical reactions and pathways that may be of value in treating disease. They also conduct preclinical and clinical testing of drugs (phase 1 and 2 trials). Industry conducts more extensive clinical trials (phase 3 trials) and markets the drugs, although there is some overlap in these roles.<sup>8</sup> NIH's overall mission and authority, as well as the requirements of the Federal Food Drug and Cosmetic Act, suggest that NIH cannot sponsor a drug through FDA's new drug application (NDA) process. This act requires those who submit NDAs to FDA to provide "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing, of such drug."<sup>9</sup> While NIH conducts its own research and funds biomedical research at other institutions, it does not have a manufacturing, processing, or packing facility.

NIH can, however, license inventions directly to pharmaceutical firms without the necessity of working through a CRADA. For example, NIH officials told us that of the 16 drugs and vaccines currently approved by FDA that contain an NIH technology, only 3 involved a CRADA. To attract private-sector partners, NIH publicizes the availability of technologies that it seeks to license directly. NIH officials told us that it has entered into CRADAs with private-sector partners in at least two other cases that were similar to paclitaxel—naturally occurring substances for which shortages had limited NIH's ability to conduct research.

The Public Health Service (PHS) created a model CRADA because the Federal Technology Transfer Act of 1986 provided few specifics about the CRADA process. In general, the model CRADA sets forth the policies of NIH and other PHS agencies on various aspects of cooperative research and intellectual property licensing that derive from the Federal Technology Transfer Act. The model CRADA has been updated several times over the years. The 1991 CRADA between NIH and BMS referred to a March 27, 1989, version of the model CRADA. The 1989 model CRADA stated that NIH would be willing to grant exclusive licenses to its CRADA

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<sup>8</sup>Phase 1 studies of an investigational new drug for cancer are generally conducted in a small group of cancer patients to test for safety; phase 2 studies are generally conducted to test for safety and effectiveness in several hundred patients who have the condition under investigation; and phase 3 studies, which are performed after preliminary evidence suggesting effectiveness has been obtained in phase 2 trials, may include several hundred to several thousand people.

<sup>9</sup>21 U.S.C. § 355(b)(1)(D) (2000).

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collaborators. The 1989 model CRADA also contained a provision known as the “reasonable price clause.” It stated that PHS has “a concern that there be a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public. Accordingly, exclusive commercialization licenses granted for [NIH] intellectual property rights may require that this relationship be supported by reasonable evidence.” NIH dropped the reasonable pricing clause in 1995, and the current version of the model CRADA no longer has any stipulation regarding the pricing of products that are developed under the CRADA.

Under federal law and NIH policy, royalty income from license agreements is shared between the inventors and the institute or center within NIH in which the technology was developed. NIH uses the royalties for multiple purposes that contribute to the technology transfer program and the research of its laboratories. Specifically, the royalty payments can be used to (1) reward employees of the laboratory, (2) further scientific exchange among the laboratories of the agency, (3) educate and train employees of the agency or laboratory, (4) support other activities that increase the potential for transfer of the technology of the laboratories of the agency, (5) pay expenses incidental to the administration and licensing of intellectual property by the agency or laboratory, and (6) support scientific research and development consistent with the research and development missions and objectives of the laboratory.

Federal laws also generally prohibit agencies from disclosing information that concerns or relates to trade secrets, processes, operations, statistical information, and related information.<sup>10</sup> Therefore the federal technology transfer process that NIH engages in with the private sector is not entirely transparent to the general public, nor are the details of the negotiations and agreements that NIH makes with industry partners publicly known. However, information may be disclosed to those who have oversight authority over the agencies that generate such information, such as the Congress and its oversight bodies. In this way, information about the details of the federal investment and return on investment in the commercialization of a drug like Taxol can be examined for policymaking purposes.

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<sup>10</sup>See 15 U.S.C. § 3710a(c)(7); 18 U.S.C. § 1905 (2000). See *Public Citizen v. NIH*, 209 F. Supp. 2d 37 (D.D.C. 2002), see also, 5 U.S.C. § 552(b)(4) (2000), which exempts trade secrets, and commercial and financial information that is privileged or confidential, from public disclosure.

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## The Development of Taxol

NIH played a role in both basic and clinical research leading to the development and use of Taxol. In 1958, NCI, a component of NIH, initiated the Natural Products Program, which screened 35,000 plant species for anticancer activity. Researchers at the Research Triangle Institute found that an extract from the bark of the Pacific yew tree had antitumor activity in 1963 and isolated the compound paclitaxel in the bark of the Pacific yew in 1971. In 1979, scientists at Albert Einstein College of Medicine discovered how paclitaxel works to prevent cell division.

In 1983, NCI filed an investigational new drug application (IND) with FDA to initiate clinical trials of paclitaxel. The IND was approved, and phase 1 trials began. In 1985, NCI began funding phase 2 clinical trials. By 1989, two studies of paclitaxel's effect on ovarian cancer had demonstrated positive results.

In August 1989, NIH announced in a *Federal Register* notice that it was seeking a pharmaceutical company that could develop paclitaxel to a marketable status.<sup>11</sup> The notice stated that paclitaxel could not be patented. Instead, NIH offered a potential CRADA partner the exclusive rights to the source data from its clinical trials. Although 20 commercial firms replied to the announcement, only 4 companies, BMS among them, decided to apply for the CRADA opportunity.

NIH chose BMS as its CRADA partner, and the CRADA, "Clinical Development of Taxol," took effect on January 23, 1991. (For details on the CRADA partner selection process, see app. I.) Under the 1991 CRADA, NCI and BMS agreed to collaborate on ongoing and future clinical studies to obtain FDA approval for the marketing of paclitaxel, and NCI would make available exclusively to BMS the data and the results of all paclitaxel studies. As part of the CRADA, BMS was to supply NCI with sufficient amounts of paclitaxel for research and clinical trials. NCI could terminate the agreement if BMS "failed to exercise best efforts in the commercialization of taxol [paclitaxel]." Following this first Taxol-related CRADA, NIH entered into another CRADA with BMS in 1998 and has had other paclitaxel-related CRADAs with two other companies (see app. II).

In 1991, a phase 2 trial of paclitaxel demonstrated its effectiveness in treating breast cancer. In 1992, BMS filed and received approval for trademark protection for the name Taxol. Also in 1992, BMS filed an NDA

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<sup>11</sup>54 *Fed. Reg.* 31733 (1989).

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for Taxol with FDA. On December 29, 1992, FDA approved Taxol for the treatment of ovarian cancer, an indication for which it had been shown to be effective in earlier studies. In January 1993, Taxol was introduced into the marketplace by BMS for the treatment of ovarian cancer.

FDA's approval of BMS's NDA to market Taxol for the treatment of ovarian cancer triggered a provision in federal law granting BMS 5 years of marketing exclusivity for Taxol as a new chemical entity under the Drug Price Competition and Patent Term Restoration Act of 1984.<sup>12</sup> The statute provides marketing protection for unpatentable pharmaceuticals, stating that during this 5-year period "no application...may be submitted" to FDA that "refers" to the approved drug, a provision that generally prohibits the introduction of a generic drug during the exclusivity period.<sup>13</sup> Prior to the expiration of this period, in June 1997, BMS received two patents regarding the administration of Taxol. In July 1997, a number of generic drug manufacturers filed applications with FDA to market a generic version of paclitaxel, and notified BMS of their intent. BMS then filed suit in a federal district court alleging violations of its most recent patents. Under federal law, this granted BMS an additional 30 months of marketing exclusivity while the issues were being resolved in court.<sup>14</sup> (See the chronology in app. III for more information on the research and development of Taxol.)

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## NIH-BMS Partnership Provided Research Results Critical to Developing Taxol's Commercial Uses

The NIH-BMS collaboration provided BMS access to NIH research results that were critical for BMS's quick commercialization of Taxol. It provided other benefits for both parties and for the health of the public as well. BMS supplied paclitaxel to NIH, enabling NCI to dramatically expand its paclitaxel research. BMS later licensed three NIH inventions that resulted from the CRADA; however, BMS ultimately decided not to use any of the inventions in its applications to FDA for approval to market Taxol for additional indications. An NIH grant led to the important discovery of a method for the semisynthesis of paclitaxel by FSU researchers.

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<sup>12</sup>Pub. L. No. 98-417, 98 Stat. 1585.

<sup>13</sup>21 U.S.C. § 355(c)(3)(D)(ii) (2000). See H.R.Rep. No. 98-857, pt. 1, at 29 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647-48, 2662.

<sup>14</sup>21 U.S.C. § 355(j)(5)(B)(iii) (2000). In theory, a company could choose to waive its right to marketing exclusivity. In the case of Taxol, NIH and BMS could have agreed to such a waiver during CRADA or licensing negotiations, but we are not aware of such discussions.

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## NIH-BMS Collaboration Gave BMS Access to Critical Research Results

The NIH-BMS collaboration gave BMS unlimited access to NIH research results that were critical to BMS's ability to quickly receive FDA approval to market Taxol. BMS submitted an NDA for paclitaxel to FDA on July 21, 1992, 18 months after the 1991 CRADA took effect, and FDA approved the drug for initial marketing on December 29, 1992. Paclitaxel was one of the first oncological compounds tested by NCI, and the public health community was highly interested in exploring its potential. The collaboration between NIH and BMS was beneficial to BMS because it gained access to the results of NIH's basic, preclinical, and clinical research studies related to paclitaxel, including NIH studies conducted both prior to and during the term of the CRADA. Prior to the signing of the 1991 CRADA, and during the first 2 years of the CRADA, NCI conducted most of the clinical trials associated with paclitaxel. These studies were important for securing FDA's initial approval to market Taxol for the treatment of advanced ovarian cancer. Five of the six studies submitted to FDA by BMS in support of its marketing application were either conducted or funded by NIH; one was conducted by BMS.<sup>15</sup> BMS subsequently applied to FDA to market Taxol for other indications, including metastatic breast cancer and AIDS-related Kaposi's sarcoma. BMS has received FDA approval to market Taxol for eight indications as of May 12, 2003.

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## NIH-BMS Collaboration Allowed NIH to Expand Its Paclitaxel Research

Under the terms of the 1991 CRADA, BMS supplied paclitaxel for NCI's own studies as well as for NCI-funded trials at other institutions that were initiated pursuant to the CRADA. Three months after the CRADA was signed, BMS began shipments of paclitaxel to NIH. BMS reported that by the end of 1991, 1.35 kilograms of bulk drug, or 45,000 vials, had been delivered. In January 1992, shipments were increased from 5,000 vials per month to 25,000 vials per month, and by April 50,000 vials per month were being provided at no charge to NIH.

BMS's shipments of paclitaxel overcame shortages that had limited NCI research. In 1989, before the CRADA, a cumulative total of fewer than 500 patients had been treated with paclitaxel. Because of BMS's efforts to expand the collection and production of paclitaxel, NCI was able to establish more than 40 treatment referral centers for therapy of patients with refractory ovarian cancer (previously treated, unresponsive ovarian cancer) and breast cancer. According to NCI, 28,882 patients were treated

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<sup>15</sup>BMS officials told us that the number of patients in the five NCI trials and the one BMS trial were very similar (186 and 159 patients, respectively).

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in its clinical trials over the course of the CRADA, and the paclitaxel was supplied free of charge by BMS to NCI for use in both the clinical trials and the treatment centers.

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### NIH Licensed Inventions from CRADA to BMS

In 1996, NIH signed an agreement to license to BMS three patented paclitaxel-related inventions that resulted from the 1991 CRADA. While the compound itself was not patented, NIH patented three methods for using paclitaxel in cancer treatment. These inventions were (1) use of G-CSF (granulocyte colony-stimulating factor) to avoid the side effects of using Taxol in higher doses, (2) a 96-hour infusion method to overcome multidrug resistance, and (3) a method for using Taxol in combination with another drug (cisplatin). BMS licensed these three inventions because it thought they had potential to provide important contributions to treatment. BMS considered adding these methods as new indications to the Taxol product label, but ultimately decided not to use any of the inventions in its applications to FDA for approval to market the drug.

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### NIH Funding Supported Development of Semisynthesis Process for Producing Paclitaxel

The supply of natural paclitaxel was a continuing problem, since the bark of the Pacific yew was scarce and it took about 10,000 to 30,000 pounds of dried bark to produce about 1 kilogram of the compound.<sup>16</sup> Under the terms of the 1991 CRADA, BMS agreed to initiate an aggressive search for alternative sources of paclitaxel to lessen or eliminate dependence on the Pacific yew. Prior to the signing of the CRADA, however, NCI had funded research at FSU that led to the development of a semisynthetic process for producing paclitaxel that started the manufacturing process with materials from another type of yew tree that was plentiful. NIH provided about \$2 million in funding to FSU for this research. Researchers at FSU patented the semisynthesis process in 1989 and subsequently licensed the patent to BMS in 1990. Under the terms of the license agreement, BMS paid FSU substantial royalties for this patent in order to increase the

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<sup>16</sup>In response to the demand for Pacific yew bark, the Pacific Yew Act was enacted in 1992. The purposes of the Pacific Yew Act are to (1) provide for the efficient collection and utilization of those parts of the Pacific yew that can be used in the manufacture of paclitaxel for the treatment of cancer, (2) provide for the sale of Pacific yew for the commercial production and sale of paclitaxel at a reasonable cost to cancer patients, (3) ensure the long-term conservation of the Pacific yew, and (4) prevent the wasting of Pacific yew resources while successful and affordable alternative methods of manufacturing paclitaxel are being developed. Pub. L. No. 102-335 § 2(b), 106 Stat. 859-860.

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supply of Taxol.<sup>17</sup> BMS officials told us that BMS did not start using the FSU invention to manufacture Taxol until 1996.

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## NIH Invested Heavily in Taxol-Related Research, but Federal Financial Benefits Have Been Limited

Although NIH estimates that it has invested heavily in research related to paclitaxel, its financial benefits from the collaboration with BMS have not been great in comparison to BMS's revenue from the drug. NIH estimates that it has invested \$183 million in research related to paclitaxel from 1977 through 1997, the end of the CRADA's term, although not all of this was for research supporting the 1991 CRADA. For one portion of its investment in Taxol, NIH estimates that its net cost for conducting clinical trials that supported the development of Taxol through the 1991 CRADA was \$80 million—NIH estimates that it spent \$96 million on the studies, and this expense was offset by \$16 million in financial support from BMS. We estimate that the paclitaxel BMS supplied NIH through the CRADA had a value of \$92 million. In addition, NIH spent an additional \$301 million on paclitaxel-related research from 1998 through 2002, some of which supported cancer research, bringing NIH's total investment in paclitaxel-related research from 1977 to 2002 to \$484 million. Overall, BMS officials told us that the company spent \$1 billion to develop Taxol. Worldwide sales of Taxol have totaled over \$9 billion through 2002. As a result of its license agreement with BMS, NIH has received \$35 million in royalty payments. The 1991 CRADA noted NIH's concern that Taxol be fairly priced given the public investment in Taxol research and the health needs of the public, but it did not require that reasonable evidence be presented to show that this had occurred. The federal government has been a major payer for Taxol, primarily through Medicare. For example, Medicare payments for Taxol totaled \$687 million from 1994 through 1999.

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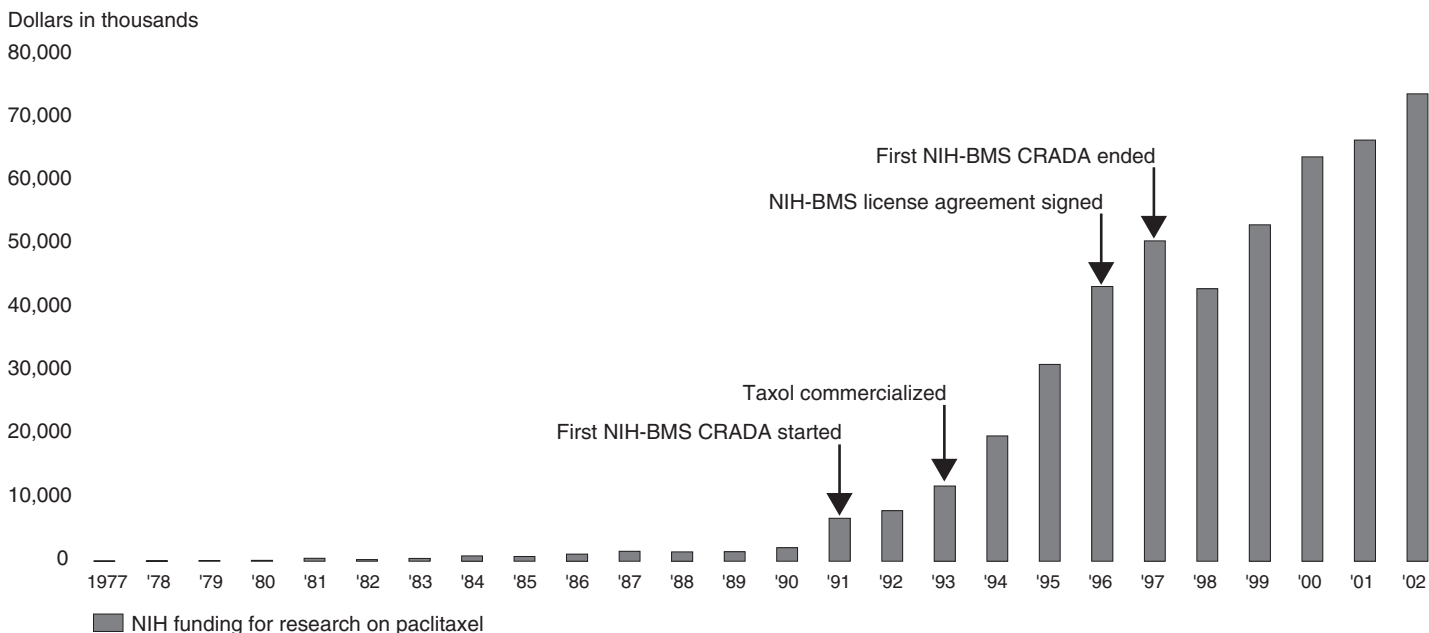
<sup>17</sup>BMS officials declined to disclose the amount of the Taxol-related royalties BMS paid to FSU. However, we estimate that FSU received a royalty rate of approximately 4.2 percent of BMS's total worldwide sales of Taxol. For example, FSU's Office of Technology Transfer website reported that FSU received \$67 million in royalties in 2000 and an FSU official told us that 98 percent of those royalties were from the license with BMS ([www.techtransfer.fsu.edu/tts.html](http://www.techtransfer.fsu.edu/tts.html), downloaded June 3, 2003). This represents about 4.2 percent of Taxol's total worldwide sales in calendar year 2000.



## NIH's Financial Investment in Paclitaxel Increased Significantly in the 1990s

Based on figures provided by NIH of its yearly expenditures for all research involving paclitaxel, we estimate that NIH spent \$183 million on paclitaxel-related research from 1977 through 1997, the end of the CRADA's term.<sup>18</sup> NIH officials told us that these figures reflect all NIH research using paclitaxel—even when it is given to patients as the standard of care in studies of other remedies—not just research investigating paclitaxel and Taxol. This figure includes spending for research on the effectiveness of paclitaxel for conditions other than cancer as well as research to develop analogues or alternative compounds to paclitaxel to increase the number of available drugs. We estimate NIH spent an additional \$301 million on paclitaxel-related research from 1998 through 2002, some of which supported cancer research, bringing NIH's total investment in paclitaxel-related research from 1977 to 2002 to \$484 million. (See fig. 1.)

**Figure 1: NIH's Funding for Paclitaxel-Related Research**



Source: GAO.

Note: GAO analysis based on data provided by NIH.

<sup>18</sup>NIH officials told us that NIH could not estimate its paclitaxel-related expenditures for years earlier than 1977.

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NIH estimates that its net expenditures to conduct clinical trials that supported the 1991 CRADA were \$80 million. NIH estimates that it spent \$96 million to conduct the clinical trials and BMS provided a reimbursement of \$16 million to offset the costs of the studies. NIH's estimate includes costs incurred during the CRADA and costs associated with clinical trials conducted prior to the CRADA, the results of which helped BMS obtain FDA approval to market Taxol. Almost all (\$15.6 million) of BMS's financial support was paid to offset clinical trial costs during the last several years of the CRADA. In addition, we estimate the paclitaxel BMS supplied to NIH under the CRADA had a value of \$92 million (based on FSS prices).<sup>19</sup>

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### NIH Has Received about \$35 Million in Royalties on Taxol Sales

NIH's financial benefits from the collaboration with BMS have not been great in comparison with BMS's revenue from the drug. In 1996, when BMS licensed from NIH three patents on methods for using Taxol in cancer treatment, it negotiated its first and only license agreement with NIH for Taxol, requiring BMS to pay royalties to NIH at a rate of 0.5 percent of its worldwide sales of Taxol. The NIH-BMS license agreement resulted in about \$35 million in royalties for NIH through 2002.<sup>20</sup> NIH reports that 10 individual inventors received 22 percent of the total \$35.3 million in royalty payments, or an aggregated amount of \$7.7 million, while NIH kept the remainder, \$27.5 million.<sup>21</sup>

Worldwide Taxol sales totaled over \$9 billion from 1993 through 2002. Sales exceeded \$1 billion annually from 1998 through 2001 (see table 1). BMS officials told us that the company invested over \$1 billion toward the development of Taxol since signing the CRADA in January 1991.<sup>22</sup> Costs included supporting clinical trials (including its payments to NIH),

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<sup>19</sup>FSS prices represent the prices at which some federal programs can purchase Taxol. NIH estimated that the paclitaxel supplied by BMS had a value of \$151 million based on average wholesale prices, which are generally higher than FSS prices.

<sup>20</sup>From 1996 through 2002, NIH's total royalty income from all its licensed inventions was \$296 million.

<sup>21</sup>NIH distributes royalty income in accordance with federal law and NIH policy. The inventors' share of royalties varied from year to year, based on BMS's sales per year. The income remaining after the inventors' share went to NCI.

<sup>22</sup>A recent analysis estimated that the average out-of-pocket cost of developing a new drug was \$543 million (in 2000 dollars). See J.A. DiMasi, R.W. Hansen, and H.G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, vol. 22 (2003).

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preparing the NDA, and finding alternative sources of the compound through yew cultivation and research on the semisynthesis process and plant cell culture techniques. For example, BMS officials told us that the company's clinical trials had enrolled over 21,000 patients by 1997.

**Table 1: BMS's Worldwide Taxol Sales, 1993-2002**

<b>Year</b>	<b>Total sales in dollars</b>
1993	162,000,000
1994	344,000,000
1995	580,000,000
1996	813,000,000
1997	941,000,000
1998	1,204,000,000
1999	1,453,000,000
2000	1,561,000,000
2001	1,112,000,000 <sup>a</sup>
2002	857,000,000
<b>Total</b>	<b>9,027,000,000</b>

Source: BMS.

<sup>a</sup>Taxol sales decreased after 2000, in part, because the first generic version of paclitaxel was released to the marketplace in late 2000.

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## 1991 CRADA Did Not Require Evidence That Taxol Would Be Reasonably Priced

At the time the 1991 CRADA was negotiated, NIH had a reasonable pricing policy that there should 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.”<sup>23</sup> NIH's standard reasonable pricing clause was modified in the 1991 CRADA. The CRADA noted NIH's concern that “there be a reasonable relationship between the pricing of Taxol, the public investment in Taxol research and development, and the health and safety needs of the public.” BMS agreed in the 1991 CRADA that these factors would be taken into account in establishing a fair market price. However, the 1991 CRADA did not require that reasonable evidence be

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<sup>23</sup>Shortly after introducing the policy of “reasonable pricing,” industry objected, considering it a form of price control, and many companies withdrew from further interaction with NIH. According to NIH, this ultimately created a barrier to expanded research relationships. The policy was revoked by NIH in 1995.

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presented to show that this would occur.<sup>24</sup> In its comments on a draft of this report, NIH stated it gathered other evidence to reach its conclusion that the price of Taxol was reasonable. NIH also entered into a CRADA with another company to develop a product that could provide competition for Taxol (see CRADA 148 in app. II). This alternative product, Taxotere (docetaxel), received its first marketing approval from FDA in 1996.

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## Federal Government Is a Major Payer for Taxol

The federal government, primarily through Medicare, has been a major payer for Taxol. Medicare payments for Taxol totaled \$687 million from 1994 through 1999, the last full year of marketing exclusivity for Taxol. Medicare payments for Taxol were \$202 million in 1999, accounting for more than one-fifth of Taxol's total domestic sales. Medicare's payments reflect, in part, the price it pays for Taxol. Compared to other federal programs, Medicare pays relatively more for Taxol than it does for other widely used cancer drugs. To assess the pricing of Taxol, we reviewed the price Medicare pays for Taxol and other cancer drugs compared to the prices paid by federal programs that directly procure these drugs.<sup>25</sup> We found that in the fourth quarter of 2002, Medicare paid 6.6 times the price these other federal programs paid for Taxol, while it paid an average of 3.0 times the price these other federal programs paid for other widely used cancer drugs.<sup>26</sup>

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<sup>24</sup>HHS-OIG, *Technology Transfer and the Public Interest: Cooperative Research and Development Agreements at NIH*, OEL-01-92-01100 (Washington, D.C.: November 1993).

<sup>25</sup>Federal agencies that directly procure pharmaceuticals have access to the FSS. Medicare does not purchase cancer drugs directly, but instead pays providers for cancer drugs that they have purchased. FSS prices are negotiated and are based on the actual best prices manufacturers charge some of their customers. Manufacturers must also sell brand-name drugs listed on the FSS to four federal drug purchasers—the Department of Veterans Affairs, the Department of Defense, the Public Health Service, and the Coast Guard—at a price at least 24 percent lower than the nonfederal average manufacturer price, a ceiling price that is lower than the FSS price for many drugs. Medicare payments are determined by the average wholesale price (AWP), a number reported by manufacturers. AWP often considerably exceeds the price a manufacturer actually receives for a drug. See U.S. General Accounting Office, *Medicare: Payments for Covered Outpatient Drugs Exceed Providers' Costs*, GAO-01-1118 (Washington, D.C.: Sept. 21, 2001).

<sup>26</sup>For this analysis, we examined the FSS and Medicare prices for Taxol and 12 other drugs for the treatment of cancer that were identified as among the top 35 drugs for Medicare Part B spending in 2001 and 2002 by the Centers for Medicare and Medicaid Services. These prices reflect solely drug procurement prices; they do not include any payments for administering the drugs.

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## Several Factors Affected NIH's Exercise of Its Broad Authority in Technology Transfer Activities Related to the Development of Taxol

Although NIH has broad authority under applicable statutes to negotiate CRADAs and license agreements with outside partners, several factors affected its exercise of that authority in the technology transfer activities related to the development of Taxol. Such negotiations involve a weighing of NIH's goals and priorities with those of a potential partner, recognizing that tradeoffs may be necessary to reach an agreement. In the case of Taxol, NIH's ability to exercise its authority was limited because it did not have a patent on paclitaxel and because its evaluation found that there was a shortage of available, qualified alternative CRADA partners. With regard to the license negotiations on the inventions resulting from the CRADA, the setting of royalties was affected by the criteria that both NIH and BMS used to help guide royalty negotiations. BMS officials told us that NIH's inventions did not contribute to BMS's successful marketing of Taxol.

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## NIH's Negotiating Position for the CRADA Was Potentially Affected by Its Lack of a Patent on Paclitaxel and by the Shortage of Qualified Alternative Partners

One factor affecting NIH's CRADA negotiating position is its ability to offer a potential partner exclusive marketing rights to an invention. In its paclitaxel negotiations, NIH's position was affected by the fact that it did not have a patent on paclitaxel.<sup>27</sup> As NIH acknowledged in the 1991 CRADA, because of this NIH was unable to grant any potential partner an exclusive patent license to market paclitaxel. NIH was able to offer potential partners access to the findings of the research it conducted prior to the CRADA and to its research during the term of the CRADA.

Another factor affecting the leverage that NIH has in negotiating a CRADA is the availability of other qualified applicants. If NIH were to be dissatisfied with the CRADA negotiations with an applicant, it theoretically could turn to another applicant and begin new negotiations, accepting the inherent delays. It also could seek multiple CRADA partners, recognizing that multiple partners may grant less favorable terms than one receiving an exclusive agreement. In the case of paclitaxel, it was advantageous for NIH to enter into a CRADA with an industry partner qualified to bring paclitaxel to the marketplace and to provide an adequate supply of paclitaxel for its work. NIH received four applications from potential CRADA partners. Using nine criteria to rank applications, including that an applicant have experience with both natural products and other drug development and be able to supply adequate amounts of

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<sup>27</sup>In its comments on a draft of this report, NIH stated that it could not patent paclitaxel because the relevant information about the compound was already in the public domain.

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the drug as needed for future clinical trials (see app. I), NIH reviewers scored the BMS application substantially higher than all of the others. While some concerns were raised about the BMS application, greater concerns were raised about other applications. For example, the applicant that received the second-highest score was cited as having no experience in the United States involving natural products and no experience in developing pharmaceutical agents in the United States and as providing incomplete responses, especially on how it would make Taxol available and how much it could supply annually.

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### License Negotiations under the CRADA Resulted in Royalty Payments to NIH

Applicable law does not restrict the royalty rate NIH can negotiate in a license agreement, although NIH's model CRADA at the time of the Taxol negotiations suggested that a ceiling be set at 5 to 8 percent. This specification has since been removed, and the current model CRADA sets no ceiling. By law, NIH is required to offer its CRADA partners the option to choose an exclusive license for any inventions that arise from the CRADA work.<sup>28</sup> NIH is not prohibited from specifying in the CRADA what the royalty rate will be, rather than waiting until a subsequent license agreement is negotiated.

When NIH and BMS entered into the license agreement 5 years after the 1991 CRADA took effect, how the parties viewed the benefits of an agreement likely affected the royalty rate negotiations. NIH officials indicated that they generally take eight factors into account in negotiating royalty rates. These include the stage of product development, the type of product, the market value of the product, the uniqueness of the materials, the scope of the patent coverage, the market timing, NIH's contribution to the product, and the public health benefit. An NIH OTT official reported that the ultimate determination of a royalty rate is not the result of a neat formula but is based on a balancing of these factors, with the public health benefit receiving the highest consideration. In contrast, BMS officials told us that the company considers three factors when negotiating royalty rates: scientific risk, coverage, and exclusivity. In the case of Taxol, a BMS official reported that the company determined it had high scientific risk (i.e., it did not know if the inventions would be successful), narrow coverage (i.e., the license was for very specific ways of treating a tumor), and a lack of exclusivity (i.e., the treatment regimens BMS licensed would not prevent other firms from marketing generic paclitaxel after BMS's

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<sup>28</sup>15 U.S.C. § 3710a(b)(1) (2000).

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period of marketing exclusivity expired), all making the inventions less valuable.

In general, NIH's leverage in negotiating royalty rates is affected by the amount of competition for a license. In 2000, NIH's director of OTT testified that the vast majority of NIH inventions require active marketing and more often than not only one firm is generally interested in licensing any particular type of technology.<sup>29</sup> In fiscal year 2000, there were 45 requests for exclusive licenses, and only 2 technologies had two applications for licenses each. For nonexclusive license requests, there were 253 requests, and only 31 had more than one application. NIH's director of OTT reported that, at that time, OTT had approximately 2,000 technologies available for licensing, 30 percent of which had been available for more than 5 years. In the case of Taxol, it is not clear whether other companies would have been interested in the inventions developed out of the CRADA, as BMS had exclusive rights to market paclitaxel at that time.

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## Concluding Observations

From the perspectives of NIH and BMS, the 1991 CRADA is an example of a successful collaboration between the public and private sectors in pharmaceutical technology transfer. Early studies supported by NIH on the clinical effectiveness of Taxol and made available to BMS under the CRADA were critical to BMS's success in rapidly commercializing its brand-name drug Taxol for the treatment of cancer. The additional supplies of the scarce paclitaxel provided by BMS to NIH under the CRADA were critical for the expansion of NIH's research.

NIH's goals in the technology transfer process emphasize public health benefits over financial considerations. In the case of Taxol, the benefit to public health was clearly demonstrated, as there were few treatments for women with ovarian or breast cancer when Taxol came on the market. However the financial return to NIH was more limited. NIH made a substantial investment in the development of Taxol. In return, NIH received royalty payments of about \$35 million from its license agreement with BMS, and received paclitaxel and financial support from BMS for the CRADA research. We noted that the federal government has spent over half a billion dollars in payments to health care providers for Taxol under the Medicare program. In light of the significant federal investment,

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<sup>29</sup>*Public Citizen v. NIH*, at 54.

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questions remain regarding the extent to which NIH used its broad authority in its negotiations with BMS on the royalty payments and the price of the drug to obtain the best value for the government.

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## Agency and Bristol-Myers Squibb Company Comments and Our Evaluation

We provided a draft of this report to NIH and BMS for their review. In its comments, NIH provided us with additional information about its expenditures related to the 1991 NIH-BMS CRADA and BMS's contributions to NIH research under the CRADA, and also presented the reasons that it did not patent paclitaxel. NIH acknowledged that the 1991 CRADA did not require that evidence be presented to assure that Taxol was reasonably priced; however, NIH states that its analysis of other information led it to conclude that Taxol was fairly priced. In response, we have incorporated the new information from NIH into the report as appropriate. However, we were not able to evaluate the basis for NIH's judgment that Taxol was fairly priced. NIH's comments are included as appendix IV. NIH also provided technical comments, which we have incorporated as appropriate.

In its comments, BMS expressed concern that our estimates of NIH's expenditures for the development of Taxol gave an exaggerated view of NIH's spending. We have revised our presentation of NIH's spending based on additional information contained in NIH's comments. BMS also expressed two concerns about our analysis of the price of Taxol to Medicare relative to other cancer drugs. First, BMS suggested that our analysis may include payments to physicians for administering the drugs in addition to the procurement price of the drugs. However, our analysis considered only the prices for drug procurement and did not include payments for physician services. Second, BMS suggested that our findings may change if our analysis excluded generic drugs and was restricted to brand name drugs. However, only 2 of the 12 comparison drugs in our analysis are generic drugs and our findings do not change if they are excluded. We found that, while Medicare generally pays more for cancer drugs than other federal programs that can directly procure pharmaceuticals, this price premium for Taxol is greater than average. BMS also made technical comments, which we incorporated as appropriate.

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As we agreed with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from the date of the report. At that time, we will send it to the Secretary of Health and Human Services, the Director of NIH, and others who are interested.



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We will make copies available to others upon request. In addition, the report will be available at no charge on GAO's Web site at <http://www.gao.gov>.

If you or your staff have any questions about this report, please call me at (202) 512-7119. Another contact and key contributors are listed in appendix V.

Sincerely yours,

A handwritten signature in black ink that reads "Marcia Crosse". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Marcia Crosse  
Acting Director, Health Care—Public  
Health and Science Issues

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# Appendix I: Selection of “Clinical Development of Taxol” CRADA Partner

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On August 1, 1989, NIH published a notice in the *Federal Register* seeking a pharmaceutical company that could effectively pursue the clinical development of paclitaxel for the treatment of cancer. Included in the *Federal Register* announcement were nine criteria for the selection of the CRADA partner:

- Experience in the development of natural products for clinical use.
- Experience in preclinical and clinical drug development.
- Experience in and ability to produce, package, market, and distribute pharmaceutical products in the United States and to provide the product at a reasonable price, and experience in doing so.
- Experience in the monitoring, evaluation, and interpretation of the data from investigational agent clinical studies under an investigational new drug application.
- Willingness to cooperate with the Public Health Service in the collection, evaluation, publication, and maintaining of data from clinical trials of investigational agents.
- A willingness to cost-share in the development of paclitaxel, including the acquisition of raw material and isolation or synthesis of paclitaxel in adequate amounts as needed for future clinical trials and marketing.
- Establishment of an aggressive development plan, including appropriate milestones and deadlines for preclinical and clinical development.
- An agreement to be bound by the HHS rules involving human and animal subjects.
- Provision for equitable distribution of patent rights to any inventions.

NIH’s Taxol CRADA Review Committee met on October 10, 1989, to review the applications of the four potential CRADA partners. The committee scored BMS’s application substantially higher than all of the others, with none of the other applications receiving a higher score than BMS on any of the individual criteria. Some of the strengths of the BMS application that were discussed were BMS’s extensive experience with natural products, its impressive record in the area of production of anticancer agents and substantial experience in preclinical drug development, and its bearing of financial responsibility for collection of the compound and preclinical toxicology studies. Weaknesses discussed were pricing and the estimates of available paclitaxel. The applicant receiving the second-highest score was cited as having no experience in the United States for natural products and no experience in developing drugs in the United States.

# Appendix II: Catalog of CRADAs and License Agreements Related to Taxol

NIH has had four CRADAs and one CRADA amendment related to paclitaxel (see table 2). Two of the CRADAs and the CRADA amendment were with BMS and concerned development of the drug Taxol. One CRADA was with Rhône-Poulenc Rorer (now Aventis) and involved research on Taxotere, a part of the taxane class of chemotherapy drugs, whose original source is the yew tree. It is also a treatment that can help destroy cancer cells in the body after previous chemotherapy. An additional CRADA, which is ongoing, is with Angiotech and the Johns Hopkins University and involves the use of paclitaxel to coat stents used in angioplasty.

**Table 2: CRADAs Related to Taxol**

CRADA number	Title	Partners	Active dates
64	Clinical Development of Taxol	NCI and BMS	1/23/91 to 12/31/97
97 (amendment to 64)	Clinical Development of Taxol: Studies on Mechanisms of Action and Resistance, Identification of Analogs Active in Resistant Cell Lines	NCI and BMS	7/17/95 to 12/31/97
686	Taxol: Studies on the Mechanisms of Action and Resistance	NCI and BMS	6/9/98 to 6/9/01
148	CRADA for the Clinical Development of Taxotere	NCI and Rhône-Poulenc Rorer	5/14/92 to 3/1/00
363	Use of Paclitaxel and Microtubule-Stabilizing Agents for the Prevention of Restenosis	NIH, Angiotech, and the Johns Hopkins University	Currently active

Source: NIH.

Although paclitaxel itself has not been patented, methods of administration of the drug have been patented. There are a few patents pertaining to paclitaxel (see table 3). The government has an interest in three of these patents: 5496804, 5496846, and 6150398. Patent 5496804 is for a method for treating paclitaxel side effects with G-CSF (granulocyte colony-stimulating factor); patent 5496846 is a method for using paclitaxel in a 96-hour infusion for breast cancer; and patent 6150398 is for a method of treating cancer by administration of paclitaxel and a DNA cross-linking antineoplastic agent (cisplatin). Patents 5641803 and 5670537 are held by BMS solely. One is a method for administering Taxol over 3 hours, and the

other is for a method of effecting tumor regression with a low-dose, short-infusion Taxol regimen.

**Table 3: Patents Related to Taxol**

<b>Patent number</b>	<b>Title</b>	<b>Assignee</b>	<b>Date approved</b>
5496804	Method for Treating Taxol Side Effects with G-CSF	Department of Health and Human Services	3/5/1996
5496846	Taxol Treatment of Breast Cancer	Department of Health and Human Services	3/5/1996
5641803	Methods for Administration of Taxol	Bristol-Myers Squibb Co.	6/24/1997
5670537	Method for Effecting Tumor Regression with a Low-Dose, Short-Infusion Taxol Regimen	Bristol-Myers Squibb Co.	9/23/1997
6150398	Methods for the Treatment of Cancer	Department of Health and Human Services	11/21/2000

Source: U.S. Patent and Trademark Office.

NIH has one exclusive patent license agreement with BMS that resulted from CRADA 64, "Clinical Development of Taxol." This license agreement covers three patents: 5496804, 5496846, and 6150398.

In addition, BMS and FSU established a major license agreement concerning the semisynthetic production of Taxol. Other NIH CRADAs involving the other industry partners (i.e., Rhône-Poulenc Rorer, Angiotech, and the Johns Hopkins University) did not result in any patented inventions or license agreements.

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# Appendix III: Chronology of the Research and Development of Taxol (Paclitaxel)

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1958	<ul style="list-style-type: none"><li>• The National Cancer Institute (NCI) initiates the Natural Products Program to screen 35,000 plant species for anticancer activity.</li></ul>
1963	<ul style="list-style-type: none"><li>• Researchers at Research Triangle Institute in North Carolina find that an extract from the bark of the Pacific yew tree has antitumor activity.</li></ul>
1971	<ul style="list-style-type: none"><li>• Researchers at Research Triangle Institute identify compound 17—paclitaxel—the active ingredient in the Pacific yew tree.</li></ul>
1979	<ul style="list-style-type: none"><li>• Researchers at Albert Einstein College of Medicine discover how paclitaxel works to prevent cell division, by means of a mechanism called tubulin stabilization.</li></ul>
1980	<ul style="list-style-type: none"><li>• Stevenson-Wydler Technology Innovation Act and Bayh-Dole Act enacted.</li></ul>
1983	<ul style="list-style-type: none"><li>• NCI files an investigational new drug application (IND) to initiate clinical trials of paclitaxel. IND is approved, and phase 1 clinical trials begin.</li></ul>
1985	<ul style="list-style-type: none"><li>• NCI begins phase 2 clinical trials.</li></ul>
1986	<ul style="list-style-type: none"><li>• Federal Technology Transfer Act enacted.</li></ul>
1987	<ul style="list-style-type: none"><li>• Hauser Chemical becomes contractor to NIH, collecting yew tree bark and manufacturing paclitaxel.</li></ul>
1989	<ul style="list-style-type: none"><li>• Researchers at Florida State University (FSU), funded by NIH, patent a process for the semisynthesis of Taxol.</li><li>• NCI publishes a <i>Federal Register</i> announcement petitioning pharmaceutical companies to compete for the right to develop paclitaxel. Four companies, including Bristol-Myers Squibb (BMS), apply.</li></ul>
1990	<ul style="list-style-type: none"><li>• FSU and BMS sign a license agreement for BMS's use of the semisynthesis process.</li></ul>

- 
- 1991
- NCI signs CRADA with BMS for the clinical development of paclitaxel.
- 
- 1992
- U.S. Patent and Trademark Office approves BMS's application to trademark the name Taxol.
  - BMS files a new drug application (NDA) with FDA for use of Taxol to treat ovarian cancer.
  - BMS obtains FDA approval in December for treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy.
  - Pacific Yew Act enacted (Pub. L. No. 102-335, 106 Stat. 859).
- 
- 1993
- BMS introduces Taxol into the marketplace for treatment of ovarian cancer.
  - BMS files supplemental NDAs with the FDA, one for further defining the optimal dose and schedule of the administration of Taxol, another for use of paclitaxel as a secondary therapy for breast cancer.
- 
- 1994
- BMS obtains FDA approval in April for treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
  - BMS obtains FDA approval in June for new dosing regimen for patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary.
  - FDA approves supplemental NDA for semisynthetic production of Taxol by using the process developed by FSU.
- 
- 1996
- NCI and BMS CRADA extended through December 1997.
  - NIH is awarded patents for Taxol Treatment of Breast Cancer and Method for Treating Taxol Side Effects with G-CSF.
  - NIH and BMS sign license agreement, whereby NIH provides BMS with exclusive rights to three NCI inventions involving Taxol. BMS is required to provide NIH with royalty payments and research support, and meet benchmarks for the clinical development of Taxol.
  - NIH begins to receive royalty payments from BMS.

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**Appendix III: Chronology of the Research and Development of Taxol (Paclitaxel)**

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|------|---|
| 1997 | <ul style="list-style-type: none"><li>• BMS obtains FDA approval in August for second-line therapy for AIDS-related Kaposi's sarcoma.</li><li>• Other drug companies begin developing generic versions of paclitaxel and file NDAs and abbreviated new drug applications with FDA.</li></ul>  |
| 1998 | <ul style="list-style-type: none"><li>• BMS obtains FDA approval in April for first-line therapy for the treatment of advanced carcinoma of the ovary in combination with cisplatin.</li><li>• BMS obtains FDA approval in June for use of Taxol injection, in combination with cisplatin, for the first-line treatment of non-small-cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.</li></ul> |
| 1999 | <ul style="list-style-type: none"><li>• BMS obtains FDA approval in October for adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy.</li></ul>  |
| 2000 | <ul style="list-style-type: none"><li>• First generic version of paclitaxel approved in September.</li><li>• Generic versions of paclitaxel enter the marketplace.</li></ul>  |
| 2002 | <ul style="list-style-type: none"><li>• BMS obtains FDA approval in June for new dosing regimen for the first-line treatment of advanced ovarian cancer: every 3 weeks at a dose of 175 milligrams per square meter of body surface followed by cisplatin at a dose of 75 mg/m<sup>2</sup>.</li></ul>   |

# Appendix IV: Comments from the National Institutes of Health



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health  
Bethesda, Maryland 20892  
www.nih.gov

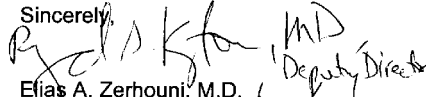
MAY 29 2003

Ms. Marcia Crosse  
Acting Director, Health Care - Public Health  
and Science Issues  
U.S. General Accounting Office  
441 G St., N.W.  
Washington, D.C. 20548

Dear Ms. Crosse:

We are pleased to have the opportunity to review and comment on the draft General Accounting Office (GAO) report entitled *Technology Transfer: NIH-Private Sector Partnership in the Development of Taxol*, GAO-03-839. Enclosed is the National Institute of Health response. It includes both general and technical comments. We believe that incorporation of these comments into the final GAO report will clarify various issues and enhance the overall accuracy of the report.

Sincerely,

  
Elias A. Zerhouni, M.D.  
Director

Enclosure



**Comments of the National Institutes of Health (NIH) on the U.S. General Accounting Office (GAO) Draft Report "Technology Transfer: NIH-Private Sector Partnership In the Development of Taxol," GAO-03-839, May 2003**

The NIH is pleased to provide comments on this draft GAO report. The development of the cancer-fighting drug Taxol is an example of how the determined efforts of scientists from not-for-profit, academic, government, and for-profit organizations came together through a variety of public-private partnerships spanning over 30 years to develop a life-saving therapy that has become a standard of care for ovarian, breast, lung, and other cancers.

In 1989, NCI was faced with a dilemma of having evidence of clinical activity with a promising new drug, but was severely hampered by the limited supply. Because it was extremely difficult to manufacture, the NCI could only obtain enough of the drug to treat a few hundred cancer patients in clinical trials. In order to expand the phase 2 studies, to develop drug combinations, to initiate phase 3 trials, to make the drug available on a compassionate basis, and to receive FDA approval, NCI advertised in the *Federal Register* for a pharmaceutical partner to help meet these goals.

As NCI's partner under a subsequent CRADA, Bristol Meyers Squibb (BMS) rapidly and substantially increased the amount of Taxol available for research and commercialization, cooperated in executing a broad research agenda exploring Taxol's usefulness in many patient populations, and provided expertise necessary to rapidly achieve FDA approval. Taxol, and more recently the generic paclitaxel, are now widely used. According to information from BMS, more than one million patients have been treated with Taxol.

Background

Examining the financial aspects of the development of Taxol in isolation from the NIH's mission tells only part of the story. To understand fully the development of Taxol, one must understand the role of NIH in leading biomedical research. In July 2001, NIH submitted to Congress a document entitled "A Plan to Ensure Taxpayers' Interests Are Protected" that described the nature of research and the arduous road that many biomedical technologies (inventions) follow to reach the public. A copy of that document is attached, but it can also be found at <http://www.nih.gov/news/070101wyden.htm>. The report explains how NIH stewardship of federal resources that support biomedical research has protected the taxpayers' interests.

The NIH mission is to sponsor and conduct medical research and advance public health. In furtherance of that mission, the NIH employs mechanisms and authorities provided under the Bayh-Dole Act, the Stevenson-Wydler Act, and subsequent legislation to assist in combining the scientific expertise of the NIH and its funding recipients with the scientific and business expertise of private-

sector companies. These laws were enacted to encourage government-owned and government-funded research laboratories to pursue commercialization of the results of their research.

The Stevenson-Wydler Technology Innovation Act of 1980 calls for the NIH and other federal agencies to execute license agreements with commercial entities to promote the development of technologies discovered by government scientists. The Act also provides a financial return to the public in the form of royalty payments and related fees paid to the U.S. Treasury. In 1986, the Act was amended by the Federal Technology Transfer Act of 1986 (FTTA), which authorizes federal agencies to enter into cooperative research and development agreements (CRADA) with non-federal partners to conduct research and to receive royalty payments directly.

The Patent and Trademark Amendments of 1980 (P.L. 96-517), known as the Bayh-Dole Act, aimed to address barriers to development and promote the synergy necessary to commercialize federally funded inventions. The Act was enacted to allow federal agencies to secure patent rights and convey the rights to commercial entities through licensing, thereby promoting the transfer of federally-funded technologies to the public and enhancing economic development. A key provision of the Act provides grantees and contractors, both for-profit and not-for-profit, the authority to retain title to government-funded inventions and makes them responsible for using the patent system to promote the use, commercialization, and public availability of inventions.

#### General Comments

##### A. Reasonable Pricing

The draft report makes several references to the wording of the reasonable pricing clause in the original BMS CRADA (#64), noting that it did not require that reasonable evidence be presented. We believe that without further elaboration, this provides the false impression that evidence was not presented or considered. The following paragraphs clarify this issue and enhance the accuracy of the report. We suggest that GAO incorporate them in the report:

As a part of the CRADA, BMS acknowledged the National Cancer Institute's (NCI) concern that there be a reasonable relationship between the pricing of Taxol, the public investment in Taxol research and development, and the health and safety needs of the public. NCI acknowledged BMS' concern that because Taxol was not patentable, market exclusivity for a period necessary to recover its investment in Taxol research and development might not be available. In addition, NCI acknowledged that due to the limited supply of natural resources for production of Taxol and the complexity of the manufacturing process, Taxol would be expensive to develop and manufacture. Both parties agreed to take these factors into consideration in establishing a fair market price for Taxol. Although the CRADA did not

require that reasonable evidence be presented, NCI collected this evidence and believed that the pricing strategy of BMS for Taxol met the requirements of the CRADA.

NCI considered the possibility of conducting a detailed cost-base analysis of the proposed price, but rejected this alternative. Instead, NCI measured the fairness and reasonableness of the proposed price by comparison with similar products and concluded that the proposed price met the reasonable pricing requirements under the CRADA because: (a) the price of Taxol fell below the median for recently approved oncology drugs, even though Taxol was substantially more expensive to produce due to its complex structure; (b) BMS established an indigent access program to make it available free of charge to patients who could not afford it; (c) medical and government institutions received the drugs at a significant discount; (d) patients receiving the drug under a compassionate-release program would continue to receive the drug free of charge following FDA approval; and (e) BMS would continue to provide Taxol free of charge to NCI-sponsored trials initiated under the CRADA. An additional factor in NCI's accepting the proposed price of Taxol as being reasonable was that the price of Taxol marketed in the United States was lower than that in Canada. This was considered significant because attention had been drawn to prices of drugs in the United States versus overseas. (See testimony of Bruce Chabner, Director, Division of Cancer Treatment, National Cancer Institute, at the Hearing "Pricing of Drugs Co-developed by Federal Laboratories and Private Companies," January 25, 1993, Serial No. 103-2.)

B. Intellectual Property Rights

On the opening page and throughout the report, GAO states that "NIH did not have any intellectual property rights to offer because the drug is a naturally occurring compound that cannot be patented." That statement is incorrect.

In general, naturally occurring compounds that are isolated and have utility would be patentable subject matter. However, in the case of paclitaxel, the previous isolation of paclitaxel, publication of the structure, and publication of antitumor activity created a bar to obtaining patent rights. Paclitaxel was in the public domain.

For a background document on the discovery, we suggest that GAO view an article entitled "Anticancer Research Honored at RTI" in the May 19, 2003, issue of Chemical & Engineering News (see <http://www.cen-online.org>). The article describes an event last month at the Research Triangle Institute's (RTI) Natural Products Laboratory in Research Triangle Park, NC. The event was the designation by the American Chemical Society of the laboratory as a National Historic Chemical Landmark due to the discovery there of the "revolutionary anticancer drugs camptothecin and Taxol (paclitaxel) by Mansukh C. Wani and the late Monroe E. Wall." It also chronicles the development of Taxol, a name given by Wall, and later trademarked by BMS.

We recommend that GAO revise its statements on the opening page and

throughout the report to reflect the actual situation -- that the NIH had no intellectual property rights to offer because the chemical was known, its activity had been published, and it could not meet the criteria for a patent.

C. Valuation of NIH's and BMS' Respective Contributions to Paclitaxel Research

On the summary page and throughout the draft report there are various statements of the estimated NIH investment in research related to Taxol since 1977. While there are some clarifying statements located in the middle of the report, we believe the \$484 million figure cited as the NIH investment needs to be clarified, both in the summary and throughout the report because it cites all funding for any research related to Taxol, paclitaxel, taxotere etc., whether conducted by NIH scientists or recipients of NIH funds. We request that GAO recalculate the value and expense figures by incorporating information from the following two paragraphs, and limit the comparison to the CRADA activity.

The amount of funds used to support NIH activities associated with the BMS CRADA has been estimated at \$96 million. This was the estimate provided by NCI in response to an inquiry from the Congressional Research Service in February 1999. The figure actually represents costs incurred during the CRADA and costs associated with clinical trials conducted prior to the CRADA but whose information was provided to BMS as a part of the CRADA and used to support the BMS application to the FDA. We believe that this figure appropriately reflects the NIH's involvement with BMS in the development of the FDA-approved drug Taxol.

Additionally, the GAO report does not address the financial contributions of BMS to the CRADA. During the CRADA period, BMS provided \$16 million to the NIH to support the costs of the clinical trials conducted under the CRADA. Under the terms of the agreement, BMS also provided quantities of Taxol (paclitaxel) at no cost to the NIH. The ability of BMS to provide large quantities of material provided the needed boost to accelerate research and move toward the actual approval of a new cancer treatment drug. The NCI estimates that the value of the material provided by BMS, based on average wholesale prices at the time, had a value of \$151 million. Adding this to the amount NIH received through royalties, the total value to the NIH would exceed \$200 million.

D. Disclosure of Commercial Information

Finally, as GAO is aware, federal CRADAs often contain trade secrets, commercial confidential information, or other privileged information that the Trade Secrets Act (18 U.S.C. 1905), the Federal Technology Transfer Act (15 U.S.C. 3710a(c)(7)(a)), and the Freedom of Information Act (5 U.S.C. 552(b)(4)) protect from public disclosure. Payments made to the NIH pursuant to CRADAs and licenses, as well as revenues from royalties arising from NIH inventions for intramural research (including CRADAs), cannot be disclosed without certain

consents (e.g., from the CRADA or the license partner). For the purposes of this report, however, the CRADA partner, BMS, voluntarily agreed to permit disclosure of its commercial information so that the study could be completed and its results made publicly available. The NIH is grateful for BMS' willingness to release its commercial information.

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# Appendix V: GAO Contact and Staff Acknowledgments

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## GAO Contact

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## Acknowledgments

Other key contributors to this report are Helen Desaulniers, Anne Dievler, Julian Klazkin, Carolyn Feis Korman, Carolina Morgan, and Roseanne Price.

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