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Drug and Vaccine Development - Background Materials, May 6, 1994

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Institute of Medicine

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

May 6, 1994

BACKGROUND MATERIALS

PHOTOCOPY
PRESERVATION

Institute of Medicine

Roundtable for the Development of Drugs
and Vaccines Against AIDS

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

May 6, 1994

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

TENTATIVE AGENDA

8:30 Continental Breakfast

9:00 **Welcome and Introduction**

- Barton Haynes, *F.M. Hanes Professor of Medicine; Director, Duke University Arthritis Center; and Roundtable Co-chair*
- Paul Volberding, *Chief, AIDS Program and Clinical Oncology, San Francisco General Hospital; and Roundtable Co-chair*

9:15 **Importance and Value of Government-Industry Collaboration on HIV Drug and Vaccine Development**

- Edward Scolnick, *President, Merck Sharp & Dohme Research Laboratories*

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

Discussion Leader: Peter Barton Hutt, *Partner, Covington & Burling*

Understanding the Legislative History of Intellectual Property Rights Involving the Pharmaceutical Industry

- Peter Barton Hutt, *Partner, Covington & Burling*

Understanding the History of Fair Pricing Clauses and Their Implementation in Government Licensing of Intellectual Property

- Thomas Mays, *Director, Office of Technology Development, National Cancer Institute*

- 10:00 Discussion
- 10:30 *Break*
- 10:45 **Impediments to Collaboration on HIV Drug and Vaccine Development: Defining the Issues**

Discussion Leader: Pat Gage, *Chief Operating Officer, Genetics Institute, Inc.*

Commentary from a Government/NIH Perspective

- Bruce Chabner, *Director, Division of Cancer Treatment, National Cancer Institute*

A View from the Pharmaceutical Industry

- Stephen Carter, *Senior Vice President, World Wide Clinical Research & Development, Bristol-Myers Squibb Pharmaceutical Research Institute*

Practical Implications of Rules Governing Intellectual Property Developed from Collaborative Relationships

- Harold Edgar, *Professor of Law, Columbia University School of Law*

- 11:30 Discussion

- 1:00 *Lunch*

- 2:00 **Overcoming Obstacles to Collaboration and Promoting HIV Drug and Vaccine Development: Proposals for Resolution**

Discussion Leader: Martin Delaney, *Co-Executive President and Director, Project Inform*

Industry Perspective

- David Barry, *Vice President, Research, Development and Medical Affairs, Burroughs Wellcome Co.*

Government/NIH Perspective

- Anthony Fauci, *Director, National Institute of Allergy and Infectious Diseases*

Congressional/Legislative Response

- Timothy Westmoreland, *Counsel, Subcommittee on Health and the Environment, U.S. House of Representatives*
- David Schulke, *Chief Health Policy Advisor, The Honorable Ron Wyden, U.S. House of Representatives*

- 2:40 Discussion
- 4:15 **Consideration of Future Directions: Summary of Salient Issues**
• Daniel Hoth, *Senior Vice President and Chief Medical Officer, Cell Genesys*
- 4:45 **Closing Remarks**
• Paul Volberding, *Chief, AIDS Program and Clinical Oncology, San Francisco General Hospital; and Roundtable Co-chair*
- 5:00 *Adjourn*

INSTITUTE OF MEDICINE

NATIONAL ACADEMY OF SCIENCES

2101 CONSTITUTION AVENUE WASHINGTON, D.C. 20418

MAR 31 1994

DIVISION OF HEALTH PROMOTION
AND DISEASE PREVENTION

FAX: 202/334-2939

Call Leslie &
ask her to add
Paul Tran to the
invitees list for
the 6th

MEMORANDUM

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

FROM: Leslie Hardy *LH* and Jennifer Holliday *JH*

DATE: March 29, 1994

SUBJECT: May 5-6, 1994 Roundtable Dinner and Workshop

As you know, the Roundtable will be concluding its activities with the upcoming and final workshop, *Collaboration Between Government and Industry: Challenges and Opportunities for HIV Drug and Vaccine Development*. The meeting will be held on **Friday, May 6, 1994** from 9:00 am to 5:00 pm in the Lecture Room of the National Academy of Sciences building, 2101 Constitution Avenue, N.W. A continental breakfast will be available beginning at 8:30 am outside of the Lecture Room. A workshop agenda and invitation list are enclosed for your information.

We plan to keep the workshop relatively small and closed so that participants may speak frankly about the problems hampering government-industry collaboration and explore possible solutions. Although there will be a number of brief didactic presentations during the workshop, we have set aside substantial blocks of time for general discussion. Among the issues we hope to explore are: potential impediments to government-industry collaboration in drug research and development (e.g., the fair-pricing clauses included in Cooperative Research and Development Agreements [CRADAs], the rules governing intellectual property developed from government-industry collaborative arrangements); the implications for progress toward discovery of novel drug or vaccine candidates and their development into products, particularly when barriers may exist that discourage or prevent government-industry collaboration; and ways to overcome existing obstacles. To inform workshop participants and stimulate discussion, we will be distributing several background items a few weeks before the workshop—for example, brief case histories of the NCI-industry experience with taxol and ddI, a brief historical account of what's happened to the rules that govern intellectual property rights from government-industry collaborations in the U.S., and a written statement documenting or describing the importance and value of government and industry collaboration in HIV drug and vaccine development.

On **Thursday evening, May 5**, Roundtable members and invited guests (see enclosed list) will meet for dinner beginning at 6:30 pm in the Members Room of the NAS building. As this will be the Roundtable's last meeting, we thought the dinner would provide an opportunity to informally discuss some of the future challenges and opportunities in the AIDS drug and vaccine development arena. The dinner session should conclude around 8:30 pm.

For those of you from out of town, IOM Travel will assist you in making airline reservations; their telephone number is 202-334-3850 or 1-800-235-2210. When speaking with an agent, please reference record locator number 5ZW8F1. A block of rooms has been reserved at the Wyndham Bristol Hotel (2430 Pennsylvania Avenue, N.W.) We will be handling the hotel arrangements through our office. Please complete and fax the attached reservation form to Jennifer Holliday at (202) 334-2939 **by April 18**. The new maximum daily reimbursement for hotel and meals is \$151, with no more than \$34 for meals; receipts must be submitted for any single expense of \$25 or more. You will receive a travel voucher at the meeting.

We look forward to seeing you in May. Please feel free to call me or Jennifer Holliday at (202) 334-2453 if you have any questions.

INSTITUTE OF MEDICINE

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

Roundtable for the Development of Drugs
and Vaccines Against AIDS
May 6, 1994

WORKSHOP

INVITEES

Moises Agosto, *Treatment Research Advocate, Department of Public Policy, National
Minority AIDS Council*

Paul Blake, *Vice President and Medical Director, Clinical Research, Development &
Medical Affairs North America, SmithKline Beecham*

Dani Bolognesi, *James B. Duke Professor and Director, Center for AIDS Research,
Duke University Medical Center*

Samuel Broder, *Director, National Cancer Institute, National Institutes of Health*

Stephen K. Carter, *Senior Vice President, World Wide Clinical Research & Development,
Bristol-Myers Squibb Pharmaceutical Research Institute*

Ben Cheng, *Information Advocacy Associate, Project Inform*

Ellen C. Cooper, *Director of Clinical Research, Community-Based Clinical Trials Program,
American Foundation for AIDS Research*

Deborah J. Cotton, *Assistant Professor of Medicine, Harvard Medical School*

Cornelia Dekker, *Vice President, Clinical Research, Biocine Clinical Research,
Chiron Corporation*

Joseph A. DiMasi, *Senior Research Fellow, Center for the Study of Drug Development,
Tufts University*

Mindy Thompson Fullilove, *Associate Professor of Clinical Psychiatry and Public Health,
Columbia University*

D.A. Henderson, *Deputy Assistant Secretary for Health, Department of Health and Human Services*

Daniel Hoth, *Senior Vice President and Chief Medical Officer, Cell Genesys*

Michael Iskowitz, *Legal Counsel, Senate Committee on Labor and Human Resources, United States Senate*

Margaret Johnston, *Acting Deputy Director, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health*

David Kessler, *Commissioner, Food and Drug Administration*

Jack Killen, *Acting Director, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health*

Mathilde Krim, *Founding Co-Chair, American Foundation for AIDS Research*

Philip R. Lee, *Assistant Secretary for Health, Department of Health and Human Services*

Ira Magaziner, *Senior Advisor to the President for Policy Development, The White House*

Thomas Mays, *Director, Office of Technology Development, National Cancer Institute, National Institutes of Health*

Teresa McGovern, *Legal Director, HIV Law Project, AIDS Service Center, Lower Manhattan*

Richard A. Merrill, *Daniel Caplin Professor of Law, University of Virginia School of Law*

Harry M. Meyer, Jr., *President (retired), Medical Research Division, American Cyanamid Company*

Charles Nelson, *Assistant Treatment Research Advocate, National Minority AIDS Council*

John F. Niblack, *President, Pfizer Research, Pfizer Inc.*

William E. Paul, *Director, Office of AIDS Research, National Institutes of Health*

John P. Phair, *Chief, Division of Infectious Diseases and Director, Comprehensive AIDS Center, Northwestern University Medical School*

Michael Saag, *Associate Professor of Medicine, University of Alabama at Birmingham*

David Schulke, *Chief Health Policy Advisor, The Honorable Ron Wyden, United States House of Representatives*

William B. Schultz, *Counsel, House Subcommittee on Health and the Environment,
United States House of Representatives*

Edward Scolnick, *President, Merck Sharp & Dohme Research Laboratories*

John D. Siegfried, *Associate Vice President and Senior Director, Pharmaceutical
Manufacturers Association*

Mervyn Silverman, *President, American Foundation for AIDS Research*

Whaijen Soo, *Assistant Vice President and Senior Director, Clinical Virology and AIDS
Research, Hoffmann-La Roche, Inc.*

Peter Staley, *Founding Director, Treatment Action Group, New York*

Harold Varmus, *Director, National Institutes of Health*

John Vernon, *Professor of Economics, Department of Economics, Duke University*

Timothy Westmoreland, *Counsel, House Subcommittee on Health and the Environment,
United States House of Representatives*

Randy F. Wykoff, *Associate Commissioner for AIDS and Special Health Issues, Food and
Drug Administration*

INSTITUTE OF MEDICINE

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

Roundtable for the Development of Drugs
and Vaccines Against AIDS
May 5, 1994

DINNER

INVITED GUESTS

Moises Agosto, *Treatment Research Advocate, Department of Public Policy, National
Minority AIDS Council*

Stephen K. Carter, *Senior Vice President, World Wide Clinical Research & Development,
Bristol-Myers Squibb Pharmaceutical Research Institute*

Ben Cheng, *Information Advocacy Associate, Project Inform*

Deborah J. Cotton, *Assistant Professor of Medicine, Harvard Medical School*

Mindy Thompson Fullilove, *Associate Professor of Clinical Psychiatry and Public Health,
Columbia University*

Daniel Hoth, *Senior Vice President and Chief Medical Officer, Cell Genesys*

Mathilde Krim, *Founding Co-Chair, American Foundation for AIDS Research*

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Manufacturers Association*

Mervyn Silverman, *President, American Foundation for AIDS Research*

Peter Staley, *Founding Director, Treatment Action Group, New York*

Randy F. Wykoff, *Associate Commissioner for AIDS and Special Health Issues, Food and
Drug Administration*

INSTITUTE OF MEDICINE

Roundtable for the Development of Drugs
and Vaccines Against AIDS

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

May 6, 1994

TO: Jennifer Holliday, AIDS Activities
FAX (202) 334-2939

FROM: _____

_____ I **will** be able to attend dinner on Thursday,
May 5, 1994.

_____ I **will not** be able to attend dinner on Thursday,
May 5, 1994.

_____ Please reserve a room for me at the
Wyndham Bristol Hotel for the night
of Thursday, May 5, 1994.

Wyndham Bristol Hotel
2430 Pennsylvania Avenue, N.W.
Washington, DC 20037
Tel: (202) 872-1680 or
1-800-372-8321

_____ I **will not** need a hotel room.

(All rooms are guaranteed for late arrival, so you may check-in after dinner on Thursday night.)

ACCELERATING DRUG AND VACCINE DEVELOPMENT FOR AIDS AND HIV DISEASE:

Tapping the Potential of Collaboration Between the NIH and the Pharmaceutical Industry¹

Patrick Gage, PhD
Chief Operating Officer
Genetics Institute, Inc
Cambridge, MA 02140

The National Institutes of Health and the U. S. pharmaceutical industry are far and away the largest investors in health related research in the United States². The mission of the NIH is to "uncover new knowledge that will lead to improved health for everyone"³, while the mission of the pharmaceutical industry is to develop effective new medicines for the treatment and prevention of disease.⁴

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

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

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

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

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

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

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

lessening the barriers⁶ to collaboration between these two institutions accelerate progress in AIDS/HIV drug and vaccine development?

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

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

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

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

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

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

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

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

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

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

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

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

Mansfield's economic analysis provides strong evidence that academic research

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

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

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

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

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

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

dramatic advances in our understanding of life processes.

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

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

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

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

[4] Modern biological research benefits enormously from collaboration,

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

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

Intellectual Property Rights in Industry-Sponsored University Research

A Guide to Alternatives
for Research Agreements

GOVERNMENT-UNIVERSITY-INDUSTRY
RESEARCH ROUNDTABLE

INDUSTRIAL RESEARCH
INSTITUTE

National Academy Press

Washington, DC

August 1993

The Government-University-Industry Research Roundtable

The Government-University-Industry Research Roundtable is sponsored by the National Academy of Sciences, National Academy of Engineering, and Institute of Medicine. The Research Roundtable was created in 1984 to provide a forum where scientists, engineers, administrators, and policymakers from government, university, and industry can come together on an ongoing basis to explore ways to improve the productivity of the nation's research enterprise. The object is to try to understand issues, to inject imaginative thought into the system, and to provide a setting for discussion and the seeking of common ground. The Roundtable does not make recommendations, nor offer specific advice. It does develop options and bring all interested parties together. The uniqueness of the Roundtable is in the breadth of its membership and in the continuity with which it can address issues.

The Industrial Research Institute

The Industrial Research Institute (I.R.I.) was founded in 1938 under the auspices of the National Research Council. Its purposes are to promote, through the cooperative efforts of its members, improved, economical, and effective techniques of organization, administration, and operation of industrial research, including means for more effective interaction with other corporate functions; to generate understanding and cooperation between the academic and industrial research communities; to afford a means for industry to cooperate effectively with government in matters related to research; to stimulate and develop an understanding of research as a force in economic, industrial, and social activities; to encourage high standards in the field of industrial research; and to promote communication and interaction with industrial research organizations in other countries. I.R.I. is an association of some 260 major industrial companies that provides a means for the coordinated study of problems confronting managers of industrial research and development.

Publications are available from:

Government-University-Industry Research Roundtable

National Academy of Sciences

National Academy of Engineering

Institute of Medicine

2101 Constitution Avenue NW (NAS340)

Washington, DC 20418

(202) 334-3486

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Preface

The Government-University-Industry Research Roundtable has a longstanding interest, beginning well before my time as Chairman, in minimizing difficulties associated with the negotiation of research agreements for industry-sponsored research in universities. In 1988, a Roundtable committee, in conjunction with the Industrial Research Institute, developed a set of model agreements to streamline the negotiation process¹. The intent was that these models would decrease the time and effort needed to develop a research agreement, as well as provide a starting point for companies and universities new to negotiating agreements.

In general, the models were well received by the academic and industrial communities.² However, one concern, intellectual property rights, continues to pose significant hurdles to successful negotiation. We have had repeated requests from academic and business officials for further guidance on negotiating intellectual property rights in research agreements. And members of our Roundtable Council, particularly Richard Zare, professor of chemistry at Stanford, have maintained that cooperative relationships will continue to be strained without some improvements in this area. In response, the Roundtable formed a Task Force on Intellectual Property Rights in Industry-Sponsored University Research. The members of the Task Force are listed in Appendix I.

The charge to the Task Force was to identify the contentious issues related to intellectual property rights and develop contract language that makes it easier to negotiate agreements for industry-sponsored university research. The focus of the effort was to clarify issues that cross institutional boundaries when university-industry research agreements are negotiated. In spite of the temptation to deal with several related issues, the Task Force concentrated its efforts on this narrow focus. Therefore, this document does not address other institutional issues that may or should impact how a company or a university approaches negotiations (e.g., issues related to conflict of interest, and incentives and rewards for investigators). Neither did the Task Force address some of the more global questions that arise when discussing university-industry research relationships:

¹Simplified and Standardized Model Agreements for University-Industry Cooperative Research, Government-University-Industry Research Roundtable and Industrial Research Institute, 1988.

²Survey to Assess the Usefulness of Two Model Agreements for University-Industry Cooperative Research, Government-University-Industry Research Roundtable, 1990

- What principles should guide universities and industries that participate in cooperative research?
- What principles should guide foreign company participation in research endeavors with U.S. universities?
- What principles should guide industry participation in university research endeavors supported by federal funds?

These questions merit full consideration, but were beyond the scope and focus of this project.

I believe that this document will serve its purpose in clarifying the more difficult issues that arise in negotiating intellectual property rights in research agreements. I hope that using this document will enable university and industry research partners to spend less time negotiating contract clauses, and more time addressing what type of cooperative relationships and research projects make sense.

I am also hopeful that the tenor of this document will modify the erroneous perception I have heard from many quarters: that university-industry research relationships will generate substantial revenue for all involved. Experience just does not bear this out. For example, at MIT—viewed by many as the archetype at forging university-industry relationships, gross revenue from all licensing operations is equal to an amount which is less than 2 percent of the university's overall research budget.

University and industry experts on the Task Force emphasize the value of the research rather than the financial gain that might be realized from tangible products of the research. University-industry negotiations and relationships benefit when each party understands the value of the interaction to the other party. Then, the sometimes competing interests of the two parties can be balanced with regard to intellectual property rights, and a "win-win" agreement and relationship can be achieved.

The audiences for this document include officials from universities and industry who seek additional understanding of key intellectual property issues in industry-sponsored university research agreements and ways to deal with those issues. Senior officials from these organizations, who are not routinely involved in negotiating research agreements, may also be able to use this document as a conceptual framework for thinking about how university-industry research arrangements can work effectively. Also, anyone interested or involved in these relationships—

including small businesses and faculty members—might use this document as a primer to learn from those who have had extensive experience in these negotiations.

I am delighted with what the Task Force has accomplished. Led ably by Al Barber, Special Assistant to the Chancellor of UCLA and Associate Member of the Roundtable Council, they carried out a difficult task with remarkable spirit and commitment. Casey Kiernan, Project Director, did an outstanding job of working with Task Force members, individually and collectively, and capturing and knitting together their views to create the scenarios and contract language that are the core of the final document. I hope you find this result of their efforts to be of use.

Richard F. Celeste
Chairman, Research Roundtable
August 1993

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I. Introduction

During the past decade, research relationships between universities and industry have flourished. A number of structures for such relationships exist. A company may sponsor a specific project involving one or more investigators, or an area of research involving a university department, center, or consortium, with one or more universities participating. Alternatively, several companies may support these structures. A collaborative arrangement, in which both the company and the university are involved in the conduct of the research project, may involve individual investigators—either as a long-term arrangement or a short-term focused project—or it may include a university department, center, or consortium.

Within these structures, universities and industry have a variety of expectations and objectives which motivate industry-sponsored research.

From an industry point of view, research relationships with universities provide a window to new information, knowledge, or different approaches to increase fundamental understanding of technologies which may be of current or future interest to the company. These relationships facilitate the transfer of knowledge from universities that may lead to commercially valuable products or processes. Access to faculty expertise and students provides a pool of candidates for consulting and recruitment.

Universities, for their part, look to these research relationships as a way to enhance the potential development and application of university-based knowledge and discoveries for the public benefit. By working with industry, universities gain access to financial support for research and training; expose academic scientists to industrial approaches to research; and increase understanding of how university research can address industrial concerns. Finally, these research arrangements provide internship and employment opportunities for students.

These industry and university expectations of research relationships fit into the larger, primary objectives of each of these two sectors. Industry focuses on profit and on obligations to stockholders. Universities focus on research, education, and services. Thus, two very different cultures are interacting. Even within these individual cultures, a great deal of diversity exists in terms of objectives, policies, and requirements.

Given the range of possible structures and expectations of university-industry research relationships, it is not surprising that

each relationship may require consideration on a case-by-case basis. Terms to include in a given research agreement will depend on: the structure of the relationship; the stage of investigation relative to commercial application (e.g. basic, applied) and field of research (e.g. biotechnology, electronics, manufacturing); the type of industry (e.g. pharmaceuticals, aerospace); the existing state of knowledge and development (e.g. a newly explored research area, an already highly developed one with patents outstanding); the experience and expectations of the university and industry investigators (e.g. new to industry-sponsored research or "old hands").

Reaching agreement for the conduct of research between two or more partners takes patience, flexibility, and an understanding of each other's objectives. Some relationships have been stalled in the process of negotiation, and some have failed, because of a lack of understanding and accommodation of natural differences in culture and expectations between universities and industry. Frequently, prospective research partners need to get to know each other before a successful agreement can be reached.³

Difficulties in negotiating agreements often are the result of the perception by one party that the other party has unrealistic expectations. The extent to which partners expect to profit financially from the arrangement underlies some of these difficulties. In addition, university and industry expectations regarding diligence in exploiting intellectual property for public benefit may differ. If a commercial product emerges from the sponsored research, all involved stand to gain: the company because it has a tangible result from its investment in a high-risk endeavor; the university because its objectives of making the results of the research available for the public benefit have been realized.

Advanced knowledge, rather than a potential product, is often the most valuable result of industry-sponsored research. The obligation of the sponsor and the university to maximize the public benefit from the research results may, but does not necessarily, require that a product be sold; internal use of the research results by the sponsor may promote public benefit by increasing efficiency and reducing production costs.

³See, for example, *Research Universities as Research Partners: How to Make It Work*, Howard Schneiderman, 1987; and *New Alliances and Partnerships in American Science and Engineering*, Government-University-Industry Research Roundtable, 1986.

The primary value of the relationship is in new knowledge generated by the research that benefits the university, the company, and the public, with the added value of training students to understand industrial R&D problems. If both parties can keep this in mind throughout the negotiation process, potential conflicts may be more easily resolved. All sides win if agreement can be reached.

II. This Document

To minimize difficulties in negotiation, the Government-University-Industry Research Roundtable, in conjunction with the Industrial Research Institute (IRI), established the Task Force on Intellectual Property Rights in Industry-Sponsored University Research Agreements (see Appendix I). The Task Force was directed to provide greater understanding of the framework of university-industry research relationships, given the diversity of attitudes and perceptions; clarify the issues and complexities related to intellectual property rights; identify and describe the key issues that make negotiations difficult; and suggest a "menu" of scenarios and contract language to handle the key issues—all in an attempt to minimize or avoid unnecessary difficulties in the negotiation of industry-sponsored university research agreements.

The Task Force chose to focus its analysis specifically on sponsorship by a single company of a single university investigator project, and collaborative research between an industry scientist and a university investigator. Issues particularly related to the licensing of technology outside of a research agreement (including licenses stemming from government-sponsored research), materials transfer agreements, clinical trials, multiple sponsorship, and consortia were not explicitly addressed.

The Task Force's decision not to address these issues is not intended to minimize their importance. Although many of the issues related to multiple sponsorship and consortia and other types of relationships are the same as those considered here, these types of relationships may pose additional issues which are more complicated by the nature of the relationship. Addressing the unique features of each of these relationships is beyond the scope of this project.

The Task Force conducted its work in meetings, conference calls, and a workshop during which the input, questions, and comments of the broader community were solicited. (See a list of workshop participants in Appendix II.) Input was also sought from the IRI University Relations Committee and the IRI University Research

Relations Directors Network. The result of these deliberations follows.

This document is divided into four sections: (1) ownership of intellectual property; (2) rights to use intellectual property; (3) procedural issues; and (4) special considerations involving copyright. The term "intellectual property," as used in both the ownership and rights to use sections, includes both patents and copyrights.⁴ Special considerations for both types of intellectual property are noted as necessary. Each section presents a discussion of the relevant issues and suggests reasonable ways of dealing with them. Suggestions for specific contract language, where appropriate, have been included in sidebars throughout the text. (A fully integrated contract is not included. The reader is cautioned that the use of the language provided in this document in the sidebars in an actual contract will require redrafting for consistency of terms and approach.)

The scenarios and the contract language described in this document are intended to provide a range of alternatives, a description of issues to consider when choosing those alternatives, and ways of navigating around potentially contentious obstacles. These alternatives may be useful as starting points for negotiating some of the most obvious and potentially difficult intellectual property rights issues.

The scenarios and the contract language neither cover every conceivable issue and problem, nor are they intended to be used as a standard approach. Each issue and approach to handling it must be considered in the context of the unique nature of the relationship and the objectives of both parties in it. The negotiations are part of the "courtship" that is necessary. Up front negotiation enables each party to learn the other's objectives and expectations in order to define a successful relationship.

III. Ownership of Intellectual Property Rights

There are three primary scenarios for the ownership of intellectual property rights: (1) the university owns the intellectual property; (2) the sponsor owns the intellectual property; and (3) the university and sponsor jointly own the intellectual property. As a matter of policy, universities generally require faculty

⁴Intellectual property arising from industry-sponsored university research should not take the form of trade secrets as this form prohibits publication or presentation of research results. Trade secrets require a level of guardianship that universities are not set up to provide, especially a state institution that must comply with a Freedom of Information Act.

members and other employees to assign to the university ownership of inventions arising from research undertaken while employed at the university. Faculty members and other university employees usually sign an employment agreement to this effect. The research agreement may provide assurances to the sponsor that such an agreement has been signed.

University policies vary on whether students, research fellows, or visiting scientists are viewed as "employees" when considering ownership of intellectual property rights. Most universities require students and research fellows to assign such rights to the university if the rights are generated in the performance of the sponsored research. There is more variance, however, among university policies on ownership of intellectual property rights of visiting academic or industry scientists participating in sponsored research.

These policies should be discussed during the negotiation of research agreements in which such personnel will be participating so that both parties know what to expect.⁵

Scenario 1: The university owns the intellectual property

Most universities own inventions conceived or reduced to practice solely by their employees during the conduct of research. In general, sponsors have accepted this position subject to other considerations such as the right to use intellectual property as discussed in Section IV on page 7.

In general, universities also own software generated during the performance of a sponsored research project, if a university scientist or other employee has created the material.

Scenario 2: The sponsor owns the intellectual property

Companies from some industrial sectors take the position that the sponsor has a right to own the intellectual property since it has paid for the research. Under this scenario, the

Contract language for "Faculty members, staff, students, and research fellows"—Each of University's faculty members, staff, students, and research fellows involved in performing investigations or providing services under this Agreement shall be obligated to University in writing, prior to such involvement, to assign his or her rights to any University Intellectual Property resulting from research under this Agreement.

Contract language for "The university owns the intellectual property"—"University Intellectual Property" means individually and collectively all inventions, improvements, or discoveries and all works of authorship, excluding articles, dissertations, theses, and books, which are generated solely by one or more employees of University in performance of the research agreement during the Contract Period. All rights and title to University Intellectual Property developed under the research agreement belong to University and are subject to the terms and conditions of this Agreement.

⁵See, for example, *Ownership of University Inventions*, B. Jean Weidemier, 1992, *Journal of the Association of University Technology Managers*, Volume IV, pages 1-20.

sponsor owns the intellectual property through contract or assignment by the university or the investigators. This scenario may apply, for example, when the sponsor has made a substantial investment in the development of the technology that is the subject of the university's research, when the sponsor is likely to be the only practical user of the resulting inventions, or if the sponsor has provided proprietary information, technology, or material which is the basis of the research.

In cases when the sponsor acquires ownership of a copyright or invention, the university retains a royalty-free right to use the intellectual property for any internal research and teaching purposes, and may retain the right to sublicense to investigators for research and teaching purposes.

Company ownership of intellectual property resulting from federally sponsored research requires the permission of the federal funding agency.⁶

Scenario 3: The university and sponsor jointly own the intellectual property

For intellectual property jointly made by employees of a university and an industrial sponsor, under U.S. law, the parties have joint ownership in and the independent right to exploit the intellectual property, unless otherwise agreed.⁸ If one party wants exclusive rights to jointly-owned intellectual property, that party needs to obtain the other party's rights, by licensing or assignment, as discussed in Section IV., Scenario 3 on page 13.

Contract language for "The sponsor owns the intellectual property"—*University shall assign to Sponsor, upon request, all right, title, and interest in University Intellectual Property. No sooner than three months following termination of this Agreement, or any extension thereof, the University shall have the right to request that Sponsor make a final decision regarding such assignment. Sponsor shall then make the decision no later than sixty (60) days after the University's request. Any assignment made by the University to the Sponsor shall include the following conditions:*

Contract language for "The university and sponsor jointly own the intellectual property"—*"Joint Intellectual Property" means individually and collectively all inventions, improvements, or discoveries and all works of authorship, excluding articles, dissertations, theses, and books, which are generated by one or more employees of University and one or more employees of Sponsor in performance of the research under the Agreement. All rights and title to Joint Intellectual Property belong jointly to University and Sponsor and are subject to the terms and conditions of this Agreement.*

⁶35 USC 202 (c)(7)(A); 37 CFR 401.14 (k) Special Provisions for Contracts with Nonprofit Organizations. If the contractor is a nonprofit organization, it agrees that: (1) Rights to a subject invention in the United States may not be assigned without the approval of the Federal agency, except where such assignment is made to an organization which has as one of its primary functions the management of inventions, provided that such assignee will be subject to the same provisions as the contractor...

⁷The assignment might include no conditions. Alternatively, some possible terms include: royalty, diligence, reservation of rights, reversion.

⁸For copyrights, and for patents in many foreign countries, the ability to license without accountability to or permission of the other party may be limited.

IV. Rights to Use Intellectual Property Under Different Ownership Scenarios

For the purposes of discussing the rights to use intellectual property, the three scenarios used in the previous section are also used here: (1) the university owns the intellectual property; (2) the sponsor owns the intellectual property; and (3) the university and sponsor jointly own the intellectual property.

Scenario 1: The university owns the intellectual property

Under this scenario, three approaches are described to acquire license rights to use intellectual property. The document then goes on to describe the scope of the license provisions considered within each of these approaches.

A. Approaches

When the university owns the intellectual property, sponsors may wish to acquire license rights to the intellectual property, including the right to use and the right to make derivative works. These rights may be in the form of an option in which the sponsor can elect a future license, or in the form of a grant of a specific license as part of the research agreement, although these are not mutually exclusive. Three approaches for transferring these rights are discussed below: the option for a license; the grant of a license; and the right of first refusal.

Approach 1: Option for a license

The research agreement provides for an option period during which the sponsor has the sole right to elect a license, to be negotiated in good faith. While an invention disclosure or filing of a patent application is of significance, many inventions for which applications are filed are never commercialized. Thus, a sponsor will typically have insufficient information at the time of filing to reach an informed decision on whether to commit to a commercial development under a license agreement. One reason for the university to conclude a license agreement, however, is to commit the sponsor to a

Contract language for "Option for a license"—*University hereby grants to Sponsor the exclusive option to elect any of the following licenses:*⁹

- i) *a non-exclusive, royalty-free license to the University Intellectual Property for any internal research and development purposes*
- ii) *a non-exclusive, royalty-free license to the University Intellectual Property without the right to grant sublicenses*
- iii) *a non-exclusive, royalty-bearing license to the University Intellectual Property including the right to grant sublicenses*
- iv) *an exclusive, royalty-bearing license to the University Intellectual Property in the field of use of _____ including the right to grant sublicenses*
- v) *an exclusive, royalty-bearing license to the University Intellectual Property including the right to grant sublicenses*
- vi) *an exclusive, royalty-free license to the University Intellectual Property including the right to grant sublicenses*

This option shall extend for _____ [time] from the disclosure of intellectual property to the sponsor, OR filing of a patent application, OR notice of patent allowance, OR issuance of a patent, OR conclusion of the contract period. Terms and conditions of these licenses are to be negotiated in good faith and agreed upon between University and Sponsor.

⁹The sponsor and the university need to discuss which choices are to be included in the research agreement. For example, an exclusive license may negate the need for the grant of a non-exclusive license.

commercialization of the invention. Both parties' interests may be substantially met if they can agree on mutually satisfactory commitment, other than commercialization, during the option period. This commitment may consist of continued funding of the research program, payment of patent costs, internal company development, or other considerations, including further funding tied to a patent application or other milestones.

The beginning and length of the option period varies widely according to the nature of the anticipated intellectual property and the industry involved. In general, universities want a short option period to enable the university to seek a third party licensee in the event that the sponsor is not interested in a license. The sponsor, on the other hand, would prefer a longer option period in which to assess the commercial potential of the intellectual property.

For intellectual property which is a potential product, such as that which may arise from research funded by a pharmaceutical company, the option period generally extends for some period beyond the initial invention disclosure or filing, and may extend beyond the termination of the sponsored research agreement.

In some industries, it takes longer to determine the commercial value of the intellectual property. For example, in many areas of technology, a single patent rarely defines an entire product, in which case, the value of a single patent may not be clear until other patents emerge from a company's patent portfolio. In such cases, an extended option period, perhaps even beyond issuance of a patent, may be appropriate. Intellectual property of these types sometimes arise from research in such industries as petroleum, chemical, and heavy manufacturing, and is typically utilized with other proprietary technologies in actual commercial use.

Approach 2: Grant of a license

In some cases the research agreement grants a specific license to the sponsor to use the intellectual property and describes the extent of the permitted use, as distinguished from an option which grants only the right to obtain a license at a later time, but no present rights. Often the

Contract language for "Grant of a license"—*University hereby grants to Sponsor any of the following licenses:*⁹

- i) *a non-exclusive, royalty-free license to the University Intellectual Property for any internal research and development purposes*
- ii) *a non-exclusive, royalty-free license to the University Intellectual Property without the right to grant sublicenses*
- iii) *a non-exclusive, royalty-bearing license to the University Intellectual Property including the right to grant sublicenses*
- iv) *an exclusive, royalty-bearing license to the University Intellectual Property in the field of use of _____ including the right to grant sublicenses*
- v) *an exclusive, royalty-bearing license to the University Intellectual Property including the right to grant sublicenses*
- vi) *an exclusive, royalty-free license to the University Intellectual Property including the right to grant sublicenses*

Terms and conditions of these licenses are to be negotiated in good faith and agreed upon between University and Sponsor.

sponsor obtains a non-exclusive, royalty-free license for internal research and development in the research agreement, though more extensive license rights may also be granted in that agreement.⁹ Some sponsors may be reluctant to fund research without knowing what effect license provisions will have on the availability and cost of the eventual product. So some license provisions may be defined in the research agreement. However, by including an option for a license in the research agreement, negotiation of most license provisions may be deferred until some time after disclosure of the specific intellectual property.

Approach 3: The right of first refusal

In practice, when the sponsor elects to take a license, the parties are almost always able to reach acceptable terms for a license agreement for the intellectual property resulting from the sponsored research. If agreement cannot be reached, mediation or arbitration can sometimes be helpful. Occasionally, in spite of these efforts, agreement still cannot be achieved within the agreed upon time. When this occurs, the university has the right to negotiate with third parties. If the university is able to reach agreement with a third party on more favorable terms than were presented to the sponsor, under the right of first refusal, the sponsor has the right to accept such a license offered to a third party.

The right of first refusal may be acceptable to a university if it is contingent upon the sponsor negotiating a license agreement in good faith during the option negotiation period. Having the right of first refusal may provide the added level of comfort that a sponsor needs to justify the research investment. However, some universities are reluctant to accept the right of first refusal under any circumstances, because the practical effect may be to impede the university's ability to interest a third party in a license. For its part, the sponsor may feel that, in the absence of detailed license terms in the research and option agreement, a right of first refusal is needed to reduce the risk that the university will prematurely initiate negotiations with a third party.

Contract language for "The right of first refusal"—*If Sponsor exercises its option, the parties will thereafter negotiate in good faith to conclude a license agreement within ____ [time]. Such negotiations shall take into account factors affecting Sponsor's ability to commercialize the product profitably, including, but not limited to, terms of any third party license which may be necessary for the manufacture, use, and sale of any product relating to the field, size of market, development time and cost, product performance relative to competing products, and whether the invention is covered by a sole or joint patent.*

In the event the parties fail to reach a mutually acceptable agreement within the negotiation period, University shall be entitled to negotiate in good faith with one or more third parties a license for any University Intellectual Property and University's interest in any Joint Intellectual Property. However, upon the conclusion of such negotiations and before any license is granted to any such third party on terms more favorable than were offered to Sponsor, University shall offer Sponsor a license on the same terms. If Sponsor is willing to enter into a license with University on such terms, Sponsor shall be granted the license instead of such third party.

B. Scope

Regardless of which of the above approaches to acquiring a license is utilized, consideration of the scope of the license is the same. Below is a discussion of possible provisions to be considered, including provisions for exclusive and non-exclusive licenses, royalty rates, field of use, and inclusion of a full license agreement.

1) Exclusive and non-exclusive license provisions

Exclusive licenses are especially important in some industries, such as pharmaceuticals, biotechnology, and chemicals, whereas they may not be as important to others, such as electronics and automobile manufacturing.

If a technology is of general use or limited value, or if it is a small part of a large system, the sponsor may choose a non-exclusive license. Sponsors often expect non-exclusive rights to inventions resulting from sponsored research to be royalty-free, but companies are generally willing to pay royalties for exclusive rights.

In some industries, pharmaceuticals, for example, if a sponsor is granted a non-exclusive license, the university may have difficulty interesting other licensees. Some potential licensees may not be willing to spend large sums of money developing a product using the intellectual property that the original sponsor chose not to develop, but could subsequently use royalty free or market in an improved form.

If the sponsor elects a non-exclusive, royalty-free license to use the intellectual property solely for research purposes, the university is still able to grant an exclusive license to a third party for commercialization of the intellectual property. If the sponsor takes an exclusive license, the university must retain the right to use the intellectual property in its own research and instructional programs.

2) Royalty provisions

Generally, royalty provisions are not included in research agreements.¹⁰ When they are, the sponsor often will agree to a range of royalty rates, deferring determination of the actual rate. The pre-specification of royalty rate—or a range of rates—does not preclude discussion of other financial considerations during negotiations of the license.

Royalty rates are influenced by a number of factors including the potential market size and profitability of the licensed product, the potential cost of commercialization, the obligation to pay royalties to more than one licensor-holder for the product, the value added to the product by the university invention, and the degree of exclusivity granted by the license. The field of research, type of invention, size of the research project, prior or background rights, stage and type of research being carried out, and the nature of the potential intellectual property, also may affect the rates. Royalty payments may be capped on a cumulative, percentage, or annual basis.

The royalty base will require definition and may be based on: net sales, net earnings, bulk manufacturing costs, number of units, products, processes, value added, and profits. No contract language is provided here for royalty provisions because these and other variables must be considered.

In the case of copyrights, universities may expect companies to pay royalties for using software, for some other types of copyrightable material, and for derivative works if the software is not considered part of the "deliverables" in a sponsored project. (See the definition of derivative works in footnote 15 on page 17.) If royalties are to be paid for derivative works, the basis and extent of this obligation may be further defined in subsequent license agreements or in the initial research agreement depending on the specificity of other intellectual property terms in the agreements and the preference of the parties.

¹⁰Under Title XIII Tax-Exempt Bonds and the House and Senate amendments to it, tax-free status of public bonds may be adversely affected under certain conditions, particularly for pre-negotiated royalty rates with exclusive licenses. Because of its complexity, competent tax advice may be necessary. See the Conference Report to the Tax Reform Act of 1986, II-683ff, especially II-685-6 and II-689.

3) Field of use provisions

Licenses to intellectual property may limit the sponsor's license rights to specific fields of use. The license may allow exclusive or non-exclusive use within specific fields.

In many instances, the sponsor may wish to obtain a license for all fields of use. The university, however, may be concerned about the ability of the sponsor to fully commercialize the licensed product in every possible field of use. In fact, such full development is an ideal rarely realized in practice. Market size, development costs, and other factors often make the development of an invention for particular applications or markets unprofitable.

Contract language is generally included that commits the sponsor to use "commercially reasonable efforts" to develop the invention within the field of use. The sponsor may develop certain applications or markets through sublicensing or joint ventures.

For certain types of products, such as pharmaceuticals, a broad field of use may be critical to commercial success. For instance, successful commercialization may ultimately depend on the later discovery of a new medical use for a compound that was not considered commercially valuable during the original negotiations. Alternatively, a drug may have multiple uses that collectively make the product sufficiently profitable to justify undertaking the research. The sponsor may not be willing to gamble resources on a subset of possible applications. At the very least, the sponsor will likely feel that competitors should not benefit, at the sponsor's expense, from the research it has sponsored.

A compromise acceptable to both the university and the sponsor may be to include all fields to which the sponsor will devote "commercially reasonable efforts."

4) Inclusion of full license agreement as an appendix

In many cases both the university and the sponsor are reluctant to negotiate a full license as part of the research agreement because it is time-consuming. However, some sponsors insist on it. When the parties have sufficient information about the probability of intellectual property resulting from the research, as well as its likely commercial value, a full license agreement may be

Contract language for "Field of use provisions"—[See contract language for option for a license and grant of a license on pages 7 and 8, respectively, where fields of use may be specified.]

Contract language for "commercially reasonable efforts"—"*Commercially Reasonable Efforts*" means efforts and resources commonly used in the _____ (e.g. pharmaceutical) industry for a product at a similar stage in its product life of similar market potential taking into account the establishment of use of the product in the marketplace, the competitiveness of alternative products in the marketplace, the proprietary position of the product, the likelihood of regulatory approval given the regulatory structure involved, the profitability of the product and alternative products, and other relevant factors.

appropriate. When included, it is usually as an appendix to the research agreement. This allows the appendix to be easily modified without affecting other provisions of the agreement. Discussion of terms to be included in the full license is beyond the scope of this document.

It should be noted that some states require disclosure upon request of information in research agreements under provisions of their Freedom of Information Act. If a license agreement is appended to the research agreement, it may become publicly available and, therefore, subject to such disclosure.

Scenario 2: The sponsor owns the intellectual property

When the sponsor owns the intellectual property through contract or assignment by the university or the investigators, the university should reserve the right to continue to use the intellectual property for internal, research and teaching purposes, and may retain the right to sublicense to investigators for research and teaching purposes.

Scenario 3: The university and sponsor jointly own the intellectual property

Under this scenario, both parties can use and license the jointly owned intellectual property without obtaining permission from the other party, unless they have signed an agreement to the contrary.¹¹ If the sponsor wants exclusive rights to commercialize jointly-owned intellectual property, the decision to include option and license terms in the research agreement should be made based on the same considerations discussed above in Section IV., Scenario 1.

V. Procedural Issues

A. Delay of Publication

University researchers must be able to publish and make presentations on the results of sponsored research. Sponsors usually obtain the right to review manuscripts prior to submission for publication or oral presentation. This is done

Contract language for "Rights to use when the sponsor owns the intellectual property"—University reserves for itself a royalty-free, irrevocable license to make and use such University Intellectual Property within the University for internal non-commercial purposes only.

Contract language for "Delay of publication"—Sponsor shall be furnished copies of any proposed publication or presentation at least 45 days before submission of such proposed publication or presentation. During that time, Sponsor shall have the right to: (i) review the material for confidential information provided by the sponsor and (ii) assess the patentability of any invention described in the material. If the Sponsor decides that a patent application should be filed, the publication or presentation shall be delayed an additional seventy-five (75) days or until a patent application is filed, whichever is sooner. At Sponsor's request, confidential information provided by Sponsor shall be deleted.

¹¹As mentioned previously, for copyrights, and for patents in many foreign countries, the ability to license without accountability to or permission of the other party may be limited.

to insure that no confidential information of the sponsor is released and to assess the patentability of any invention described in the material. Commonly, sponsors have 45 days to review the material, and another 30 to 75 days to prepare and file a patent application. Thus the period allowed for review and patent application filing is generally less than 120 days.¹² Periods of time are negotiable, however, and in certain rapidly moving fields shorter periods may be appropriate.

B. Procedures for patents

1) The university owns the invention

It is customary for the university to file the patent application, and most companies are willing to reimburse the university for reasonable patenting costs if they wish to obtain a license to the patent.¹³ The sponsor usually has the right to review and comment on the application and subsequent prosecution of the case including patent expenses. When a sponsor pays for filing a patent

¹²There are two possible ways for giving the sponsor time to review research findings to be reported in the publication or presentation of dissertations, theses, and their oral defense without interfering with the student's matriculation:

- (1) Dissertations, theses, and their defense may be considered separate from other publications and presentations. The presumption would be that the university and the sponsor are working together to assure an adequate dialogue—particularly when a graduate student is participating in the research—so that, at the time of defense and publication, the sponsor has already had adequate consultation on the material. This is especially true if the student has been giving public seminars on the material as part of a job-hunting process.
- (2) The research agreement may spell out that, at the completion of the thesis, the major professor will request that the thesis be sequestered at the library until the sponsor has completed its review. This approach allows time for sponsor to review the thesis, but it does not take into account the fact that the thesis defense often is considered a public presentation, and therefore, it too would be subject to review.

¹³In many instances, the sponsor and the university may want to establish a procedure for reimbursement costs. Some procedures include: consultation and review of costs; sponsor monitoring of the preparation, filing, and prosecution of the patent application; sponsor pre-approval of outside patent counsel or of all costs; or sponsor carrying out the patent application filing and prosecution task in the university's best interest.

Usually, sponsors are closely involved in the process so that consultation and review or monitoring are typically acceptable to both parties. Some companies, however, as a matter of policy, require pre-approval of costs to be reimbursed. In the absence of such a policy, the paperwork and time associated with pre-approval can require more effort than either the university or the sponsor may want to undertake. Lastly, on occasion, the sponsor is better able to prepare and file a patent application, and it will take the lead for the university. This procedure can create difficulties, however, because of the potential for liabilities and conflict of interest.

¹⁴Once a patent application has been filed in the United States, the patent applicant has 12 months in which to file corresponding foreign Convention patents, if the U.S. filing predates any public disclosure. (Some countries, Taiwan, for example, do not allow Convention filing).

Contract language for "Patent procedures when the university owns the invention"—University shall promptly notify Sponsor of any University Intellectual Property disclosed to it by the researcher(s). Such disclosure shall be provided and maintained in confidence. Sponsor shall have up to forty-five (45) days from the receipt of the disclosure by Sponsor in which to request the filing of patent application(s).

University shall promptly file and prosecute patent applications, using counsel of University's choice after due consultation with Sponsor. University shall keep Sponsor advised as to developments with respect to application(s) and shall promptly supply copies of all papers received and filed in connection with the prosecution in sufficient time for Sponsor to comment. Sponsor's comments shall be taken into consideration.

Sponsor shall reimburse all reasonable out-of-pocket costs incurred in connection with such preparation, filing, and prosecution of patent applications. Such applications shall include all items considered by Sponsor to be of commercial interest and importance.

Within nine (9) months of the filing date of a U.S. patent application, the Sponsor shall provide to the University a written list of foreign countries in which applications should be filed.¹⁴

[Contract language continued on next page.]

application, such costs may be considered a credit toward future royalty payments. Absent an agreement by the sponsor to pay patent costs, the university should be under no obligation to file a patent application or to continue prosecution.

The research agreement may include language to allow the sponsor to discontinue paying patent costs. The consequences of such action should be addressed in negotiations.

In the case of a non-exclusive, royalty-bearing license, the patent costs may be paid by the initial licensee, who may be reimbursed on a *pro rata* basis from revenues obtained from other licensees. In the case of a non-exclusive license when the sponsor does not reimburse patent costs, the university retains the right to decide whether to apply for or maintain patents without further obligation to the sponsor.

2) The university and sponsor jointly own the invention

In the case of joint ownership of an invention, the university and the sponsor together should decide which party is responsible for filing and prosecuting the patent application. The other party retains the right to review the patent prosecution documents, and patent costs are usually shared. When the sponsor has an option to obtain an exclusive right to commercialize the joint invention, the sponsor generally pays all patent costs, with what would have been the university's share of such costs being deducted from royalties.

Contract language for "Patent procedures when the university owns the invention," continued—
If Sponsor elects to discontinue the financial support of any patent prosecution, in any country, University shall be free to continue prosecution at University's expense.

In such event, University shall have no further obligation to Sponsor in regard to such patent applications or patents in such country. In the event University does not file in a reasonable time an application on the invention, as directed and paid by Sponsor, or intends to discontinue prosecution of any patent application or maintenance of any patent, University shall so notify Sponsor and Sponsor may elect to continue prosecution and maintenance at Sponsor's sole expense.

Contract language for "Patent procedures when the university and the sponsor jointly own the invention"—*The University and Sponsor shall decide which party shall be responsible for the prosecution of patent applications on joint inventions. If Sponsor has an option to obtain an exclusive license to the joint invention, Sponsor shall be responsible for all patent costs; otherwise patent costs shall be shared. Whichever party is responsible for patent filing and prosecution will provide the other party with an opportunity to comment on papers filed in connection with the patent application. Such comments shall be taken into consideration.*

C. Confidential information

Most universities will agree not to disclose to third parties confidential information that is provided by the sponsor for use in the sponsored research. Similarly, most companies will agree to protect university confidential information. Some universities require that the university investigator(s) personally sign a confidentiality agreement to safeguard confidential information received from the sponsor, rather than the university signing. Other universities will assume this liability for persons acting within the scope of their employment.

The sponsor and the university may further agree that only confidential information directly relevant to the research project will be exchanged, unless the receiving party agrees in writing to accept additional confidential information. In practice, this concern is generally more important to the sponsor, who wants to confine disclosure to information relating to the research project to avoid potential conflicts over ownership of inventions that arise from the sponsor's own research.

Sometimes, confidential information will be disclosed by both parties during the course of the research. Rather than deal with this issue in the research agreement, the parties may enter into a separate confidentiality agreement at the time confidential information is disclosed. Otherwise, disclosures not covered by a confidentiality agreement may be considered public disclosure.

The parties should be aware of the terms of their state's Freedom of Information Act, which may limit the conditions under which confidentiality can be maintained.

Contract language for
"Confidential information"—
During the term and any subsequent extension of this Agreement, and for a period of ____ years thereafter, the parties shall not use or disclose to any third party without prior written consent of the other party, any Confidential Information of the other party. For the purposes of this Agreement, "Confidential Information" means all information which is disclosed or provided to one party to this agreement (Receiving Party) by the other party (Disclosing Party), whether in written form, or in oral or electronic form which is reduced to written form, and is designated in writing as confidential. The Receiving Party shall have no obligations with respect to any portion of such Confidential Information which:

- (a) is or later becomes generally available to the public by use, publication, or the like, through no fault of the Receiving Party; or*
- (b) is obtained without an obligation of confidentiality from a third party who had the legal right to disclose the same to the Receiving Party; or*
- (c) the Receiving Party already possesses, as evidenced by its written records, pre-dating receipt thereof from the Disclosing Party; or*
- (d) the Receiving Party independently develops without reference to Confidential Information of the Disclosing Party; or*
- (e) is required to be disclosed by law.*

[Contract language continued on next page.]

Contract language for
"Confidential information,"
continued—*During the term of the Agreement, the parties will not disclose to each other any information which is confidential or proprietary to the Disclosing Party or any third party, (1) except as is necessary for the Disclosing Party to fulfill its obligations under this Agreement, or (2) unless the Receiving Party has agreed in writing to accept such disclosure. All other communications between the parties shall be on a non-confidential basis.*

VI. Special Considerations Involving Copyright

In some research agreements, copyrightable intellectual property, which may take various forms, is treated differently than patentable intellectual property.¹⁵

¹⁵Definitions relevant to issues of copyright in research agreements:

"Author" means the person, using his or her own independent efforts, who creates an original work by translating an idea into a fixed, tangible expression that is entitled to copyright protection.

"Derivative Work" means any work substantially based on one or more preexisting works, such as revisions, annotations, elaborations, translations, or modifications, which as a whole represent an original work of authorship. A work is derivative if it would be considered infringing on the original copyright if the material or pre-existing work from which it was derived has been taken without the consent of the original copyright holder.

"Employer" means the hiring party who had the right to control the manner and means of the author/employee's work. Copyright protection will be afforded the employer by statute for works made by its author/employee in the regular course of business.

"Fair Use" means the use of a copyrighted work for purposes such as criticism, comment, news reporting, teaching, scholarship or research that do not infringe the copyright after consideration of the following factors: (1) the purpose and character of the use, including whether the use is of a commercial nature or is for nonprofit educational purposes; (2) the nature of the copyrighted work; (3) the relative amount and substantiality of the use compared to the whole copyrighted work; and (4) the effect of the use on the marketability or value of the copyrighted work.

"Improvements" on a preexisting work, by their very nature, tend to be derivative works. If the work is a software program, improvements may take the following general forms: (1) error corrections—such as "maintenance" or "bug" corrections; (2) additional features—"enhancements;" or (3) a substantial rewrite of the program having new features, yet retaining "portability" from the original program.

"Originality" means that the work is independently created and not copied from other works. Originality of a derivative work means any variation of an original work which is sufficient to render the derivative work distinguishable from its prior work in any meaningful manner.

"Owner" means the person entitled to a claim of copyright. This person must be either the author or have succeeded to the right of the author (e.g., employer).

"Work Made for Hire" means a work prepared by an employee within the scope of his or her employment or a certain work specially ordered or commissioned, and so designated in writing.

In general, copyrights protect the original expression of ideas in a tangible form, while patents protect original ideas (inventions) that are reduced to practice. Hence, the expression of an original idea may be protected by a copyright, while an invention arising from the idea may also be protected by a patent. For example, consider a new drug XYZ that is a patentable invention.

Disclosing the composition of drug XYZ in a patent protects the drug composition. One can write an article or book about the drug, its composition, its uses, or its efficacy without infringing the patent. The author would own a copyright to his or her "literary work" on drug XYZ, and others would be prohibited from copying this article or book. However, one author's ownership of a copyright does not mean that another author cannot write a different article or book on the same subject.

A. Forms of copyright

In industry-sponsored university research, copyright issues arise over information and data; articles, dissertations, theses, and books; research reports; software; and other copyrightable works generated during the sponsored project. Each of these categories of material may require special contract language in the research agreement.

1) Information and data

Original expression of information and data developed in the performance of sponsored research, such as a report or manuscript, may be copyrightable, but alternative forms of expression or use of the information and data by other parties may not be protected by the copyright. Sponsors and universities both may have concerns about how information and data are used and how to protect potentially commercially valuable ideas they contain. In some universities, determining who owns the copyright will depend on whether the information and data are "deliverables" of the sponsored project. Many universities and sponsors have found that it is easier to deal with rights to information and data if the discussion centers on use rather than ownership.

Contract language for "Information and data"—The Sponsor may use all information and data developed by the University under the research agreement, except as otherwise specified, that is obtained by Sponsor, in any manner without further license from or payment to the University.

2) Articles, dissertations, theses, and books

In general, copyrights to articles, dissertations, theses, and books are not intellectual property to which the sponsor has rights under the research agreement. Many university intellectual property policies do not claim these "scholarly

works" as works for hire, nor do they require employees or students to assign these works to the university. However, these materials may be subject to review by the sponsor under the publication clause of the agreement, and the sponsor may use any information and data described in the materials.

3) Research reports

Research reports are usually required under the research agreement. Universities, on behalf of the authors of the reports, may assign copyright to the report delivered to the sponsor. The university, however, will explicitly reserve the right to continue to use data and information contained in the report. If the report is published by the sponsor, the university may require acknowledgment of the university's contribution.

Pharmaceutical companies that rely on clinical trials carried out by universities customarily claim ownership of the case-report forms. This claim is made in an effort to ease compliance with requirements of the Food and Drug Administration. However, the university may retain ownership of the copyright to the final report provided to the sponsor, and grant to the sponsor the right to use the data and information contained in the report. Clinical trials represent a special case for copyrights in research agreements, but this point is also relevant to other situations.

4) Software

Distinctions may be made between object code and source code, although both forms are copyrightable. While universities prefer to retain ownership of both types of code, some institutions may be willing to assign to the sponsor the object code specifically developed for the sponsor. It is generally assumed that the sponsor's application of the object code is not readily useful to other potential licensees. Universities, however, will generally not assign title or give an exclusive license to the source code, if this would impede their ability to use such code for other research or to make derivative works, or to use it to create and license out object code for applications other than the sponsor's.

Contract language for "Research reports"—University hereby assigns its copyright to the Research Report to Sponsor. Notwithstanding the foregoing, University reserves the right to reproduce and use any portion of the Report for non-commercial purposes.

5) Other copyrightable works

Materials that fall into this category include films, videotapes, music compositions, posters, and artwork. Such works generally are owned by the author, with the rights and acknowledgments negotiated in the research agreement.

Such works may sometimes be assigned to the sponsor, if they are considered deliverables under the research agreement. Deliverables can be treated as research reports or as intellectual property.

B. Software issues

Two issues that are of special consideration for software are derivative works and improvements.

1) Derivative works

The right to make derivative works resides solely with the copyright owner. However, the copyright owner may authorize others to make derivative works. In the case of licenses to copyrightable material, therefore, a licensee would need specific authorization from the copyright owner to develop derivative works. Generally, the university will retain the non-exclusive right to make derivative works for its own purposes, even if it grants the sponsor an exclusive license to the software and to derivative works.

If the sponsor has a license to make commercially available derivative works, it may expect to pay a royalty based on those works. In order to fairly assign royalties, it may be necessary to distinguish among enhancements, improvements, modifications, and derivative works, although these terms are not mutually exclusive.

Both parties should determine whether software used in the research incorporates software owned by others, because this software owned by others may become incorporated into new software arising from the research.

2) Improvements

Rights to improvements in software made by the university may be included in the rights granted under a

Contract language for
"Derivative works"—*In the event
that Sponsor acquires a license to
copyrightable University
Intellectual Property, such license
specifically includes the right of the
Sponsor to make Derivative Works,
subject to the definition of
University Intellectual Property
agreed to by the parties.*

research agreement, when the improvements are made within a defined period after the research agreement ends. In such cases, the university and sponsor should discuss the possibility of options and licenses to improvements. Generally, if the improvement by the university is small, a royalty-free license to the improvement is granted. If it is a substantial enhancement, such as a new algorithm for software in a major piece of equipment, a separate license may be required.

There are several different types of improvements possible.¹⁶ The university and the sponsor need to agree on the definition of "improvements" for the purposes of the research agreement.

Contract language for
"Improvements"—Improvements¹⁶
to copyrightable University
Intellectual Property made by
University within ____ months
following termination of this
Agreement shall be provided to
Sponsor on a non-exclusive,
royalty-free basis, subject to the
definition of University Intellectual
Property agreed to by the parties.
(For the purposes of this
Agreement, "Improvements" means
_____.)

VII. Conclusion/Summary

Four major intellectual property rights issues have been addressed in this document: (1) ownership of intellectual property; (2) rights to use intellectual property; (3) procedural issues; and (4) special considerations involving copyright. Given the different nature and culture of universities and industry, the scenarios and corresponding contract language represent compromises that university and industry representatives on the Task Force believe will provide negotiators with reasonable options for dealing with these issues and with a framework for the general consideration of intellectual property rights within research agreements.

The objective of the Task Force was to facilitate the negotiation of intellectual property rights in research agreements between universities and industry. To the extent this document is helpful in those endeavors, the Task Force will have accomplished its main objective.

¹⁶See footnote 15 on page 17.

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CASE STUDIES

1. TAXOL®

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2. DDI

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

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

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

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

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

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

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

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

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

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Industrial Perspectives on Innovation and Interactions with Universities

Summary of Interviews with
Senior Industrial Officials

GOVERNMENT-UNIVERSITY-
INDUSTRY RESEARCH
ROUNDTABLE

INDUSTRIAL
RESEARCH
INSTITUTE

National Academy Press

Washington, D.C.

February 1991

The Government-University-Industry Research Roundtable

The Government-University-Industry Research Roundtable is sponsored by the National Academy of Sciences, National Academy of Engineering, and Institute of Medicine. The Research Roundtable was created in 1984 to provide a forum where scientists, engineers, administrators, and policymakers from government, university, and industry can come together on an ongoing basis to explore ways to improve the productivity of the nation's research enterprise. The object is to try to understand issues, to inject imaginative thought into the system, and to provide a setting for discussion and the seeking of common ground. The Roundtable does not make recommendations, nor offer specific advice. It does develop options and bring all interested parties together. The uniqueness of the Roundtable is in the breadth of its membership and in the continuity with which it can address issues.

The Industrial Research Institute

The Industrial Research Institute (IRI) was founded in 1938 under the auspices of the National Research Council. Its purposes are to promote, through the cooperative efforts of its members, improved, economical, and effective techniques of organization, administration, and operation of industrial research, including means for more effective interaction with other corporate functions; to generate understanding and cooperation between the academic and industrial research communities; to afford a means for industry to cooperate effectively with government in matters related to research; to stimulate and develop an understanding of research as a force in economic, industrial, and social activities; to encourage high standards in the field of industrial research; and to promote communication and interaction with industrial research organizations in other countries. IRI is an association of some 260 major industrial companies that provides a means for the coordinated study of problems confronting managers of industrial research and development.

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PREFACE

As a natural extension of earlier Roundtable efforts that mapped the diversity of university-industry research alliances and culminated in the 1986 report, **New Alliances and Partnerships in American Science and Engineering**, the Roundtable, in conjunction with the Industrial Research Institute, has examined industrial perspectives on how innovation occurs and on how alliances with universities are expected to contribute to technical change and competitiveness within individual companies. This examination was carried out initially through individual discussions with seventeen senior research managers (see Appendix A) representing a range of fields of research as well as a variety of sizes and types of companies. The questions used to guide the sessions are listed in Appendix B. The results of the individual interviews were summarized and reviewed by the industry interviewees, a few members of the Roundtable Council, and senior federal R&D officials at a meeting in October 1990. Comments from that meeting have been incorporated into the summary of the interviews presented here.

The objective of the Roundtable in undertaking this project was to add a stronger component of industrial views to the ongoing discussions of university-industry alliances—discussions that, in the view of many Roundtable Council members, have been dominated by the perspectives of the university community. The results achieve this objective fully and effectively. We have here, concisely stated, the collective views of seventeen knowledgeable and experienced industry officials who have participated in many components of the innovation process across a broad spectrum of industry and in a variety of types of interactions with universities. Readers may not agree with all that is said in these pages, but given the caliber of the interviewees, these points of view deserve the attention of those considering the nature of university-industry alliances, their expected results, and their operating procedures.

This being said, it is also important to recognize the limitations of the interview results. Not all industry sectors are represented, nor are all the types of industry officials responsible for promoting innovation. These gaps certainly result in missing perspectives given the variation we found as a function of the experience of the individual interviewees, their industrial sector, their specific company and particular job, and the size of their company. The perspectives summarized here, therefore, should not be interpreted as general statements about the issues but rather as a collection of opinions of seventeen officials, albeit seventeen very knowledgeable and experienced individuals. Likewise, publication of these views does not represent endorsement by either the Industrial Research Institute or the Research Roundtable.

In my opinion, however, most of the conclusions presented in this document are totally consistent with the perspectives of most industry officials involved in the development of technological products and processes. The fact that these views may not be consistent with the perspectives of university officials illustrates that a serious gap in understanding persists between universities and industry. I hope that the views presented here help to break down some of the current misconceptions.

The industry officials interviewed provided sometimes varying views and sometimes a consensus on issues concerning innovation—its process and its primary sources; roles for universities, including training and serving as "centers of thought"; and collaboration of companies with universities, in-house, with other firms, and with federal laboratories. Each topic is introduced in the paper with a general statement that portrays the views of the majority of interviewees. The full complexity and diversity of views and the nuances among them are captured in the remarks attributed to individual interviewees that follow each general statement.

The central themes that emerged from these interviews are: most innovation occurs through incremental improvements to existing products or processes; industry is the primary source for innovation; the primary role for universities is in training and education; and industry needs to collaborate with universities, other companies, in-house research divisions, vendors, and federal laboratories to maximize knowledge transfer and to identify emerging new technologies. These themes are more fully described in the summary to this paper. I heartily endorse these conclusions. In addition, the commentary on generic, precompetitive research, intellectual property, and federal laboratories has profound implications for public policies and university-industry relationships. A difference of opinion continues to exist between university and industry officials in these areas because, I believe, university officials tend to have a somewhat myopic opinion of the university role in innovation. It is my hope that the commentary presented here will pave the way for beginning to address the implications for public policy, initially by means of creating an understanding of how many from industry view these issues.

By design, most of the views of industry officials presented here concern universities and industrial collaborations with them. I also want to point out, however, that the industry officials did not shy away from acknowledging their large competitiveness problems. On the contrary, some officials were critical of the ability of U.S. industry to advance an idea to market, as compared to Japan and other competitor nations. The issues involved in competitiveness go beyond relationships that U.S. firms have with universities and thus are outside the scope of this paper. Suffice it to say that although these relationships and collaborations are valuable to both parties, they are not going to solve the competitiveness problems for U.S. industry.

In closing, on behalf of the Roundtable Council, I want to thank the people responsible for the preparation of this valuable document. Foremost are the industrial officials who were interviewed, as listed in Appendix A; Nathan Rosenberg, professor, Department of Economics, Stanford University, and Richard Nelson, professor, School of International and Public Affairs, Columbia University; provided overall guidance for the project and conducted most of the interviews; Charles Larson, executive director, Industrial Research Institute, helped us in identifying the interviewees; and Casey Kiernan, senior program officer, Research Roundtable, made it all happen—she did an outstanding job of organizing and summarizing the individual interviews and preparing this summary document. I commend it to your attention.

John D. Macomber
Chairman and President, Export/Import Bank of the United States
Former Chairman and CEO, Celanese Corporation
Member, Roundtable Council, 1987-1990

February 1991

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INNOVATION AND TECHNICAL CHANGE

How innovation is viewed is important in thinking about how it occurs and what roles universities can play in the innovative process. For the purposes of these interviews with seventeen senior research managers (see Appendix A), innovation was considered as the conception of an idea and its movement toward and embodiment in a commercially successful product or process. Technical change and technical advance are steps in and contributors to the process of innovation.

Breakthrough Discovery versus Incremental Advance

In many industries, technical advance occurs most often through small incremental improvements to existing products and processes rather than as large technical breakthroughs. It is the incremental technological advance that is the dominant step in the process of innovation that is related to competitiveness and international trade. This view—stressed by most interviewees as the most important perspective on the process of innovation—is one that affects industrial approaches to technical change and collaboration. Incremental advance most often occurs in industry; universities play a small role, according to interviewees, because university scientists often tend not to operate on or understand industry's short-term schedules or the tools involved in developing an incremental improvement.

The interviewed industrial officials stated that during the early stages of a large, breakthrough discovery, however, industries often need to interact closely with universities to gain a more thorough understanding of the science underlying the discovery. Thus universities sometimes play a major role following a major breakthrough, when it is necessary to establish a base of understanding on which the breakthrough can be bolstered and continue to grow. Industry looks to universities to fill this role but does not want universities to become oriented toward product development, according to interviewees.

The reputation of a research lab is often based on feats of invention rather than incremental improvement...in spite of the fact that most of its staff are involved in incremental development and, typically less than 10 percent are doing truly creative breakthrough research, according to Albert Westwood. Procter & Gamble also continuously works to change or improve products through a combination of evolutionary and revolutionary product improvements. Geoffrey Place feels this is fundamental to P&G's success.

Hubert Schoemaker noted that the basic research in biotechnology conducted at universities and the initial hybridoma products speak to

the significant role for universities in this emerging field. As biotechnology matures and the focus turns more to product development and incremental improvements, Centocor and other biotechnology firms may rely less on universities than they currently do.

Sources of Innovation and Technical Change

Most industry officials interviewed believed that, whereas universities are at the forefront of scientific discovery, product- and process-oriented technical change occurs within industrial firms for most fields. Industry is the primary source of innovation because industry culture fosters entrepreneurial awareness of profitable emerging fields and ideas. In addition, industry scientists and engineers know more about a technology—its detail and its system—than do academic scientists and engineers. The limited role of universities in innovation has not been recognized because of the misconception that technological change generally occurs through a remarkable breakthrough that will revolutionize an industry, because of the excitement that accompanies such radical new ideas regardless of how infrequently they occur, and because university scientists tend to have a simplistic understanding of how product development and commercialization occur, according to interviewees.

Peter Boer believes that the forefront of innovation often comes from industry. Industrial scientists have a good nose for profitable emerging fields. They tend to be better at setting goals and at interdisciplinary research, and can assess what needs to be done to develop a field; they are better than academics at seeing the broader scope and the long-range outcome.

For new advance, Rodney Hanneman stated that Reynolds Metals adopts alternative materials where strategically appropriate and synergistic with existing materials and products using the existing infrastructure (e.g. Reynolds Plastic Wrap and vinyl siding). In-house experts conduct complex and expensive process-oriented R&D using full scale systems involving many disciplines to achieve such advance. Technical advance also tends to come from in-house research at Inland Steel. There, according to Howard Piolet, innovation develops out of specific needs for a better system or widget.

Centocor is oriented to look outward for its sources of technology and to rely heavily on academic collaboration. These collaborations provide access to a tremendous pool of government-funded basic research that is critical for small businesses. For small biotechnology companies like Genentech and Centocor, according to David Botstein and Hubert Schoemaker, advance requires close connection with universities. In this

field, as in superconductivity, innovations come from universities. Allied-Signal also looks to universities for advances, but only those 20 years or so into the future; advances that are not even conceived of in the present. Lance Davis noted though that "next generation products" at Allied-Signal, like many other firms, are developed in-house.

Place noted that the foods business at Procter & Gamble, on the other hand, is an industry that is not driven by technology change; it is low technology and has a limited science base. There is a fair amount of research into food products at universities, but it is not at the cutting edge.

At the same time, an enormous amount of basic research is being conducted in universities to add to the knowledge base that supports both the processes of incremental technological advance and breakthrough discoveries. How much companies rely on universities, however, varies as a function of the technical field, the maturity of the industry, the stage of research, and the size of company.

For many reasons that will be discussed below, there are limits to the role that research divisions—from universities or industry—can play in the innovation process, according to industry officials. However, interviewees also noted that without university research there would be a considerable lack of depth in the level of scientific understanding about products and processes. The industry interviewees recognized the role of universities in providing understanding and techniques that enable companies to solve problems, invent, and design effectively.

Not much new product technology comes from universities unless Procter & Gamble leads a project on an innovation, according to Place. University contribution is through access to knowledge, not access to technology. Universities do not have a sophisticated understanding of the commercial needs, so when they apply knowledge to a need, they are frequently off base.

Westwood considers that Martin Marietta has had few if any products come directly from university research. However, coupled university and company programs have often been very productive. Udo Axen agreed stating that Upjohn sees little that academics are doing directly that the company may want to buy into; universities generally have not been a source of new pharmaceuticals beyond biotechnology. Universities are not equipped to develop products through a multidisciplinary approach.

Much of International Paper's work is in process optimization and product design that involves such technological development, according to Keith Hall. Most work is done internally; universities do not have

appropriate equipment. However, some R&D in the pulp and paper industry emphasizes "better" trees. This R&D is carried out in cooperatives run by universities.

Joel Birnbaum noted that in computing, new research is generally carried out by entrepreneurs and industrialists; universities can then take the time to search for fundamental understanding which leads to refinement and the second wave of innovation. A prototype then often comes out of university research with new experimental tools often calling for new measurement capacity. Universities do not need to carry out the initial breakthrough, but a relationship should be sought to take advantage of creating complete and correct systems.

KEY ROLE FOR UNIVERSITIES IN TRAINING AND EDUCATION

A key role for universities is the training and education of scientists and engineers. This message was highlighted and repeated throughout the interviews as the most important and significant role for universities. Most interviewees stated that U.S. colleges and universities are doing a good job of teaching science and engineering students the fundamentals, although educating students is not always a priority for faculty members. Many commented that there is room for improvement in certain areas, however, including management skills, communication skills, quality assurance, and a team approach to problem solving. Some interviewees noted that training students for academic careers does not fully prepare students for industrial careers—teaching focuses on the single investigator rather than on a team approach.

Multidisciplinary training is essential to achieve the team approach required in industry. Birnbaum noted that many of the most creative employees in computing tend not to come from computer science or computer engineering departments. Rather, a high percentage were trained in other fields and were turned on to computers to solve problems. These people may have worked as a member of a research team in a way computer science students at many schools do not (many computer science students are trained individually with a solo thesis). The university's competitive culture may serve the academic system well, but it does not serve the industrial system, according to Boer. Most university education is in defined disciplines. For many industries including the construction industry, according to Tim Killen, research is problem-oriented, and requires interdisciplinary approaches.

Axen believes, however, that the fact that universities do not train in a project-oriented approach is not necessarily bad because Upjohn wants the best students in each discipline. Upjohn can then combine disciplines into a project team of experts in important areas. Upjohn does not want to create hybrid scientists, but wants team players who are not tied to their own disciplines.

The consensus among industry interviewees was that companies need both trained specialists and generalists to ensure a strong R&D effort. University graduates do not enter industry as "finished products"; many have yet to learn anything about industrial practice and the realities of the marketplace, according to a number of interviewees.

Centocor, like other firms, seeks out researchers who are not only scientifically talented, but also who understand that: time is money, product focus is essential, and communication and management skills are critical to success in industry research. These skills are often not

emphasized at the university, and Centocor must invest heavily to develop them in its employees. Westwood concurred. He believes that the real inadequacies in U.S. college and graduate education are the unmet need to teach people to think and become problem-solvers rather than technicians. How to determine what are good problems to pursue, what can be done, and what ought to be done (including value judgments, ethics, and humanity issues) are lessons yet to be taught in universities. Place believes that university students are trained to be deductive as opposed to inductive and have great trouble creating hypotheses in highly uncertain areas. He believes that the problem is getting worse, particularly in the life sciences where students receive an increasingly narrow training and where fewer and fewer students can develop a broad hypothesis for research. The education function needs to be changed to provide adequate preparation for the breadth of interaction needed in industry.

On the other hand, Robert Frosch stated that universities should not transform the education process from one of depth to one of breadth. GM Research Laboratories needs Ph.D. specialists rather than generalists. Scientists frequently get a general education at the bachelors' degree level, and then go on for specialization and depth. Engineers, however, are on track too soon, are too narrowly educated at the bachelors' degree level, and thus, become technicians. Engineering students need a broader education beyond engineering disciplines and business.

Frosch believes that although universities are responsible for training researchers, they should not be concerned with the specifics of the industry. After a student is hired, the firm can teach the specifics of its business and further leadership skills, according to Hanneman.

There was concern among many of the interviewees about the questionable quality of precollege education, and the potential for shortages in science and engineering talent.

Ora Smith thinks U.S. graduate schools are fundamentally in good shape, but he is very concerned about undergraduate institutions and high schools. In Allen Heininger's view, math and science education in K-12 grades are especially needy and critically important if the U.S. is to remain competitive. Hanneman is also concerned about the quality and quantity of technically prepared students in the education pipeline. He sees the emerging shortage of U.S.-born engineers as coming from inadequacies in motivation, role models, and the U.S. educational system prior to and during high school. Hanneman noted that European

education is far superior through high school and that the U.S. provides a less positive climate for science and technological advance.

All interviewees recognized the important role of universities in cooperative training and education, and in continuing education in order to maintain a knowledgeable workforce. Industry officials expressed the belief that continuing education and cooperative training are essential in supplying them with the capacity to keep their employees educated in the state-of-the-art technical expertise and equipment.

INDUSTRIAL COLLABORATION FOR INNOVATION

Although most firms look to themselves as a source of incremental technological advance, all industry interviewees acknowledged their reliance on other organizations and institutions for scientific and technological breadth and for in-depth understanding. Collaborative efforts are forged—with universities, other companies, federal laboratories, and in-house departments—to allow a firm access to new and emerging ideas, bright minds with varying perspectives, and financial leveraging for precompetitive R&D.

In general, industry interviewees stated that they find the most fruitful form of collaboration to be a "bottom-up" scientist-to-scientist approach with one-on-one relationships rather than "top-down" management decisions for collaborative arrangements. Although a number of interviewees indicated that they participate in collaboration that did not arise from a "bottom up" approach, primarily with university centers, consortia, or affiliates programs, all see these as mechanisms for accessing expertise—of consultants or recruits—or for promoting good will. Interviewees emphasized the importance of informal as well as formal interactions for collaboration; often long-term interactions begin as informal discussions among potential collaborators.

Most industry participants expressed skepticism about the results of generic research contributing to competitive advantage, and thus they are not willing to support it to a large extent. Many stated the belief that it is the role of the federal government to pay for the major share of this type of research. In the interest of the national welfare, many firms are willing to spend a small amount—less than 2 percent of their R&D budget—on precompetitive, generic research, although there is some variation by industry. In addition, precompetitive research is not generally pursued through company-financed consortial arrangements with universities either, according to industry interviewees. Companies would want to retain proprietary status for any discoveries that might emerge and would prefer not to lose competitive advantage through the sharing required in a collaborative program.

Procter & Gamble is less internally focused with respect to science and technology than it was a decade ago, Place noted. This change has been driven by two factors; the need for external expertise as the business moved into diverse areas of technology, and the movement of environment and safety issues and concerns into all areas.

Environmental concerns are key to the paper industry, now and in the future according to Hall. Research on environmental concerns at International Paper is conducted through cooperatives with vendors, competitors and with other industries.

Bell Laboratories research scientists, on the other hand, do not often need to collaborate because they usually have the capacity to do the work in-house. They consider the Laboratories to be a peer of universities, and as a "captive university" to AT&T, according to Robert Lucky.

According to the industry interviewees, the amount and type of collaboration that a company will undertake is based on the stage of the research, the scientific field, and the size of the company and R&D effort. For small companies, in particular, external collaboration is critical, because these firms often have limited R&D budgets and therefore need to maximize research capacity by leveraging work through collaboration.

Collaboration with Universities

Although industry does not rely on universities for commercially viable innovative technologies, all interviewees acknowledged the importance of collaboration with universities. Industry needs new knowledge from universities in order to build new technologies and to improve old ones. In fact, a company will occasionally support university research in an area that is new to the company and that also extends the university's research program into new topics. In addition, industry officials increasingly participate on advisory committees at universities to provide their perspectives on promising long-term research frontiers. Collaborations also occur with consultants from academia who provide perspective, analysis, and special expertise for many industry projects.

Smith pointed out that there are only a finite number of relationships with universities that a company can sustain. For every dollar spent on research, \$10 needs to be spent on development, and \$100 on design and building. Currently, Conductus is focusing on development and design and, therefore, can only participate in selected opportunities to leverage those developments in the best way possible. Collaboration with universities is also self-limiting by the number of in-house lab scientists who care about the research project and are willing to put in the time for collaboration as well as by financial constraints, according to Boer and others. A few interviewees noted that university contracts are a financial cost at the margin of the company's portfolio, and can be put on hold if need be during times of financial stress.

Martin Marietta prefers to fund university research that will stretch it into an area where the firm has only limited expertise, according to Westwood. Otherwise, the flow of information tends to be from the company to the university. This work at the margin of Martin Marietta's

current capabilities will permit the firm to expand its know-how and understanding. Similarly, GM Research Laboratories funds only basic research or specific technology that is not close to the firm's proprietary research, Frosch noted. W.R. Grace also does not establish contracts with universities in technologies where the firm has a vested interest. Rather, it seeks to create relationships around emerging technologies in key scientific areas for the company. Boer believes that the company has no choice but to stay abreast with university research applicable to key areas for the company. A high percent of Procter & Gamble's drug discoveries or therapies will come from understanding underlying mechanisms, not primarily from a new drug structure, Place said. Therefore, it is important to work with universities whose scientists are highly competent in relevant research. Cost, talent, speed, and degree of protection dictates the amount of collaboration that P&G will seek from universities on any given project. In-house research can be done much faster at high cost if need be.

University Misconceptions about Commercialization and the Process of Innovation

According to a number of industry interviewees, many university officials erroneously believe that discovery of new ideas represents the most significant step in the process of innovation, and that universities are the key source. While the creative aspect of invention should not be minimized, even in the rare breakthrough event the development of an idea into a commercial product is a long, costly, and often unsuccessful process. Interviewees stated that many university officials tend to have an inflated view of the importance of university research efforts in innovation. Most often ideas from university scientists are too embryonic to be quickly or easily commercialized.

Some industry interviewees expressed the concern that universities in the wake of increasing financial constraints and limitations on the support of basic research will take on product discovery as part of their mission and research. They stated that this would be a mistake. Universities should not attempt to orient their research more closely to product discovery; this is not an appropriate role for universities, nor is it a task for which they are generally well suited, said the interviewees. Rather, they must continue to teach, to foster creativity, and to advance the frontiers of knowledge through long-term basic research. Most, if not all, interviewees commented that this role does not conflict with the need for university-industry collaboration. On the contrary, they explained that this role creates the underlying structure for the nature of collaborations and the expectations that universities should have when entering into cooperative programs with industry; universities can provide the trained manpower to address long-term basic research questions related to industrial goals. In addition, it

was noted that for a few particular industries—not represented in the IRI-Roundtable study—applied research at universities is germane to industrial development.

Boer finds that 50 to 60 percent of the industry-university relationships have poor convergence of goals, i.e., typically where W. R. Grace is seen mainly as a source of money. In the other 40 to 50 percent, however, the relationship is successful, persists for a long time, and funding tends to increase. W.R. Grace is generally loyal to those who establish ideas and move them forward. Money spent at universities should be focused on long-term basic research, but universities also must understand the goals of industry: to link discovery and commercial reality. Boer views successful projects as those where convergence on a meaningful societal goal has occurred and both intellectual and commercial achievements are attained. Boer agreed that W.R. Grace contracts may cause a shift in direction of university research, but he pointed out that this is a voluntary process beginning with a proposal from a faculty member.

Heininger believes that since World War II, university research has tended to focus on the source of funds and has de-emphasized interaction with the users of the output of research. Government funding by peer-review decisions means that university scientists have played a key role in deciding what research to fund and this has emphasized the pursuit of scientific knowledge, while not necessarily providing a balancing input as to what society's needs are likely to be from other points of view. Heininger acknowledges that the needs of industry cannot be the only important criteria for the conduct of basic research, but he believes the selection process for investing in R&D may be part of the reason for our current competitiveness problem. Place believes that universities should continue to conduct basic research; that if industry and technical growth were the "customers" for the results of academic research, the use of discoveries and the education system would be drastically altered.

Universities as Network Nodes

The process of innovation requires a complicated network of interactions and exchange of ideas among companies, universities, federal laboratories, vendors, and customers, and universities are part of the glue that holds the network together, according to interviewees. The network facilitates communication of new knowledge and ideas, and contributes to in-depth understanding of existing ones, often via interaction at meetings arranged by professional societies.

Lucky sees universities as important "centers of thought." Bell Laboratories gets information from universities by hiring students who know what is happening in these "centers of thought." An open line of communication exists between the Bell Lab's research division and universities so that if a breakthrough occurs at universities, AT&T is in a good position to take advantage of the discovery. Lucky likened closing down universities to closing down coffee shops in Paris at the turn of the century and asking whether there would have been an effect on art. Universities are enormous producers of ideas. For the purpose of general knowledge development and access to new ideas from academia, Procter & Gamble has an exploratory-research program. Through this program, P&G hears about ideas that the firm would not have been aware of if it had not funded the program.

Since R&D activities in the pulp and paper industry are interdisciplinary, it is difficult to put together an effective group with all relevant expertise, according to Hall. Using the existing university network can help International Paper establish focused interdisciplinary teams, in spite of the fact that universities try to enter industrially innovative fields primarily because they see this as a source of money.

One-Scientist-to-One-Scientist Relationships: a "Bottom-up Approach" to Collaboration

Many interviewees prefer to set up collaborations between universities and firms on a one-to-one basis. The working relationship between the industry scientist and the university scientist is crucial to recognizing a potential product or a goal, assessing the appropriate time frame, identifying the risk and "marketability" of an idea, and assessing the credibility of the researchers involved, according to interviewees. Almost all interviewees agreed that one-to-one research collaboration is the most likely type of university-industry interaction to foster communication of innovative ideas. University consultants to industry also provide an important mechanism for one-to-one interactions.

One key ingredient for successful collaborations with universities, according to Axen, is who initiates the collaboration. He believes it must come from a scientist from each sector working together, include in-house technology capacity as part of the project team, and have truly complementary research. If the systems overlap too much, scientists in-house and in the university become competitors rather than collaborators. In general, when the collaboration comes from Upjohn and university administrators in a top-down approach, it does not work.

Boer noted that in the past too much emphasis had been given to top-down ideas for partnership. These may be good at the "slogan level", but are not good at the motivational level. W.R. Grace now prefers using a bottom-up approach originating between a professor and an internal scientist.

Geographic Proximity

In establishing relationships with universities, geographic proximity is very important to most firms, according to a number of industry interviewees, in order to maximize the potential for communication and interaction.

Conductus was formed with a conscious effort to nucleate the company around universities where fundamental work on superconducting materials (as well as some device work) is being done. Allied-Signal and Reynolds Metals also tend to have closer association with geographically proximate universities to maximize the ability for one-to-one exchange.

However, for Upjohn, having access to research is the number one priority; geography is secondary. In fact, the company created a European Discovery Centers program because it did not have a significant image or presence in Europe.

Consortia, Centers, and Affiliates Programs

Consortia and centers that include the participation of several companies may be good at promoting basic science but are not effective at commercialization: they are too remote from the marketplace; they provide uncertain commercialization benefits given the generic nature of the work; and there is a strong motivation for individual industrial members to develop products in-house rather than share results, according to a number of industry officials interviewed. Consortia and centers may be effective in addressing generic issues in the development of new technologies and providing a networking source, interviewees noted, but they are unlikely to play a significant role in the process of innovation.

Generally, industrial affiliates programs are not profitable, according to industry interviewees, and generally, companies are less and less interested in participating. Those that continue to support such programs tend to do so either as good will gestures or to have access to students and faculty for recruitment.

W.R. Grace has joined a number of consortia, and subsequently has dropped out of most of them because they were not meeting W.R. Grace's needs for competitive advantage. In their primary form,

university-based consortia are strong interdisciplinary faculty groups working on industrial issues of common interest to leverage financial investments. Boer believes that: the value for a company to join a consortium is inversely proportional to the amount of knowledge it has about the subject—creating the possibility of proprietary technology leaking to competition if one

participates actively; often faculty do not collaborate actively with member companies; and it is time-consuming to find out what is going on in a consortium.

International Paper participates in consortia in forest research, according to Hall. The company does not expect proprietary information from consortia arrangements and sees no advantage other than that the firm is the largest landowner in the U.S. and, therefore, has the most potential for advance. For a modest investment, consortia provide the company with access to cutting edge research.

Place believes that sometimes creating a structure for interaction gets in the way of the potential when two individuals—one in-house researcher and one university researcher—want to work together to address a particular problem or system. The one-on-one approach is the vehicle of choice for collaborating with universities from the perspective of Procter & Gamble and other industries.

Large Multimillion-Dollar Alliances

In general, most firms do not opt for large multimillion-dollar partnerships with universities or university departments, according to industry interviewees. Indeed, only a few of the interviewees work in companies that are involved in large alliances.

From Heining's point of view, both of the large university alliances in which Monsanto has participated—with Harvard and with Washington University—have not yet demonstrated success. He noted, however, that others within Monsanto view the alliances quite differently and believe them to be very successful. The bottom line is that products need to be eventually developed if a major collaboration is to be judged successful for both parties, Heining believes. Otherwise, Monsanto's participation becomes a charitable donation to the university. No product leads emerged from the 12-year project with Harvard. The current interaction with Washington University cannot be judged yet, but to date no products have been developed. Primarily, those ideas touted thus far have been failures because the assumption that a product was

ready for development was premature. Heininger says that at this point in a well-run in-house project, Monsanto would have expected products by now.

Many of the interviewees noted that they had some skepticism as to the ultimate commercial success of these partnerships. Some commented that while the projects are viewed as great successes from the university perspective because they provide a large source of funds in support of worthwhile basic research efforts, the industry perspective is that their success in promoting innovation and commercialization remains to be seen.

Intellectual Property Rights

Industry interviewees complained about difficulties in negotiating intellectual property rights and patenting and licensing agreements in university-industry partnerships. The probability of any commercially viable product or process evolving from an alliance with a university is remote, according to a number of interviewees, because of the type of research that companies support at universities. Interviewees noted that, ironically, industry in general is becoming more flexible in the conditions of its support for university research while universities are becoming more stringent in negotiating intellectual property rights for potential discoveries based on the slim chance that a significant, commercially viable breakthrough will occur and hence will result in an opportunity for the university to reap great financial rewards. Industry interviewees stated that these expectations are, in general, unrealistic and arise from the views held by many university officials regarding the innovation process and the role of breakthrough discoveries in that process. Furthermore, these expectations on the part of university officials can cause divisiveness on the campus between university administrators adamant about claiming intellectual property rights and university scientists who wish to conduct the research without burdensome policies, and between the university and industry participants, according to interviewees.

Martin Marietta is not overly sensitive to how the intellectual property issue is handled in contracts with universities because, in Westwood's view, the probability of any moneymaking product being developed is very low. However, he resents any university lawyer or financial spokesman declaring that the company has no rights to outcomes of research that the firm has funded at a university. Westwood's opinion is that these people do not understand the R&D process, and are sometimes so rigid that further useful dialogue is not possible.

Hanneman observed that at Reynolds Metals, most patents from academia are usually not crucial from a business viewpoint. Internally generated technology is often sufficiently complex that it is unlikely that

a competitor will stumble onto an exact replica. Because this industry is more mature than some, it is less likely that a competitor will develop a broad dominating patent.

Because Conductus and Centocor are small companies, they are more dependent on patents that come from outside the firm. Exclusivity is important in many technologies in order to limit others from doing the same work. Universities must find a way to grant exclusivity to firms in which faculty are involved, according to Smith. This is often viewed as a conflict of interest. Rather, it should be viewed as a mutuality of interests to maximize the chances of marketing the discovery.

In-house Collaboration

Many of the industry interviewees noted that the problem of bridging between basic research ideas and product development that occurs in university-industry collaborative research is also present within a company; the same breakdowns in communication and understanding can occur between research divisions and development divisions. Some interviewees stated that the research divisions of their firms view themselves as part of the academic system, and they conduct similar long-term basic research. These research divisions feel pressures comparable to that felt by universities to move into more applied areas of research because of financial constraints.

According to Smith, senior technology managers tend to think somewhat nostalgically that if corporate laboratories could conduct R&D that might or might not be relevant to the company's interests—the way they did 15 years ago—then everything would be alright. This method of searching for breakthroughs worked in the past because the U.S. had no competition and money was cheap. The system has changed, however, and many R&D facilities have not evolved. Better relations with management will stabilize corporate laboratories more. The focus must be on closer cooperation with corporate laboratories reaching out to meet the needs of business units.

AT&T has a difficult time fostering communication and interaction between Bell Laboratories scientists and scientists in product development divisions. When scientists in development sections have research problems, they do not always share them with scientists in the research division. Even if research scientists work on a development problem, often they are not familiar with the "real world" problems that affect the system once scale-up and other considerations are taken into account. AT&T tries to create formal and informal networks for

communication between the development and research sectors of Bell Labs. In fact, Bell Labs has even established a "thief of the month" award to the scientist who takes someone else's idea to market. Lucky anticipates that Bell Labs research will become more relevant to AT&T in the future.

There is currently some pressure on the technical and research staff of GM's Research Laboratories to be more applications-oriented like the manufacturing and development divisions. The oscillating shift through the years from operations to research and back again is real and may be healthy: if a division is too research-oriented, it is viewed as an ivory tower; if it is too operations-oriented, it can become too dependent and, therefore, too short-term oriented. The relevance of science is important, according to Frosch, but when a company allows irrelevance in its research, the firm also creates the opportunity for an unexpected advance.

A major function of the corporate research lab at Martin Marietta is, according to Westwood, to acquire needed knowledge from the outside (as a systems integrator firm) and to transmit it in a timely and understandable fashion to an in-house "receptor." The lab carries out research only when the needed knowledge is not obtainable elsewhere. More often than not, a problem or a need in marketing is identified, and the industrial scientists reach back into science to pull up a new idea, i.e., technology needs drive the science.

Schoemaker stated that Centocor's in-house research effort is designed to improve and accelerate the lengthy and expensive process from discovery to commercially approved product. Centocor's scientists do not carry out true exploratory research; they are product-focused. To achieve effective technology transfer, research scientists at Centocor must maintain a tight technical focus, promoting product development and resisting the tendency to stray into the basic end of research. They must also stand on equal ground with their counterparts in academia because successful collaborations require mutual professional respect between the scientists involved. Centocor scientists are trained to spot important technical breakthroughs and product opportunities early on, and to effectively bring them into the company at the optimal time.

Collaboration with Other Companies

For conducting precompetitive research, sometimes companies will collaborate with each other to leverage expenditures and to reach a new level of understanding about

a technological advance, according to interviewees. Some development work can also be undertaken with company-company collaboration, primarily with foreign firms. Partnerships of this sort can be successful because they do not violate U.S. antitrust laws, nor do they usually involve competition between the two firms, given that often the markets for two firms willing to collaborate in such ventures tend not to overlap.

Occasionally, Reynolds Metals deals with a competitor in a joint development, to a point. Hanneman stated that this works when neither firm alone would have been able to independently justify carrying out the research at that time. The aerospace industry sometimes operates by joint ventures to create an industry-wide team. Davis pointed out that Allied-Signal eventually competes with other industrial team members, but cooperation is worthwhile in the early stages to leverage the expense of development. Joint ventures are particularly useful with foreign companies where access to foreign markets would otherwise be difficult. Piolet noted that Inland Steel also collaborates with other companies (e.g. Nippon Steel).

The use of strategic partners will be increasingly important for aerospace companies as the defense industry tends to have reduced capability to drive the development system. International markets and cost reduction will become increasingly important factors along with speed to market and ecologically clean products, according to Westwood.

Collaboration also occurs between firms when the cost of conducting the R&D is prohibitive for one firm alone, when the general topic and issues of concern cross individual company and industry sector boundaries (e.g. meeting environmental regulatory requirements), and when the collaboration will contribute to the credibility of the research.

Heininger predicts that companies will have to consolidate because of federal regulations. Large companies will get larger and the small ones, less able to meet regulatory requirements, will gradually disappear.

Research collaborations with small firms can be advantageous to larger firms: these large firms can explore a new field with minimum risk or investment by providing financing for the research to be conducted in an atmosphere relatively free of bureaucratic constraints.

Partnerships with vendors can also be important in addressing how to convert old equipment and machinery for use with newer products or processes, and to conduct trial work, according to some industry interviewees.

Collaboration with Federal Laboratories

Some interviewees have R&D interactions with federal laboratories, but few strong collaborative arrangements exist between these laboratories and the firms represented in the interviews. Industrial officials noted that the primary issue that gets in the way of industry-federal laboratory collaboration is that the laboratories do not have a clear mission related to the development of civilian technology or an understanding of industry as a customer.

Monsanto does not interact much with federal laboratories even though it started and operated one for over 40 years. Similarly, Martin Marietta has not used Oak Ridge as a resource as much as company officials hoped it would, in part to avoid any criticism regarding some perceived privileged position.

Westwood believes that the federal laboratories need to review their focus, and to recognize U.S. industry as their most important customer. They will have to learn more about this customer in order to be of assistance and this will require extended visits, sabbaticals, joint programs, etc.

Industrial interviewees observed that since the enactment of the Federal Technology Transfer Act of 1986, federal laboratories have been in a state of change, and some laboratories have adapted more rapidly than others. Although traditionally the laboratories have not collaborated effectively with industry, their collaborative capacity has not yet been proved or disproved in their current but changing form, according to industry interviewees. Some of the interviewees stated that the federal laboratories can be a greater asset than they now are and that the time may be ripe for enhancing their collaborative interactions with industry. The interviewees were quick to add, however, that change on a small scale by federal laboratories was likely to have a negligible effect on interactions with industry. Interactions between federal laboratories and industry will increase substantially only if the missions of the laboratories can be changed dramatically to focus on the needs of industry.

SUMMARY

The purpose of this document is to add the perspectives of seventeen senior industrial officials to the ongoing discussions of how innovation occurs and how alliances with universities contribute to technical change and competitiveness within individual companies. It is important to note that the term innovation was considered by these industrial officials as the conception of an idea and its movement toward and embodiment in a commercially successful product or process.

The perspectives presented in this document are not intended to represent generalized conclusions for all of industry, but rather should be interpreted as a collection of opinions of the seventeen industrial officials interviewed. As is reflected in the text, diverse perspectives exist among these industry officials.

Four central themes emerged from the interviews:

- In many industries, innovation usually occurs through in-house incremental improvement to existing products or processes rather than the rarer breakthrough event that revolutionizes a product or process.
- Industry is the primary source for innovation. Universities play only a limited role in this realm. Interviewees noted that the role of universities varies depending on the maturity of the field, the type of innovation—incremental or breakthrough—and the "culture" of the company.
- The primary role for universities is as educator and provider of talent. This function is universities' greatest contribution to the process of innovation, according to interviewees. Providing in-depth, fundamental understanding of scientifically and technologically new or emerging ideas is another significant role for universities. According to interviewees product development should not be an academic role.
- The challenge for industry is to determine the adequacy of the knowledge base; to identify emerging technologies and barriers to knowledge transfer; and to define approaches to collaboration for maximum input of new knowledge. No company is large enough or smart enough to meet all of its knowledge needs within the firm. Interviewees stressed that industry must maintain relationships with universities, companies, and federal laboratories on topics relevant to their company's technological focus.

APPENDIX A

Industrial Officials Interviewed

Udo Axen, Vice President, Planning and Administration, The Upjohn Company

Joel S. Birnbaum, Vice President and General Manager, Information Architecture Group, Hewlett-Packard Company

F. Peter Boer, Executive Vice President for W.R. Grace and Group Executive for Corporate Technical Group, W.R. Grace and Company

David Botstein, Professor and Chairman, Department of Genetics, Stanford University School of Medicine

Lance A. Davis, Vice President, Research & Development, Allied-Signal, Inc.

Robert A. Frosch, Vice President, Research Laboratories, General Motors

Ralph E. Gomory, President, Alfred Sloan Foundation

F. Keith Hall, Chief Scientist and Director, Science & Exploratory Development, International Paper Company

Rodney E. Hannemen, Vice President of Corporate Quality Assurance and Technology Operations, Reynolds Metals Company

S. Allen Heininger, President Elect, American Chemical Society

Timothy S. Killen, Manager, Engineering & Construction Technologies, Bechtel National, Inc.

Robert Lucky, Executive Director, Research Communications Science Division, AT&T Bell Laboratories

Howard Piolet, Scientist, Inland Steel Company

Geoffrey Place, Vice President, Research and Development, The Procter & Gamble Company

Hubert J.P. Schoemaker, Chairman and CEO, Centocor, Inc.

Ora Smith, President and CEO, Illinois Superconductor Corporation

Albert R.C. Westwood, Vice President for Research and Technology, Martin Marietta Corporation

APPENDIX B

Questions for Discussions with Industrial Officials

Character of Technological Advance

- How would you characterize technological advance in your industry?
 - Is it principally new products or processes or both?
 - Do technical advances come about incrementally, in discrete steps, or both?
 - To what extent are the important advances patentable?
 - Has technical advance accelerated or slowed over the last decade in your industry?

Sources of Technological Advance

- In your industry, what is the role and importance of the following sources of technological advance?
 - R&D done by your company and other firms in the industry
 - Work of equipment and material suppliers
 - Work done by and ideas from customers
 - Research in government labs
 - University research
 - Other

University Training and In-Company Training

- How important are universities in providing the right kind of training if one is to be an effective R&D engineer or scientist in your industry?
- What must a new university trained scientist or engineer learn at your firm before he or she can be effective in R&D?
- Does your industry look to industrial training institutes (e.g. the Wang Institute) as an important source of trained people?

University Roles

- What is the role and the importance of the following possible university contributions to technological advance in your industry?
 - As a source of inventions or prototype new products or processes
 - As a source of new knowledge that enables your firm to better identify and conduct its inventive efforts

- As a window to a world-wide knowledge base
 - As a source of research techniques and new equipment
 - As a source of educated young engineers and scientists
 - As a source of consultants
 - Other
- What type of formal structures—in your company and in your industry (e.g. technical societies)—facilitate one-on-one interactions between industry scientists and engineers and university scientists and engineers?
 - Are universities providing functions that others could perform (e.g. private consulting or research organizations, or industry consortia), or that you could do yourself? What criteria do you use in deciding to interact with universities rather than to conduct similar efforts in-house?
 - If not to universities, to what other organizations and arrangements does your company look to provide the kinds of inputs listed above?
 - private research and consulting organizations
 - trade or technical associations
 - industry-wide laboratories or consortia
 - government labs

New Alliances

- What kind of alliances between your company and universities have come into place in recent years (e.g. industrial collaborations funding university research, industry participation in university-based or affiliated research, technology centers, etc.)?
- What other kinds of alliances are forming in your industry?
- What does your company expect from these alliances?
- Does your company's participation in new alliances reflect activities and attitudes that are typical of your industry?
- What are barriers to new alliances? What are new approaches to alliances?



Returns to R&D on New Drug Introductions In the 1980s

**Henry G. Grabowski and
John M. Vernon**

Duke University

Conference Paper

Competitive Strategies in the Pharmaceutical Industry
Washington, D.C.; October 27-28, 1993

Returns to R&D on New Drug Introductions in the 1980s

Henry G. Grabowski and John M. Vernon

Duke University

September 1993

Abstract

This study finds that the mean IRR for 1980-84 U.S. new drug introductions is 11.1%, and the mean NPV is 22 million (1990 dollars). The distribution of returns is highly skewed. The results are robust to plausible changes in the baseline assumptions. Our work is also compared with a 1993 study by the OTA. Despite some important differences in assumptions, both studies imply that returns for the average NCE are within one percentage point of the industry's cost of capital. This is much less than what is typically observed in analyses based on accounting data.

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The profitability of the pharmaceutical industry has recently become the subject of increased attention by public policymakers. Both the Clinton Administration and several legislators have called attention to the fact that the industry's return on stockholder equity has been more than double that of the median firm in the Fortune 500 Firms listings. Furthermore, there have been calls for price controls on pharmaceuticals as a strategy for health care cost containment.

While pharmaceutical profitability is a relevant subject of inquiry for both academics and policymakers, accounting measures of the return like those appearing annually in *Fortune* are not a very good basis to evaluate this industry's market performance. Stauffer (1972), Fisher and McGowan (1983) and other authors have demonstrated that accounting measures are a poor proxy for the underlying internal rate of return (IRR) of a firm or industry. The basic reasons are problems of bias due to both timing and aggregation. Furthermore, accounting measures of profitability are subject to significant distortion in industries with high rates of intangible capital investments like pharmaceuticals. The consensus from empirical studies is that the returns to equity for pharmaceuticals are overstated by at least 20 to 25% for this latter reason (Clarkson, 1977; Grabowski and Mueller, 1978; Megna and Mueller, 1991).

In the current paper, we present an alternative approach for evaluating pharmaceutical industry profitability. In particular, we focus on the cohort of new chemical entities (NCEs) introduced

by drug firms in the first part of the 1980s. For these NCEs, we estimate annual cash flows over the product life cycle. Our basic objective is to compute IRRs and NPVs for the representative NCE introduction over this period. Our investment life cycle approach, using NCE cohort data, avoids the timing and aggregation problems associated with profitability studies based on income and investment data from corporate accounting statements.¹

Of course, our approach also has limitations. We must make forecasts of future sales revenues and cash flows that are necessarily somewhat uncertain. It is also true that the returns estimates that we obtain apply only to NCEs and not to profits resulting from existing, older products or non-pharmaceutical activities. Nevertheless, we think analyses of the returns to recent cohorts of NCE introductions are likely to shed more light on the pertinent policy questions facing legislators than aggregate accounting-based studies of profitability.

Our analysis builds on prior work on the returns on NCEs introduced in the 1970s (Grabowski and Vernon, 1990; Joglekar and Paterson, 1986). Our previous analysis found that returns over the full decade of the 1970s were generally in line with the industry's cost of capital, but that returns in the latter half of the period exhibited a significant upward advance. More recently the Office of Technology Assessment has conducted an analysis of the profitability of 1981-83 NCEs (OTA, 1993). Their study utilizes an approach similar to our earlier analysis, but they change some of the primary assumptions. A major finding of the OTA study is that

1981-83 NCEs had a positive present value of 36 million dollars or surplus revenues above break-even values of approximately 4%. These findings have been cited by one of the study's sponsors, Representative Henry Waxman, as evidence that competition does not work in the prescription drug market.²

Aside from the OTA report, a number of industry developments make an analysis of the 1980s NCE returns especially interesting at this time. First, both R&D costs for new drug introductions and prescription prices have significantly increased in real terms during the 1980s. In addition, important legislation was passed in 1984 that significantly altered both the effective patent terms in this industry and the ease of entry by generic competitors after patent expiration (Grabowski and Vernon, 1992). There is also evidence suggesting that the rapid growth of managed care during the past decade is beginning to have significant effects on price competition among pharmaceutical firms (Ito, 1992; Chinburapa and Larson, 1991).

This paper is organized as follows. In the next section, we present a description of the data samples and methodology for the returns to 1980-84 NCEs. The primary results are given in Section 2, which includes a comparison of returns in the 1980s with our prior findings on returns to 1970s introductions. Section 3 then compares the assumptions and findings of our analysis to those in the OTA study. The final section offers a summary and concluding remarks.

I. Data Samples and Methodology

A. Overview

The objective of this section is to explain the key assumptions and methodology used in estimating the returns to the 1980-84 NCEs. At the outset we should note that a detailed discussion of the methodology is provided in our 1990 paper; hence, we will give a fairly brief treatment here--emphasizing areas in which the present study differs materially from the 1990 study. More detailed information on the data inputs is also provided in an appendix available from the authors.

The basic sample is 67 NCEs approved by the Food and Drug Administration (FDA) and introduced into the United States between 1980 and 1984. Our sample includes all NCEs originating from and developed by the pharmaceutical industry, except those in a few therapeutic classes where the R&D process is likely to be non-representative.³ For each NCE, annual cash flows are estimated over the drug's projected product life. Industry mean values are then constructed for this portfolio of NCEs and compared to mean R&D costs per NCE obtained from an analysis by DiMasi et al. (1991). The R&D costs include discovery costs common to all NCEs and the costs associated with R&D failures. From these estimated values, we compute after-tax IRRs and net present values for the industry's total portfolio of new drugs for the 1980-84 period.⁴

B. Cost of Capital

In our earlier study, we employed a 9% real cost of capital based on our own capital asset pricing model (CAPM) analysis of the cost-of-equity capital in the 1970s for pharmaceuticals. A more comprehensive study by Myers and Shyam-Sunder (1990) has recently been completed of the real cost of capital for the pharmaceutical industry during the 1980s. Their study was commissioned by the Office of Technology Assessment. They found that the real after-tax cost of capital on equity plus debt for the pharmaceutical industry, varied between 10 and 11% during the 1980s.

Relying on the findings from the Myers and Shyam-Sunder study, we use a 10.5% rate for the cost of capital for our sample of 1980-84 NCEs. However, it should be borne in mind that their cost of capital estimate is based on all the business activities of drug firms, while we are focusing here on investment in new prescription drugs. As Myers and Shyam-Sunder indicate in their analysis, investments in new drugs would be expected to have a higher cost of capital, *ceteris paribus*, than investment in less research-intensive businesses activities of pharmaceutical firms such as proprietary drugs, generic drugs, and basic chemicals.⁵ Hence, from this perspective, the 10.5% value estimated in their analysis is a conservative estimate of the cost of capital for investment in new drugs.

Our approach to the cost of capital may also be compared to that of the OTA (1993). They utilize a variable cost of capital (COC) over the investment period for new pharmaceuticals. In

particular, they employ a COC of 14% for the initial stages of the research process, which then steadily decreases to a COC of 10% for the later phases of development. They use a 9.8% COC on investments in plant and equipment and cash returns from market sales. By contrast, our COC of 10.5% is based on the average riskiness of drug industry investment over the whole product life cycle.

While a plausible theoretical case can be made that earlier-stage R&D is riskier and warrants a higher COC when a firm considers projects sequentially in the R&D decision-making process, (Myers and Shyam-Sunder, 1990), no empirical studies currently exist that allow one to quantify the structure of risks by R&D phase.⁶ Hence, we think it is preferable to employ a single benchmark COC value when evaluating returns on the representative NCE introduction from the industry's total portfolio of NCEs. In fact, our approach utilizes a lower COC than the blended rate implicit in the OTA analysis. This is discussed in Section III below.

C. R&D Costs

While we do not have R&D specific data for each of the NCEs in our sample, a major study of R&D costs for pharmaceuticals is now available. The study, by DiMasi et al (1991), is based on a representative survey of U.S. drug firms, and utilizes cost data on a random sample of 93 drugs first tested in humans between 1970 and 1982. These drugs had an average introduction date of 1984. The

DiMasi study also performed a cross check of the findings on R&D costs using publicly available aggregate industry data on R&D expenditures and NCE outputs.

Based on the data given in the DiMasi study, we were able to calculate the out-of-pocket R&D costs for a typical new drug introduction in each of the twelve years prior to marketing. It should be noted that these costs are the average costs per NCE, and that they include the costs of failures.⁷ Expressing these R&D costs in 1990 dollars and capitalizing them to the date of marketing at a real cost of capital of 10.5% gives \$280.5 million as the mean R&D investment cost per '80-'84 NCE introduction.

Because we compute cash flows on an after-tax basis, R&D costs should be after tax as well. R&D investments can be expensed for tax purposes. Based on empirical analysis of major U.S. pharmaceutical firms discussed further below, we use an effective tax rate of 33%. Hence, on an after-tax basis, the relevant R&D investment cost per '80-'84 NCE becomes \$187.9 million (i.e., 67% of \$280.5 million).

In addition to the R&D costs described above, R&D costs are undertaken by firms during the marketing period to modify and improve the particular NCE. These improvements include new indications, new product formulations, and new dosage levels of the originally approved NCE. All of these product changes require separate data submissions and approval by the FDA, usually in terms of a supplemental NDA. Since these product improvements can be thought of as spillovers from the original NCE introduction, it is

appropriate to incorporate them into both the R&D costs and sales revenues for NCEs.

Based on a separate analysis by DiMasi, we estimated out-of-pocket R&D costs per NCE for product improvements of \$31.8 million (before tax).⁸ We allocated these ongoing R&D costs equally over the first eight years of marketing. The discounted present value of R&D costs for product improvements are then equal to \$20.8 million (pre-tax) and \$14 million (after tax). Adding these costs to the ones for the originally approved NCE given above, yields a figure of \$201.9 million for total R&D costs on an after-tax basis. This is the number we compare with the present value of post-launch returns per NCE introduction.

D. U.S. Sales Revenues

The first step in estimating the returns stream of cash flows was to assemble data on the U.S. sales for each NCE. Annual drugstore and hospital sales were obtained from audit data sources (IMS America) for the period 1980 through 1991. This provided up to 12 years of actual sales data for the drugs in our sample.

The next task was to extrapolate future sales over the market life of each product. Twenty years was selected as the market life for the 1980-84 cohort. We utilized a standard life-cycle curve for prescription drug sales, in conjunction with information on the NCE's patent expiration date, to extrapolate sales over the assumed 20-year life.⁹ Most of the drugs in our sample have effective

patent lives between 9 and 13 years. Our extrapolation procedure is illustrated in Figure 1.

Sales data and projections are presented in Figure 1 for a particular product from the top sales decile. This product has 10 years of actual sales data and 13 years of patent protection. By year 10, this product was in the mature portion of its product life cycle. Using our representative life-cycle curve, the product is projected to have relatively stable sales to year 13. A significant decline in sales is then projected after year 13 due to generic competition and product obsolescence.

The estimated sales loss upon patent expiration for this and the other leading NCEs in our sample is derived from a recent study of generic competition in the period after the 1984 Waxman Hatch Act was passed (Grabowski and Vernon, 1992).¹⁰ Specifically, we were able to compile total sales on 14 NCEs from our previous study for four years after patent expiration. The average percentage declines in the first four years following patent expiration were 30%, 21%, 12% and 12%, respectively.¹¹ Thereafter a 10% decline is employed in our sales projections until the final four years of market life (where a 20% decline rate is utilized).¹²

In our prior work on the 1984 Waxman Hatch Act, we found that this law greatly facilitated generic entry and contributed to a much more rapid sales decline by brand name firms in the post-patent period. However, since patent expiration for most drugs in this study will not occur until the mid 1990s and beyond, the experience of past introductions provides only a rough benchmark

for future projections. Nevertheless, we think that the erosion of sales to generic competitors is likely to intensify in future periods. This is because the market is still adapting to the greater availability of generics. Furthermore, managed care programs, which are extensive users of generics, are growing rapidly over time (Ito, 1992). The potential effect on industry returns of faster sales erosion for future patent expirations is examined in terms of the sensitivity analysis.

Figure 2 shows the resulting U.S. sales profiles (in 1990 dollars) for the top two deciles (ranked by tenth-year sales) as well as for the mean and median drug. These curves exhibit a life-cycle pattern frequently observed in pharmaceuticals. In particular, sales increase rapidly in the years after market introduction, reach a peak in year 10 or 11, and then decline steadily over the remaining years of market life.

Figure 2 also illustrates the highly skewed distribution of sales which exists for new product introductions in the pharmaceutical industry. In this regard, peak sales of the top decile are several times that of the next ranked decile. Furthermore, mean sales are significantly greater than the median. This same pattern of skewness was observed in the sales of 1970-79 NCEs (Grabowski and Vernon, 1990, p. 811).

E. Global Sales

The revenues discussed so far refer to U.S. sales revenues only. As in the earlier study, we use a foreign sales "multiplier" to estimate global sales. Our baseline value for the ratio of

global sales to U.S. sales is 2.0. This multiplier was determined by examining domestic and worldwide sales in 1991 for the top 25 products in our sample of NCE introductions (the tenth-year sales of these products accounted for 90% of total tenth-year sales for our sample). As in our earlier work, we perform a sensitivity analysis to examine the impact of alternative values.

F. Pre-Tax Contribution Margins and Other Assumptions

To obtain cash flows from sales, sales are multiplied by the pre-tax "contribution" margin (i.e., pre-tax profits plus R&D costs as a percent of sales). In our 1990 study, we used margins derived from income statement data from the pharmaceutical divisions of several major health oriented firms. In that analysis we found that margins increased throughout the 1980s from about 33% in the late 1970s to just under 40% in the late 1980s. More recent data suggests that margins have increased moderately in the 1990s. Based on this analysis, we think that 40% is a reasonable mean value to use in the baseline case for 80-84 introductions.¹³ However, as for other important parameters, we examine alternative values in a sensitivity analysis.

We also followed the assumptions used in our 1990 study for promotional expenditures in the first three years of product launch (promotion equals sales in year 1, declines to 50% in year 2, and falls to 25% in year 3). Because of these heavy product launch expenditures in the first three years, contribution margins are less than 40% over this three-year period. However, as a product

matures, promotional and administrative costs decline, and margins increase over time. Our model is set up so that margins average 40% over the full product life cycle.¹⁴

We estimated capital expenditures for plant and equipment to be equal to 40% of tenth year sales.¹⁵ Half of these outlays were assumed to occur in the first two years before marketing and the other half during the first 10 years after marketing. For working capital, it was assumed that accounts receivable represent 1.3 months of annual sales and inventories are 5 months of sales (valued at manufacturing cost). Working capital is recovered at the end of the final year of product life.

G. Tax Rates

An analysis of income tax data on eight major pharmaceutical firms yielded an average effective rate of 35% during the 1970s (1970-1981). The average effective tax rate for these same firms was 32% during the 1980s (1981-91). Looking forward in time, it is reasonable to expect that effective tax rates for pharmaceutical firms in the 1990s will be at least equal to those of the 1980s.

Average effective rates in pharmaceuticals have been below the statutory corporate tax rate historically because of various tax credits and deferrals.¹⁶ The difference between the average and statutory rates was particularly large in the 1970s and early 1980s. (The corporate tax rate was 46% over this period while the average effective rate was in the mid-30s.) The 1986 Tax Reform Act lowered the statutory corporate rate from 46 to 34%, but it

also curtailed the ability of firms to utilize particular credits. As a consequence, the gap between effective and statutory rates for pharmaceutical firms has narrowed considerably since 1986.¹⁷ The 1993 Budget Reconciliation Act is likely to contribute to a further convergence in these rates.¹⁸

Based on our empirical analysis of average effective rates in the pharmaceutical industry, a 33% tax rate is utilized as a representative baseline tax rate for our analysis of 1980-84 NCE introductions. (This is the mean average tax rate over the 1971-91 period.) As in the case of other parameters, this rate is subjected to a sensitivity analysis.

H. Cash Flow

Cash flow in each year is equal to after-tax profits plus depreciation charges. It should be noted that after-tax cash flows are affected by differences in book and tax depreciation. In particular, book depreciation is based on the straight-line accounting method, while tax depreciation is based on an accelerated schedule, as specified in the U.S. tax code. Accelerated depreciation for tax purposes results in deferred taxes and positive cash flow in the early years of market life in our model, which then reverses in later years.

II. Empirical Findings

A. Mean Industry Performance

Using the above data and assumptions, the representative NCE for the 1980-84 period has the pattern of cash flows over the life cycle shown in Figure 3. In particular, there are 12 years of investment in R&D and capital investment in which cash flows are negative in value. Product introduction occurs in year 1. Cash flows are negative in the first few years of market life due to the heavy launch expenditures in this period. After turning positive in year three, cash flows grow rapidly to a maximum in year 11 (the year in which sales revenues peak). They then decline in value until the final year of market life, year 20.¹⁹

The internal rate of return for the baseline case shown in Figure 3 is 11.1%. This can be compared directly with our real cost-of-capital estimate of 10.5% for investment in pharmaceutical industry activities. While these results indicate positive economic returns to investment in new drug R&D, profitability is much less than what might be inferred from a naive comparison of aggregate accounting returns data.

The first row of Table 1 further shows that the capitalized value of R&D investment costs in the baseline case is 201.9 million dollars. The discounted value of post-launch returns emanating from this R&D investment is 224.1 million dollars. Hence, the NPV for the representative 1980-84 NCE introduction is 22.2 million in 1990 dollars.

To put this result in perspective, in our 1990 paper, we reported the analysis of the returns to NCEs introduced in the United States in 1970-79. This analysis employed the same sample selection criteria. Our focus was on the mean returns for this entire period (the IRR averaged a little over 9%), but we did some analysis of the two sub-periods 1970-74 and 1975-79. We found that the NPV and mean IRR in the later sub-period were significantly greater than those for the earlier one. In particular, the IRR was estimated to be 10.0% for the 1975-79 period, compared to 7.1% in the 1970-74 period.

Our findings for the 1980-84 cohort of NCEs suggest that the IRR has increased moderately over the 1975-79 period (11.1% versus 10.0%), but the NPV in the two periods remains essentially unchanged in value (both are approximately 20 million in 1990 dollars). (This latter result reflects a somewhat higher cost of capital for the 1980s compared to the 1970s.) Thus, the major upward shift in observed pharmaceutical returns that occurred in the later 1970s has continued into the 1980s.

As we noted in our earlier work, the latter half of the 1970s corresponded to the first introduction of several commercially important new drug therapies, based on the innovative principles of rational drug design. Breakthrough drugs like Tagamet (an anti-ulcer compound introduced in 1977) were not only large commercial successes, but also created a new period of optimism about technological opportunities and the ability of firms to exploit accumulating knowledge emerging from basic biomedical research.

The 1980s also witnessed a significant change in the domestic economic environment with rising domestic drug prices and profit margins. All of these developments contributed to the upward shift in the IRR that was first observed for the 1975-79 cohort of NCEs and which has been maintained for the 1980-84 cohort.

Our findings do indicate a moderately lower NPV for 1980s NCEs than that found by the OTA in their recent work (22 million versus 36 million dollars). However, they utilize a shorter interval for their NCE sample period (1981-83) and also make some different assumptions. The findings of the two studies are compared in Section III below.

B. Sensitivity Analysis

Of course, there is uncertainty about certain parameters. For this reason we also show in Table 1 how the NPV and IRR performance measures vary with these parameters. For example, changing the contribution margin from 35% to 45% causes significant changes in the IRR--the IRR varies from 10.1% to 11.9%. As discussed above, average profit margins have been in the neighborhood of 40% in the late 1980s. The relevant issue then is whether changes in real drug price or costs will occur throughout the 1990s--leading to significantly different margin values over future periods. The movement toward managed care would suggest more price discounting and lower margins in the 1990s. But this could be offset, at least in part, by lower marketing and distribution costs in this new environment.

The alternative values selected for the next two parameters in Table 1--the international multiplier and the tax rate--cause the IRRs to vary only moderately from the baseline case. At the present time, however, cost containment efforts toward pharmaceuticals appear to be intensifying in several European countries (Burstall, 1991; Munnich, 1993; Mattison, 1993).²⁰ A more detailed model of the international sector is probably appropriate. It might be feasible in future work, for example, to allow for different sales profiles and margins in foreign and domestic markets, if such data can be obtained.

The next issue considered is post-patent sales losses. Our baseline case embodies assumptions on the sales erosion of pioneer brands consistent with what we observed in the first several years after the 1984 Hatch-Waxman Act was passed. However, as noted above, most of the drugs in our sample face patent expiration in the mid 1990s and beyond where there is the prospect of increasing generic competition.

In order to test the sensitivity of our results to increased generic competition, some alternative scenarios were examined. In these scenarios, pioneer sales losses after patent expiration are 25% and 50% lower than what was assumed in the baseline case. The effect of these changes is shown in Figure 4. Under the 25% greater decline in post-patent sales the NPV drops from 22 million to 13 million dollars in value. In the 50% decline case, NPV is only 3.4 million dollars, just barely above break-even value. These changes are illustrative of the fact that evolving

developments in the health care system could have a material effect on the returns to new drug introductions.

The next set of sensitivity analyses in Table 1 shows the change in NPVs associated with a change in the cost of capital. This is a parameter which can have a substantial effect on net returns. A 10% cost of capital would result in a net present value of over 40 million, while an 11% cost of capital would cause the NPV to be approximately break even in value. We noted above that Myers and Shyam-Sunder's cost-of-capital estimates are based on all pharmaceutical firm activities, while we are focusing here on investments for prescription drugs. Given this fact, a 10.5% cost of capital for pharmaceutical activities is probably on the conservative side.

The final sensitivity analysis in Table 2 analyzes the effect on NPVs of changes in regulatory review time. This is an interesting issue to consider, given the recent passage of a user fee on new drug applications (HR 6181). The user fee is to be dedicated to hiring additional FDA reviewers with the objective of speeding up the review process. Currently the average new drug takes two and one-half years to obtain regulatory approval. The goal of the FDA under the new user fee scheme is to reduce this by at least one year.

The results in Table 2 indicate that NPVs are sensitive to regulatory review time. In particular, a one-year shortening in review time would have permitted the average NCE in our sample to increase its NPV from 22 to 40 million dollars.²¹ The user fee on

a new drug application is only a small fraction of this amount. However, the schedule of user fees includes charges for supplemental NCEs as well as annual fees for all registered products and manufacturing facilities).²² An analysis of the private and social benefits of drug user fees is an interesting issue for further research. The sensitivity analysis presented in Table 2 suggests that if user fees are indeed successful in substantially shortening review times, this could have significant incentive effects for pharmaceutical R&D.

C. Distribution of Returns

In Figure 5, the decile distribution of present values of post-launch returns for our sample of 1980-84 NCEs is presented. These are exclusive of R&D costs. Clearly, this is a highly skewed distribution. The top decile has an estimated present value of \$1 billion. This is more than five times the present value of average R&D costs (\$202 million). Note also, however, that only the top three deciles exceed the average R&D cost. The fourth decile at \$177 million is significantly below average R&D costs.²³

A very skewed distribution was also observed in the case of 1970s NCE introductions. In both that analysis and the current one, the top two deciles accounted for a dominant share (over 70%) of the total present value generated by these NCEs. In our prior analysis of NCEs for the entire decade of the 1970s, it was also true that only the top three deciles had present values in excess of average R&D costs.

The importance of top-ranked drugs to drug industry performance can be further illustrated by excluding Zantac, the top-ranked compound in our sample, in order to see how average present values are changed. Zantac, an anti-ulcer drug, was introduced in 1983 and has since achieved worldwide sales in excess of 3 billion dollars. If we exclude this one "blockbuster" compound from the sample, the average present value of post-launch returns declines by 33 million dollars, and the average NPV for the remaining 66 compounds is estimated to be -\$10.6 million. Hence, if the top-ranked compound for the 1980-84 cohort of drugs was never introduced, the representative drug would fail to achieve break-even status.

It is important to note that while the majority of the 67 NCEs have present values substantially below the fully allocated average R&D cost, it is still true that many of these "unprofitable" drugs do contribute to firms' profits. That is, in many cases an "unprofitable" drug more than covers its own incremental development and capital costs. However, as discussed above, the average R&D cost also includes an allocation for drugs that drop out along the development path and are never marketed. The R&D costs of these unsuccessful drug candidates, as well as common discovery costs, must be covered from the sales of successfully marketed drugs. Hence, with such a skewed distribution, it is critical that a firm have an occasional big winner or drug in the top few deciles, if it is to cover all costs of R&D over the long run.

III. Comparison with OTA Report

In early 1993, the OTA published an analysis of returns on R&D to 1981-83 NCEs. Their principal finding was that the average NCE had an NPV of 36 million dollars (in 1990 dollars). This may be compared to the 22 million dollar average NPV for our sample. The OTA did not compute IRRs since they used a variable cost of capital over the R&D investment period.

Some general observations may be made about these results. First, the differences in the two studies are not that large if one considers the average pre-tax R&D investment for the typical NCE is in the neighborhood of 300 million dollars. Second, the findings of both studies are at odds with claims that there are large excessive returns in pharmaceuticals, an inference frequently made from simple accounting rate comparisons across industries. In particular, our work implies that realized returns are within one percentage point of the industry's cost of capital, and this result is implicit in the OTA's findings as well. (Increasing their various costs of capital by one percentage point each, the OTA's NPV becomes -6 million dollars.)

Table 2 provides a comparison of the main assumptions employed in the two studies. There are a number of dimensions in which the two studies are the same, but there are also significant differences. With respect to the R&D cost values, both studies rely on the estimated values from the DiMasi et al. study. Both studies also rely on the same audit data source to generate sales over the first half of sales life cycle. However, OTA uses a

smaller sample (1981-83 NCEs) and a more aggregative approach for projecting future sales values.

Figure 6 shows a plot of OTA's global sales revenue curve compared to the one utilized in our analysis. Despite some differences in sample selection procedures, the sales values are quite close for the first nine years.²⁴ These initial years are based on audit data in the two studies. However, our sales curve peaks later (year 11), and our sales values significantly exceed the OTA's in years 10 through 13. This results from the more disaggregate approach utilized in our analysis where each NCE's patent life and life cycle is separately considered.²⁵

It is clear that the higher NPV for OTA's baseline case does not result from the basic input values on R&D costs or sales values. The R&D costs values used in the two studies are the same, and our sales values yield higher rather than lower NPVs. Similarly, the average contribution margins used in the two studies are close in value, and this is not a significant factor in explaining the higher NPV of the OTA study.

In looking at the other assumptions presented in Table 2, we see that the two studies utilize quite different approaches with respect to the cost of capital and tax rates. Specifically, OTA uses very different values for these two parameters in its treatment of R&D investment and post-launch returns. This asymmetry plays an important role in understanding the differences in the two studies.

To demonstrate that the assumptions on the COC and effective tax rates were a major source of the different findings in the two studies, we performed the following experiment. We substituted the OTA's assumptions on the COC and tax rates into our model while holding all other factors the same as in our baseline model.²⁶ We found that the NPV in this modified baseline case increased to \$40 million (when both parameters were changed) and to \$57 million (when only the effective tax rate parameter was changed).

Hence, the higher estimated baseline NPV for the OTA study can be largely explained in terms of these parameters.²⁷ Moreover, the single most important factor leading to a higher NPV in the OTA analysis is the large differential in tax rates utilized for R&D versus post-launch returns.²⁸ In particular, OTA's tax rate on revenues--32%--is based on an analysis of average effective taxes for drug firms during the 1980s, while their rate on R&D costs is the statutory corporate tax rate--46%--during the 1970s. Although statutory corporate rates changed significantly in 1986, the effective tax rates for drug firms have not changed greatly over the past two decades (Section I-G).

We believe one must be consistent in the tax rate concept employed on both sides of the investment equation and that effective rates are analytically more appropriate in this situation than statutory ones. In point of fact, the principal tax benefits enjoyed by research-intensive multinational drug firms--foreign-source income deferrals²⁹ and the possession tax credit³⁰--reduce the effective tax rate on both R&D costs and revenues. Given that this

is so, we think the most reasonable tax rate parameter to use in our model is the average effective rate for pharmaceuticals during the period under study.³¹

In any case, while there are important differences in the assumptions of two studies, the resulting differential in baseline NPVs is not large. Furthermore, the findings can be generally reconciled in terms of the assumptions about the corporate tax rate and cost of capital, which work in offsetting ways. The reconciliation of these two independent studies lends strong support, in our view, to the general results presented here.

IV. Summary and Conclusions

The estimated mean return on pharmaceutical industry NCE introductions for the first half of the 1980s was 11.1%. This may be compared with the estimated (real) cost of capital of 10.5% over the same period. This corresponds to an NPV of 22 million dollars in 1990 dollars. As in our earlier work, the distribution of present values on post-launch returns for new drug introductions is highly skewed, with the top few deciles accounting for a very large share of total present values. Furthermore, only three of ten drugs had present values for post-launch returns in excess of average R&D costs.

We performed an extensive sensitivity analysis of our main results. We found that our results are generally robust to plausible changes in the baseline values. This analysis also can be used to gain insights into the potential effects of several

evolving policy developments, such as cost containment programs and user fee requirements. Our analysis suggests that returns on NCE introductions are especially sensitive to government policies influencing R&D times and the margins realized on new drug sales.

Our work is also compared with a recent study by OTA. Although there are some important differences in assumptions, both studies find modest positive returns to the average NCE introduction of the early 1980s. In each case, realized returns are within one percentage point of the cost of capital.

Our findings do not provide general support for the assertion frequently made by policymakers on the basis of accounting data, that returns on pharmaceutical R&D are large and persistent compared to the financial risks involved. It is true that the returns distribution in pharmaceuticals is highly skewed, and that top-ranked decile drugs have earned very large returns. It does not follow, however, that this group of drugs should be subjected to price controls or profit constraints. Our analysis indicates that expected returns are highly sensitive to the performance of the top decile drugs. Imposing constraints on this class of drugs would significantly lower the average expected returns on future NCE introductions, and especially, make R&D on high-risk, high-return compounds subject to greater uncertainty.

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Footnotes

*We would like to especially thank Judy Wagner of the Office of Technology Assessment for making available the work sheets from their analysis of the returns to R&D for 1981-83 NCEs. This allowed us to make comparisons with our analysis as discussed in Section III of the paper.

¹Baber and Kang (1991) in a recent paper have shown how the internal rate of return can be derived from an accounting approach (i.e., the cash flow recovery return) under very special assumptions. They have applied this approach to the pharmaceutical industry. However, it remains to be seen how sensitive their findings are to the special assumptions that are employed. In addition, in contrast to our approach based on individual innovations, their analysis uses aggregate corporate-level data which includes non-pharmaceutical businesses.

²Congressman Waxman's comments, however, contained major distortions in the OTA findings on drug industry profitability. In particular, he asserted that the OTA study implied there is two billion dollars in excess drug industry profits (New York Times, Feb. 26, 1993, P. C1). However, this two billion dollar figure is based on an extrapolation of OTA's small estimated surplus for 1981-83 NCEs to the full universe of pharmaceutical sales revenues (including those of older NCEs, generic drugs, etc.). By contrast, the OTA report emphasizes the fact that "dollar returns on R&D are

highly volatile over time," and hence its findings are applicable only to the period and NCEs investigated in the study.

³In particular, we omit new drugs in the cancer area because they were typically developed jointly with NIH. In addition, we excluded two drug approvals for schistosomiasis, one for malaria and one for tapeworm because these drugs are also likely to have non-representative R&D costs. Similarly, drugs discovered by universities and non-profit institutions are excluded because the R&D costs of these compounds may not be representative of drugs originating in industry. The group of excluded drugs have significantly smaller mean sales than the 67 NCEs in our sample.

⁴Because of the length of the innovative process in pharmaceuticals--12 years of R&D and clinical testing and then 20 years or so of market life--there is always a judgment call as to the most current vintage of NCEs that one can meaningfully evaluate. The 1980-84 vintage, for example, permits 12 years of actual sales data for the NCEs introduced in 1980 and fewer years for the 1981-84 vintages. Sales data for remaining years of commercial life must be forecast. NCEs introduced after 1984 would require significantly more forecasting of sales data than we believe to be feasible.

⁵A recent analysis by Conroy, Harris and Massaro (1992) finds support for this hypothesis in terms of a multiple regression analysis of shareholder risk. Specifically, they find the beta

coefficient measure of equity risk commonly derived from the CAPM is positively and significantly related to a firm's research intensity. Their work is based on an analysis of a sample of firms from four industries including pharmaceuticals.

⁶OTA uses CAPM stock market analyses of biotechnology firms as a rough way to gauge the riskiness of discovery research in pharmaceuticals. They also assume a linear decline in the cost of capital over later stages of the R&D process. The riskiness of pharmaceutical R&D by phase is currently being studied by Professor Myers and his colleagues at MIT.

⁷The uncapitalized R&D outlays expressed in 1990 dollars (millions) from year t-11 to year 0 (market introduction is year 1) are 16.5, 20.9, 20.9, 17.8, 8.1, 8.1, 9.6, 10.9, 8.2, 7.5, 0, 0.

⁸The R&D cost data collected as part of DiMasi et al. study allows one to make a rough estimate of average R&D for product improvements. In particular, data were supplied on the annual aggregate R&D expenditures for both NCEs and for product improvements by the 12 firms in the participating survey. Using this information, and allowing for an average lag of 10 years between R&D expenditures on existing products and NCEs, it was estimated that out-of-pocket R&D expenditures for existing products were 24.9% of those incurred for NCEs. Applying this percentage to our estimate of out-of-pocket expenditures per approved self-originated NCE yields 31.8 million in 1990 dollars as the cost per

approved NCE for ongoing R&D (DiMasi, private correspondence, 1992).

⁹The standard product life cycle utilized in this analysis is based on the representative sales pattern for past NCE introductions (Grabowski and Vernon, 1990). In our prior analysis, we employed a market life of 25 years. Since the rate of sales decline after patent expiration is expected to be significantly greater for 1980s NCEs compared to 1970s NCEs, we felt that a 20 year life was a more plausible assumption in the present analysis. Given the fact that any returns realized after year 20 are heavily discounted in present value terms, the results for the baseline case are not very sensitive to whether a 20- or 25-year market life is assumed.

¹⁰The actual patent lives for the 30 largest selling NCEs were obtained in order to incorporate the impact of generic competition at patent expiration using the approach outlined above. This sample of products corresponds well with those used in our 1992 analysis of generic competition (discussed below). We neglected generic competition for the smaller selling NCEs because they are unimportant empirically and also because it is uncertain whether generic competitors will emerge for these less profitable drugs.

¹¹In contrast to the approach used in our published study of the 1984 Act (Grabowski and Vernon, 1992), the sales erosion rates used for this study are based on total prescription drug sales

(rather than the most frequently prescribed dosage size) and are computed from the year of patent expiration (rather than the date of first generic entry).

¹²Using our prior study of returns to 1970s NCEs as a guide, the amount of error introduced into the current present value analysis from extrapolated sales values should be minimal (Grabowski and Vernon, 1990). This is because we have actual sales data for most compounds through their peak sales period, and the last segment of the sales life cycle for major products is subject to intensive competition from both new drug introductions and generics. In addition, sales and cash flow after year 10 are heavily discounted in present-value terms.

¹³This margin value is net of depreciation charges. As discussed in Section G, depreciation charges are added to after-tax profits in each period to obtain cash flows in the post-launch period.

¹⁴Specifically, we employed above-average margins in years 11 through 20 of market life. This is the mature phase of the life cycle. Promotional and administrative costs are much lower in this phase of the life cycle, contributing to higher than average margins. In addition, we found in our generic pricing study that drug firms facing generic competition tend to increase or maintain price on older drugs while unit sales decline, in accordance with a segmented market model (Grabowski and Vernon, 1992). However,

with the growth of managed competition, price discounting of older drugs is now becoming prevalent. This could constrain the margins realized on older drugs in future periods.

¹⁵This value is based on analysis of the incremental change in gross fixed assets to the incremental change in sales for a sample of pharmaceutical firms over the relevant period. Our prior work on 1970s NCE introductions used a larger ratio of capital expenditures to tenth-year sales (50%). The lower value for 1980 NCEs, which emerged from our analysis of aggregate balance sheet data, is consistent with the significant increase in average sales per unit of output of 1980 NCEs compared to 1970 NCEs.

¹⁶These include the fact that pharmaceutical firms have extensive sales and manufacturing operations outside the United States. This has allowed these firms to obtain tax deferrals and credits which have lowered their average effective corporate income tax rate.

¹⁷Since 1987, the differences in the average effective rate and the statutory rates for our sample has been less than 5%, while it was over 10% in the period 1970-85.

¹⁸OBRA 93 significantly reduces the possession or Section 936 tax credit. This is a provision of the tax code that has been extensively utilized by pharmaceutical firms with manufacturing plans in Puerto Rico (GAO, 1992). While firms continue to calculate this tax credit as before, they are now subject to one of

two alternative limitations. The first alternative limits the credit to a percentage of employee compensation and depreciation deductions in Puerto Rico. The second alternative limits the amount of credit on a fixed percentage basis over time (60% of prior benefits in 1994 down to 40% by 1998). An analysis of this new tax provision by Arthur Andersen (1993) indicates that pharmaceutical firms are expected to elect the second option.

¹⁹Not shown in the figure is the recovery of working capital that occurs at the beginning of year 21. In present value terms, the working capital recovery amounts to only \$2.3 million.

²⁰The most drastic changes have occurred in Germany. This country now reimburses pharmaceuticals based on a system of reference prices with drugs grouped by common therapeutic classes. In addition, beginning in January 1993 Germany also implemented global budget caps on pharmaceutical expenditures. Furthermore, if overruns occur in the budget for pharmaceuticals, physicians' incomes are partially at risk for funding the shortfall. This has caused some marked changes in physician prescribing behavior with significant declines in total pharmaceutical expenditures (Munnich, 1993).

²¹In this analysis, we only consider the effect of shorter review times on the capitalized value of R&D costs. We abstract from any benefits in terms of additional revenues from increased effective patent lives. With the passage of the 1984 Hatch-Waxman

Act, most drugs are eligible for compensatory increases in effective patent life equal to time lost in regulatory review (Grabowski and Vernon, 1992). Hence, only for those drugs for which patent restoration is constrained under the Act would there be an increase in patent life from reductions in regulatory review time. We abstract from an analysis of any benefits of this kind in the present study.

²²Congress authorized user fees on pharmaceuticals in October 1992 (HR 6181). This act mandates a \$100,000 NCE application fee in the 1993 fiscal year, rising to \$233,000 in five years. Supplemental NCE applications for new indications, dosage forms, etc. cost \$50,000 each, with a similar rise in fees over time. In addition, there is an annual fee for each currently registered product (\$6,000 initially) and on each manufacturing plant (\$60,000 initially). The legislation stipulates that these fees shall only be collected and available for increases in resources allocated for the review of human drug applications. The FDA must report annually to Congress on how it utilizes the fees and on its progress in achieving time approval goals. (It may be noted that in early 1993, OMB proposed a big increase in FDA user fees to replace existing budgetary appropriations for the FDA, but this was not accepted by Congress.)

²³We do not have R&D costs by each drug in our sample so it is possible that these costs are also correlated with sales. The analysis of average R&D costs by DiMasi does indicate significant

variance in development costs across drugs, but there is no evidence of the extreme skewness that is observed here for both NCE sales and post-launch returns. Furthermore, it is not clear how R&D costs vary with NCE sales. In this regard, both our analysis and that of the OTA's indicate that top-selling 1980s NCEs had longer than average effective patent life, which is indicative of shorter development periods. *Ceteris paribus*, this would cause R&D costs to be negatively correlated with sales performance. However, if firms can anticipate which products are likely to be important commercially, they have incentive to increase out-of-pocket R&D costs in order to accelerate development (i.e., through parallel clinical trials, etc.). It is not obvious how these different forces balance out. This is an important issue for further empirical research.

²⁴The use of a shorter sample period by the OTA results in higher average sales per NCE. In particular, our analysis indicates the sales of the mean NCE sample in years 1980 and 1984 are less than those in each of the years 1981 through 1983. Hence, the sample time period chosen by the OTA causes their sales to be significantly higher than in our analysis. However, this effect is essentially offset by another difference in the sample selection process. Specifically, we exclude all compounds discovered in the universities and government laboratories, and those in certain therapeutic categories like cancer. (We exclude these NCEs because they could have different R&D costs. See footnote 3.) OTA

includes these NCEs which tend to have smaller sales than the sample mean.

²⁵The OTA uses the mean patent life (9 years) to establish their sales curve peak. However the largest selling drugs typically have longer effective patent lives than the average NCE. Hence, on a sales-weighted basis, the average effective patent life is longer than 9 years. In addition, some commercially important drugs have been successful in extending patent life through product line extensions. The OTA attempts to capture the latter phenomenon strictly through a slower average rate of sales erosion after patent expiration. By contrast, we incorporate new patent life information for those products with major product line extensions. As a consequence of these factors, our sales curve peaks later and exceeds the OTA's in years 10 through 13.

²⁶The OTA compounds R&D costs on a monthly basis and post-launch returns on an annual basis, while we utilize annual compounding for both series. In the experiments discussed above, we also adopt the OTA conventions on compounding in conjunction with its variable cost of capital and effective tax rates.

²⁷Other differences between the two studies include the sales life cycle curve (discussed above) as well as differences in the level and timing of the capital investment and promotional expenditures. However, these tend to work in offsetting ways. On balance, they have a small effect on the difference in NPVs.

²⁸The importance of OTA's assumptions on taxes is also illustrated by the fact that the mean NCE in their analysis has a negative pre-tax NPV of -18 million dollars, compared to a positive after-tax NPV of 36 million dollars.

²⁹Multinational firms are taxed under the U.S. code on the basis of their worldwide income. However, income from foreign sources with lower tax rates can result in a tax benefit to U.S. firms, at least until this income is repatriated. But R&D performed in foreign countries with low corporate income taxes (like Switzerland) must be offset against foreign income. More importantly, under a 1977 Treasury Department Regulation (Section 1.861-8) a portion of a multinational's domestic R&D expenditure must be allocated to its foreign revenues. This regulation was suspended in 1981 by Congress and then reinstated on a less onerous basis after 1986. Hines (1993) provides a good discussion of the changes in this regulation over time and an analysis of their impact on multinational firm R&D behavior.

³⁰As discussed earlier, the possessions tax credit has been utilized by pharmaceutical firms to shelter income associated with their Puerto Rican manufacturing subsidiaries. But under rules devised by Congress in 1982, a fraction of the parent firm's worldwide R&D must be allocated to the income sheltered in Puerto Rico under both the cost-sharing and income splitting options (U.S. Joint Committee on Taxation, 1982; pp. 79-96). Prior to that time, some pharmaceutical firms had transferred the patent rights

emerging from their worldwide R&D to their Puerto Rican manufacturing subsidiary at little or no cost in order to increase the sheltered income on products produced there. But these practices were challenged by the IRS and subjected to subsequent tax liabilities by the U.S. tax court (e.g., Eli Lilly and Co. vs. Comr., 84 T.C. 996, 1985; G. D. Searle & Co. vs. Comr., 88 T.C. 252, 1987).

³¹Furthermore, even if the OTA's approach could be justified in part on the basis of a historical analysis, it provides little insight for prospective policy questions. The statutory corporate tax rate is now 35%, and there has been a convergence in effective and statutory tax rates since 1987 (footnote 17). Hence, OTA's assumption of a large difference in tax rates for R&D and revenues is clearly not applicable to current and future NCE introductions.

Table 1

Returns to 1980-84 NCEs

Case	Present Value Cash Flows (after tax)	Present Value R&D Costs (after tax)	NPV	IRR
Baseline	224.1	201.9	22.2	11.1
at 35% margin	187.6	201.9	(14.3)	10.1
at 45% margin	260.6	201.9	58.8	11.9
at 1.9 international multiplier	212.9	201.9	11.0	10.8
at 2.1 international multiplier	235.3	201.9	33.4	11.3
at .25 tax rate	257.1	226.0	31.2	11.2
at .40 tax rate	195.2	180.8	14.4	10.9
at 25% greater sales decline after patent life	214.7	201.9	12.8	10.8
at 50% greater sales decline after patent life	205.2	201.9	3.4	10.6
at 10% cost of capital	238.2	195.3	42.9	----
at 11% cost of capital	210.7	208.7	2.1	----
at 1-year reduction in regulatory review time	224.1	184.0	40.1	11.6

NOTE: Baseline case assumes 10.5% cost of capital, international multiplier of 2.0, tax rate of 0.33, and margin of 0.40.

Table 2		
Comparison of Our Assumptions with OTA's Analysis		
	<u>OTA</u>	<u>G&V</u>
<u>Sample</u>	1981-83 NCEs	1980-84 NCEs
<u>R&D Investment</u>	Based on DiMasi et al.	Based on DiMasi et al.
<u>Cost of Capital</u>		
R&D Investment	10-14%	10.5%
Returns	9.8%	
<u>Tax Rate</u>		
R&D Investment	46%	33%
Returns	32%	
<u>Sales Life Cycles</u>		
Patent Exclusivity	9 years	NCE Specific
Sales Loss after Patent Expiration (Initial 3 years)	18%; 8.5%; 6.0%	30%; 21%; 12%
Product Life	20 years	20 years
<u>Global Sales Multiplier</u>	2.0	2.0
<u>Contribution Margin</u>	40.8% (plus adjustment for depreciation)	40% (plus adjustment for depreciation)
<u>Capital Expenditures</u>	25 million	40% of tenth-year sales

Figure 1

Historical/Projected U.S. Sales—Product A

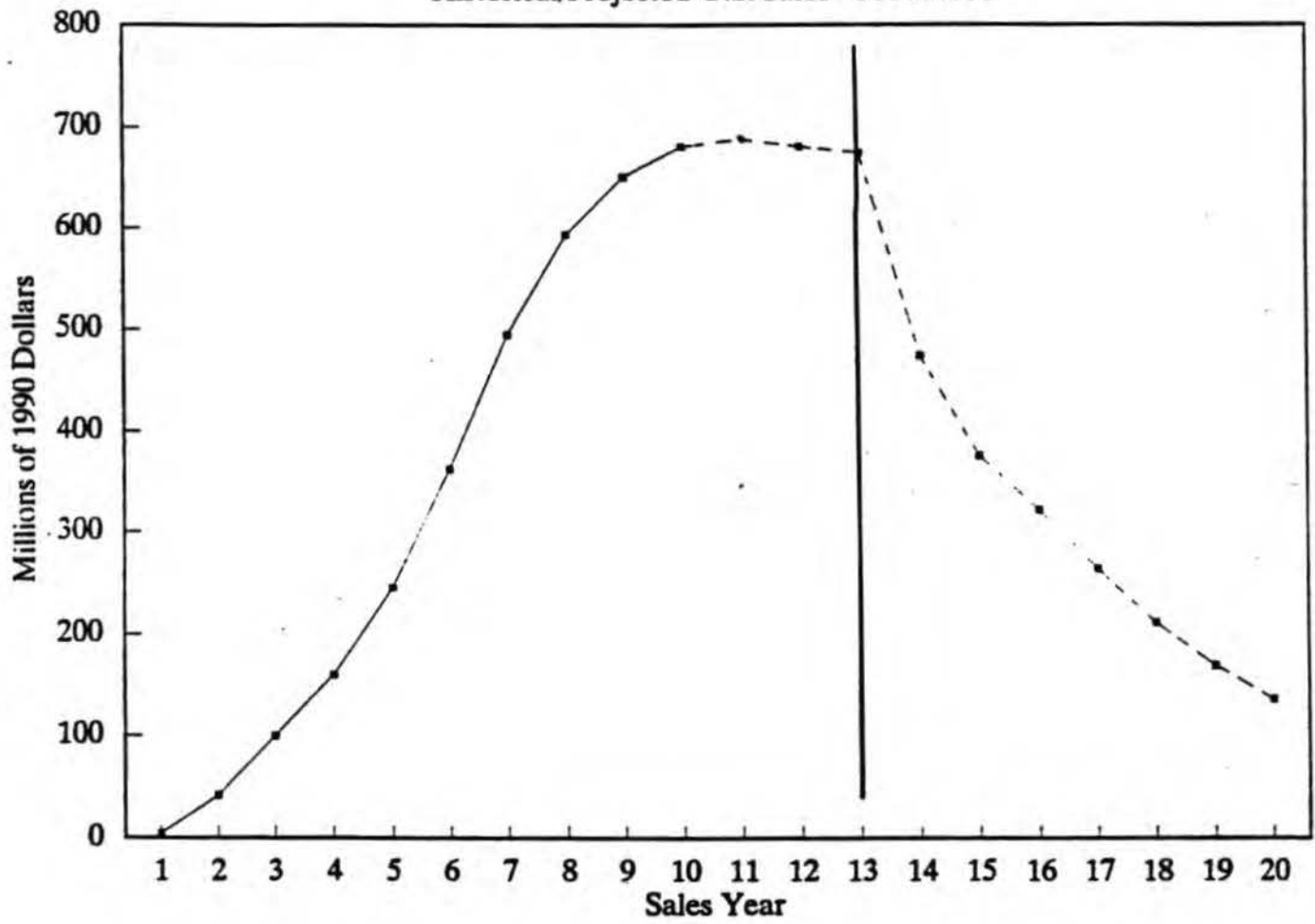


Figure 2

U.S. Sales Profiles of 1980-84 NCEs

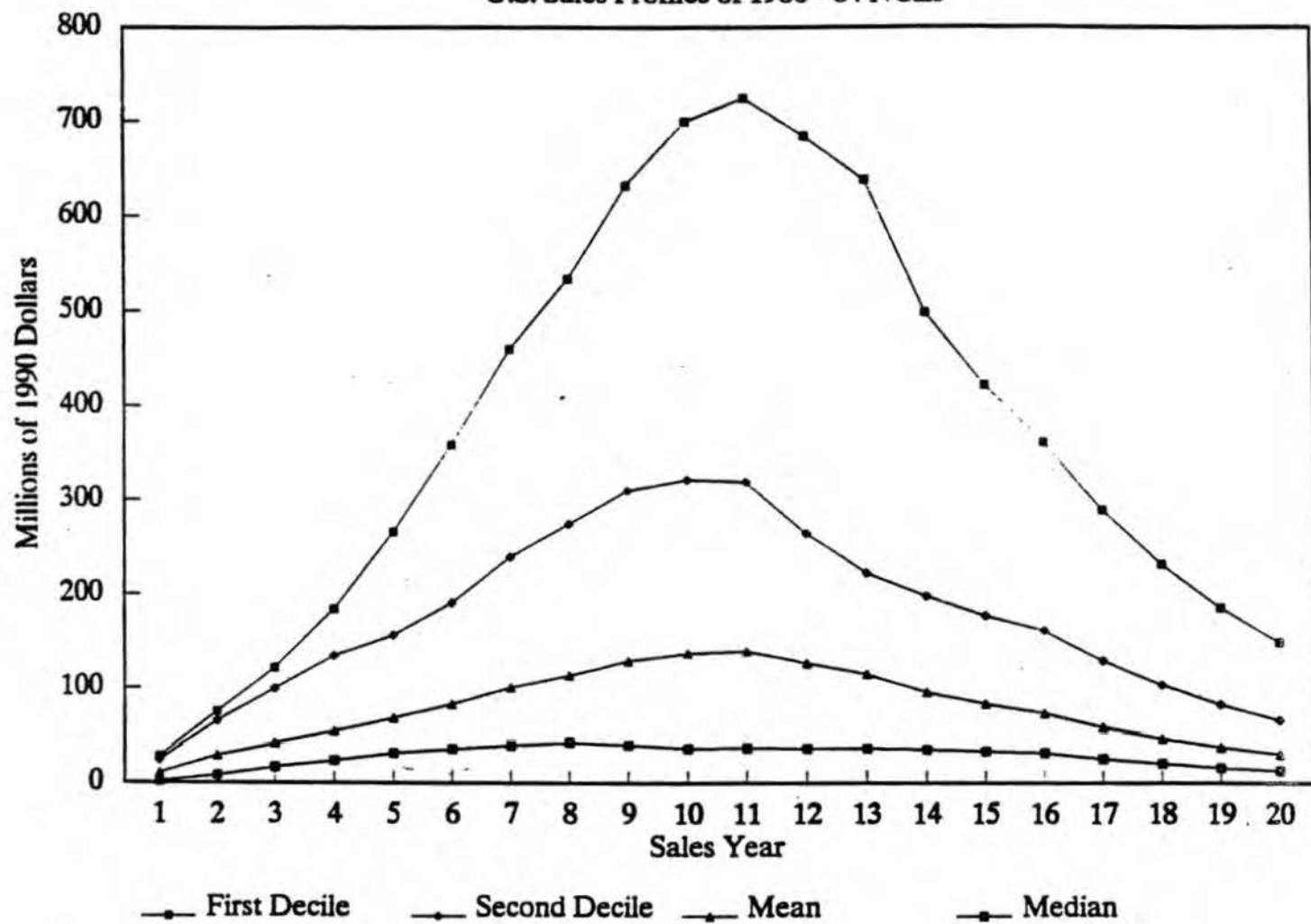


Figure 3

Total Cash Flows for Mean 1980-84 NCE

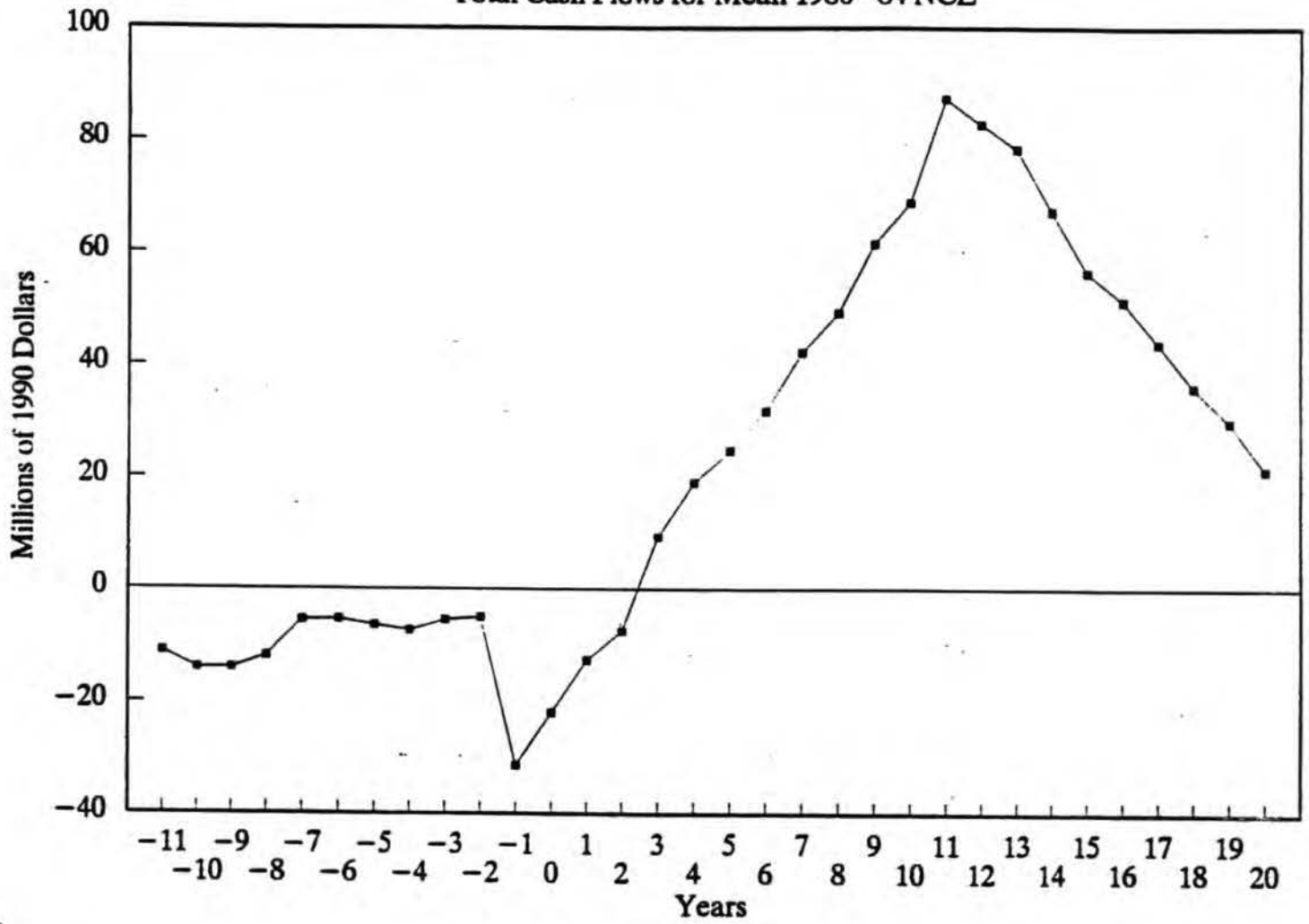


Figure 4

Base U.S. Sales vs. Two Greater Erosion Profiles Post-Patent

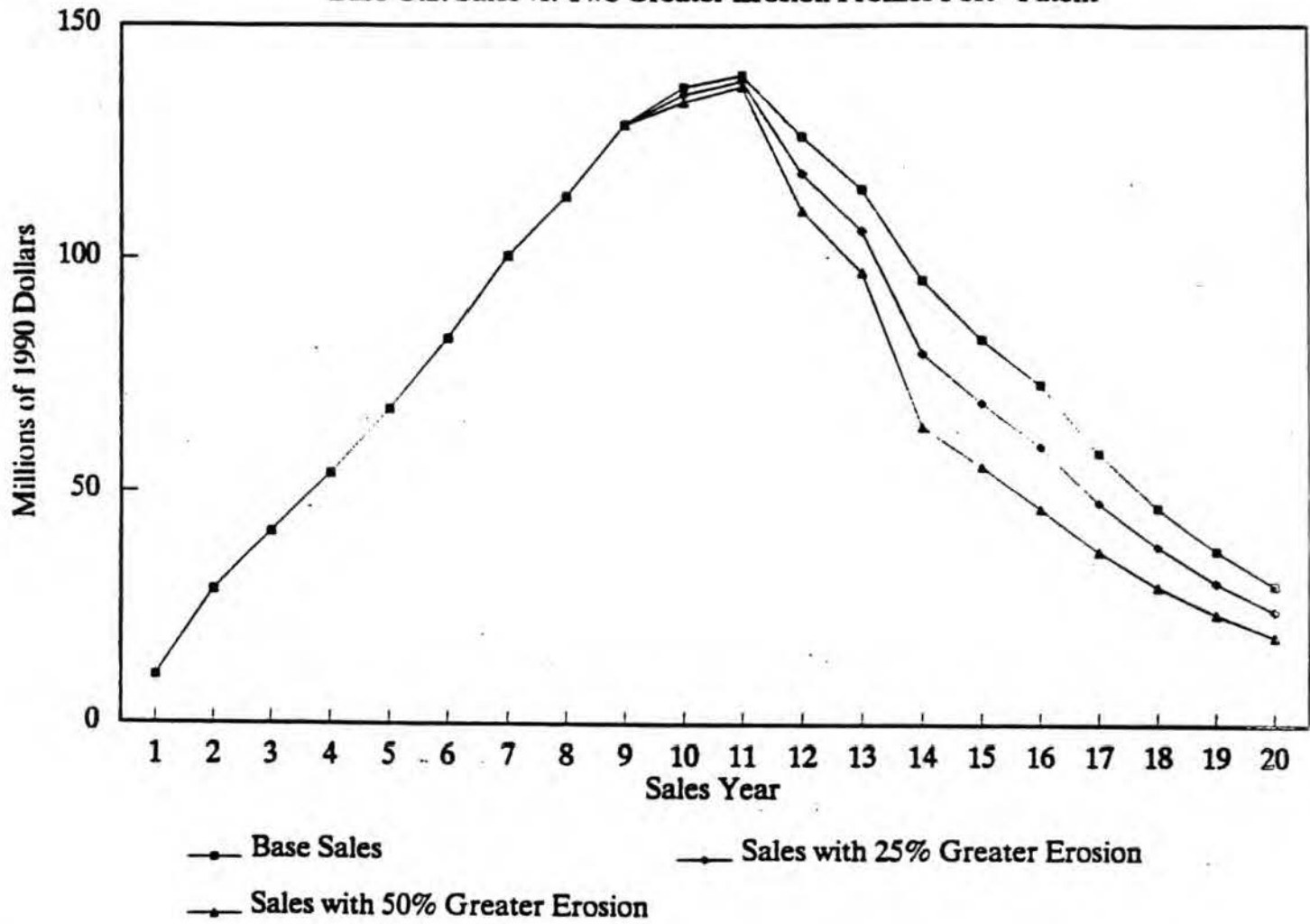


Figure 5

Present Values by Decile: 1980-84 NCEs

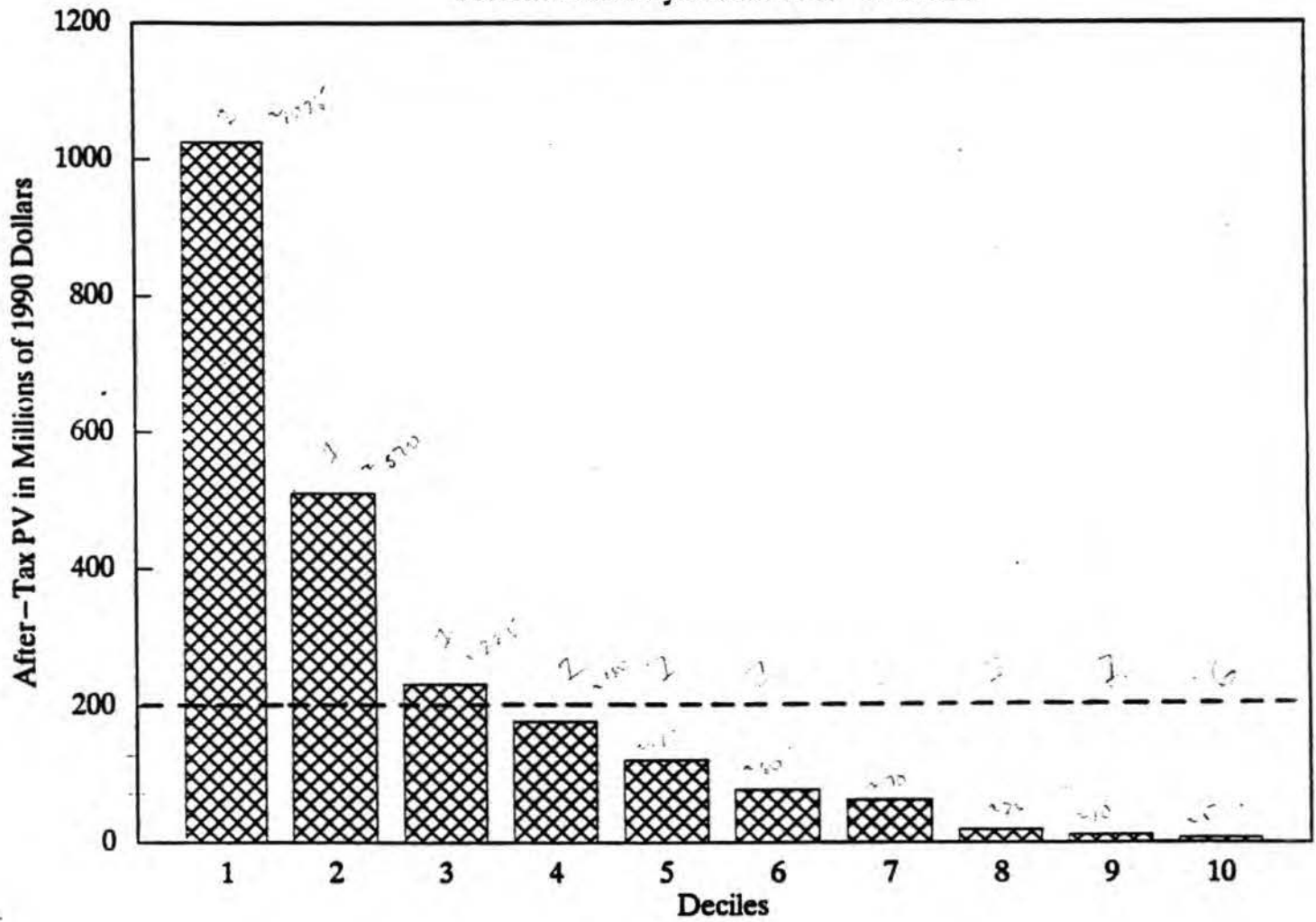
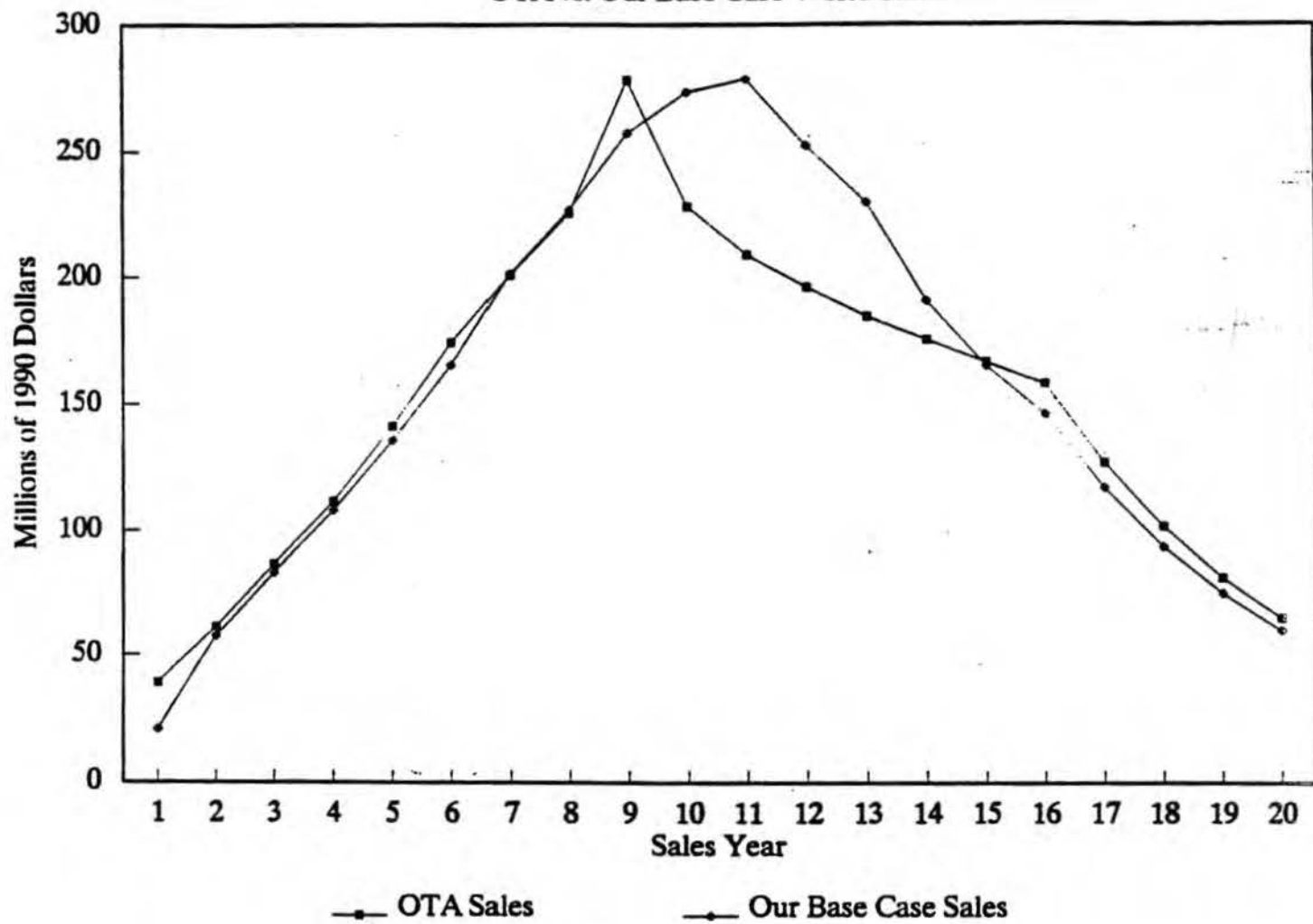


Figure 6

OTA vs. Our Base Case World Sales



Supplemental Appendix (Preliminary Draft)

Returns to R&D on New Drug Introductions in the 1980s

Henry Grabowski and John Vernon

Health Care Reform and Pharmaceutical R&D Incentives:

An Analysis of Some Additional Scenarios

President Clinton's health care reform proposal would expand prescription drug coverage to all Americans for the first time. This expansion of drug benefits might be expected to increase the returns to pharmaceutical R&D and enhance the search for new medicines.¹ At the same time, however, Clinton's health care proposal contains several other provisions that are likely to adversely affect drug innovation incentives. Potentially most important in this regard are proposals on the pricing of breakthrough new drugs.

A breakthrough drug committee of the National Health Board would be created. It would have the authority to solicit information from firms about the factors underlying pharmaceutical prices to issue reports about their "reasonableness." Furthermore, the plan would give the Secretary of HHS the authority to negotiate a special rebate for any new drugs that the Secretary determines

¹A major expansion in pharmaceutical benefits would occur through the provision of outpatient coverage of prescriptions for the elderly through the Medicare program. However, drugs covered under Medicaid would be subject to a rebate of at least 15% off the average manufacturing price. They would be governed by reimbursement procedures similar to what currently exist for the drugs covered under Medicare.

are excessively or inappropriately priced. If a manufacturer is unable to negotiate a price that the Secretary determines to be reasonable, the particular drug may be excluded for coverage under Medicare. Moreover, this negotiated price is likely to become the model for other health care providers.

The Clinton Administration's health care plan therefore appears to be establishing a regulatory framework for drug price controls and, in particular, one which is focused on commercially important new drugs. Other drug cost containment measures implicit in the Clinton Administration's plan include the encouragement of formularies by accountable health plans and government agencies as means of promoting price discounts in pharmaceuticals. The plan also provides strong encouragement to utilize generic drug products.² One would expect the approved health managed care plan to adopt similar policies.

In this appendix, we present some "extreme case" scenarios that might result from Clinton's proposed health reform plan. In particular, taking our 1980-84 data and returns model as the base case, we consider the effect on returns if there should be a government policy that results in constraining the top decile of NCEs to "break even." We also examine a scenario in which generic erosion of sales after patent expiration becomes unusually great--

²For example, in the proposed medicare coverage, the benefit only covers generic drugs unless the physician specifically indicates that a brand name medication is required. Even when the physician indicates this, the Secretary may require physicians to obtain prior approval before prescribing brand name products if a generic substitute is available.

in particular, sales fall by 90% in the year after patent expiration. A combination of these two cases is also reported.

Top Decile of NCEs Constrained to Break Even

The simplest way to describe this simulation is to refer to Figure 6 in the text which shows the present values by decile for the 67 NCEs in our sample. We assume that the government focuses its attention on the top decile of NCEs. Through possibly constraining the top decile's prices, the result is to eliminate the present value of cash flows of the top decile above the average R&D cost. In particular, under the first scenario analyzed, the top decile of drugs have their present values reduced from \$1,026 million to \$201.9 million. That is, government policy has constrained the present value of cash flows to equal average R&D costs. We assume that all other deciles are unaffected.

Table A1 presents the implication for the mean NCE introduction. The main result is that the NPV falls from the base case value of \$22.2 million to -\$60.2 million. Similarly, Table A1 presents the effect of broader restraints that eliminate the excess returns to the second and third deciles, respectively. The NPV falls from -\$60.2 million, when only the top decile is restrained, to -\$91 million and -\$94 million when the restraint extends to the next two deciles.

Returning to the top decile case, we have calculated that a 23% cut in revenues in each year would cause the top decile to just cover average R&D costs. This could be interpreted as a 23% price cut in each year with costs remaining at the level that they were

before the price cut. The assumption is that output is unchanged and therefore costs are not changed either. (One exception is that accounts receivable were reduced to reflect the lower revenues.) Under this assumption, the IRR can be calculated for the mean of the 67 NCEs to be 8.8% (as compared to our estimated cost of capital of 10.5% and a mean IRR of 11.1%).

Of course, we recognize that under the envisioned health care reform, the organizational structure for drug delivery will be different. In particular the prescription of pharmaceuticals will emanate primarily from managed care organizations which will likely employ drug formularies. Hence, firms will have to employ different marketing strategies and may also be able to reduce the costs of promotion and related overhead expenses in such an environment. Hence, the "price cut" might be even more than 23% if the government achieves our assumed target of constraining the top decile's NPV to zero.

For comparative purposes, based on the same assumptions as above, price cuts of 17% and 3.8% would reduce the second and third deciles' NPVs to zero. For our sample of all 67 NCEs, the price cut necessary to make the mean NCE have a zero NPV is 2.9%.

Severe Generic Competition upon Patent Expiration

Returning now to our base case, we turn to the effect on returns of severe generic competition. In our base case, we assumed average percentage declines in sales in the first four years following patent expiration to be 30%, 21%, 12%, and 12%. To examine the effect of severe government and market pressures after

patent expiration to use lower priced generics, we simply assume that sales fall 90% in the year after patent expiration and remain at that level for four years. Thereafter, sales follow a 10% decline for the remainder of market life.³

Figure A1 shows the sales profile for our base case compared with the severe generic competition case. As shown in Table A2, the NPV for the mean NCE falls to -\$7.7 million from the base case value of \$22.2 million, and the IRR falls from 11.1% to 10.3%. Hence, the observed change in NPV for the mean NCE under the severe generic erosion scenario (-\$29.9 million) is significantly less than the change when only the top decile drugs are constrained to a zero NPV (-\$82.4 million). This reflects the fact that the severe erosion case takes effect only after a patent life of approximately 10 to 12 years, and events which occur later in the product life cycle are heavily discounted in an NPV analysis.⁴

As a final scenario, we consider the combined effect of severe generic competition as described above and the zero NPV constraint the top decile. This case is depicted in Figure A2. The results are summarized in Table A2. The combined effect of these two

³We assume that severe generic erosion applies to all NCEs for which we applied patent erosion in the text (i.e., the top 30 NCEs); however, the price cuts are restricted to the top decile only.

⁴In a world dominated by managed care institutions and drug formularies, the first patent expiration for a class of therapeutically similar drugs is likely to trigger severe sales erosion, not only for the brand going off patent but also for all the other NCEs in that class. This is an interesting issue to consider in future research assessments of the growth of managed care organizations and health care reform scenarios.

changes is less than additive (i.e., a total drop in NPV of \$96.6 million) which is what one would expect from the interactive effects of these changes.

Summary

If enacted, the Clinton Administration's health care reform proposal can be expected to lead to many fundamental changes for the pharmaceutical industry. The objective of the analysis in this appendix was not to model these changes in a comprehensive fashion. Rather we have selected a few policy directions presented in the plan and attempted to highlight their potential consequences through an analysis of some extreme value scenarios. Of particular interest is the specter of the incipient price controls, oriented toward the most commercially successful NCEs.

As shown in our "extreme case" experiments, limiting the NPV of top decile drugs to average R&D cost, so that these drugs just earn the industry cost of capital, implies that the NPV of the average 1980-84 NCE drops dramatically (-\$82.0 million). Of course this is before any compensatory adjustments in other costs. But it is illustrative of the disproportionate effect on R&D returns of the top decile NCEs and of the highly skewed distribution which characterizes new drug returns. By contrast, an alternative extreme case scenario, involving almost total utilization of generic drugs after patent expiration, leads to a much smaller negative effect on expected returns to the mean NCE. The impact of different cost containment approaches on the incentives for

innovations remains an important topic for further research and policy analysis.

TABLE A1

Government Price Constraints on Top Decile Drugs--
Implications for the Mean NCE Introduction

<u>Case</u>	<u>PV Cash Flow</u> <u>(mil '90 \$)</u>	<u>R&D Costs</u> <u>(mil '90 \$)</u>	<u>NPV</u> <u>(mil '90 \$)</u>	<u>Δ NPV</u> <u>(mil '90 \$)</u>
Baseline	224.1	201.9	22.2	----
Top Decile Constrained to Breakeven	141.7	201.9	-60.2	- 82.4
Top 2 Deciles Constrained to Breakeven	110.8	201.9	-91.0	-113.2
Top 3 Deciles Constrained to Breakeven	107.8	201.9	-94.0	-116.2

Table A2

Alternative Scenarios on Generic Price Erosion
Implications for Mean NCE Introduction

<u>Case</u>	<u>Mean NPV</u> <u>(mil '90 \$)</u>	<u>Δ NPV</u> <u>(mil '90 \$)</u>	<u>Mean</u> <u>IRR (%)</u>	<u>Cost of</u> <u>Capital (%)</u>
Baseline	22.2	----	11.1	10.5
Severe Erosion after Patent Expiration	- 7.7	-29.9	10.3	10.5
Top Decile Constrained to Zero NPV	-60.2	-82.4	8.8	10.5
Combined Effect: Severe Erosion and Top Decile Constrained to Zero	-74.4	-96.6	8.2	10.5

Figure A1

Base Case Mean Sales vs. Severe Erosion

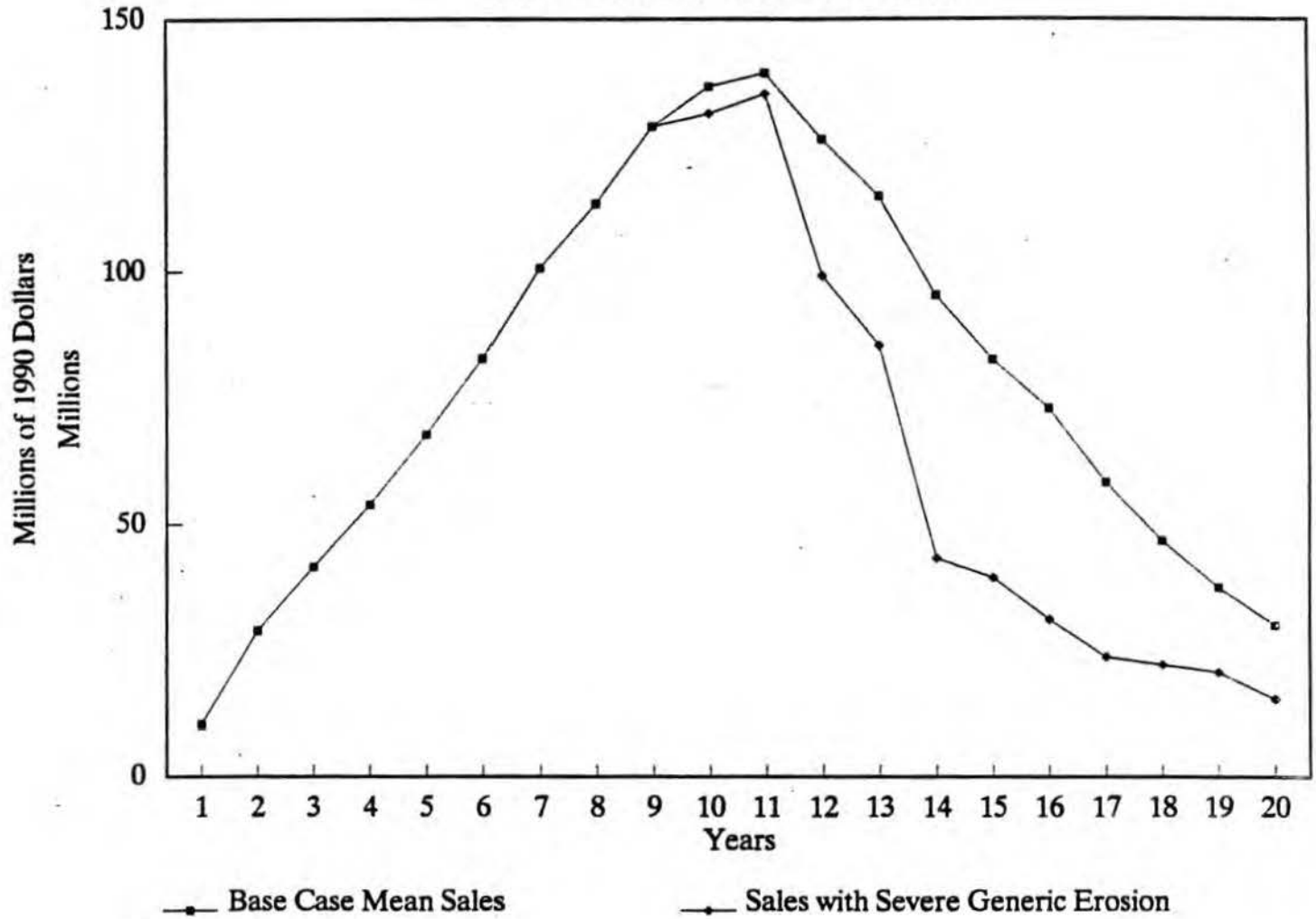
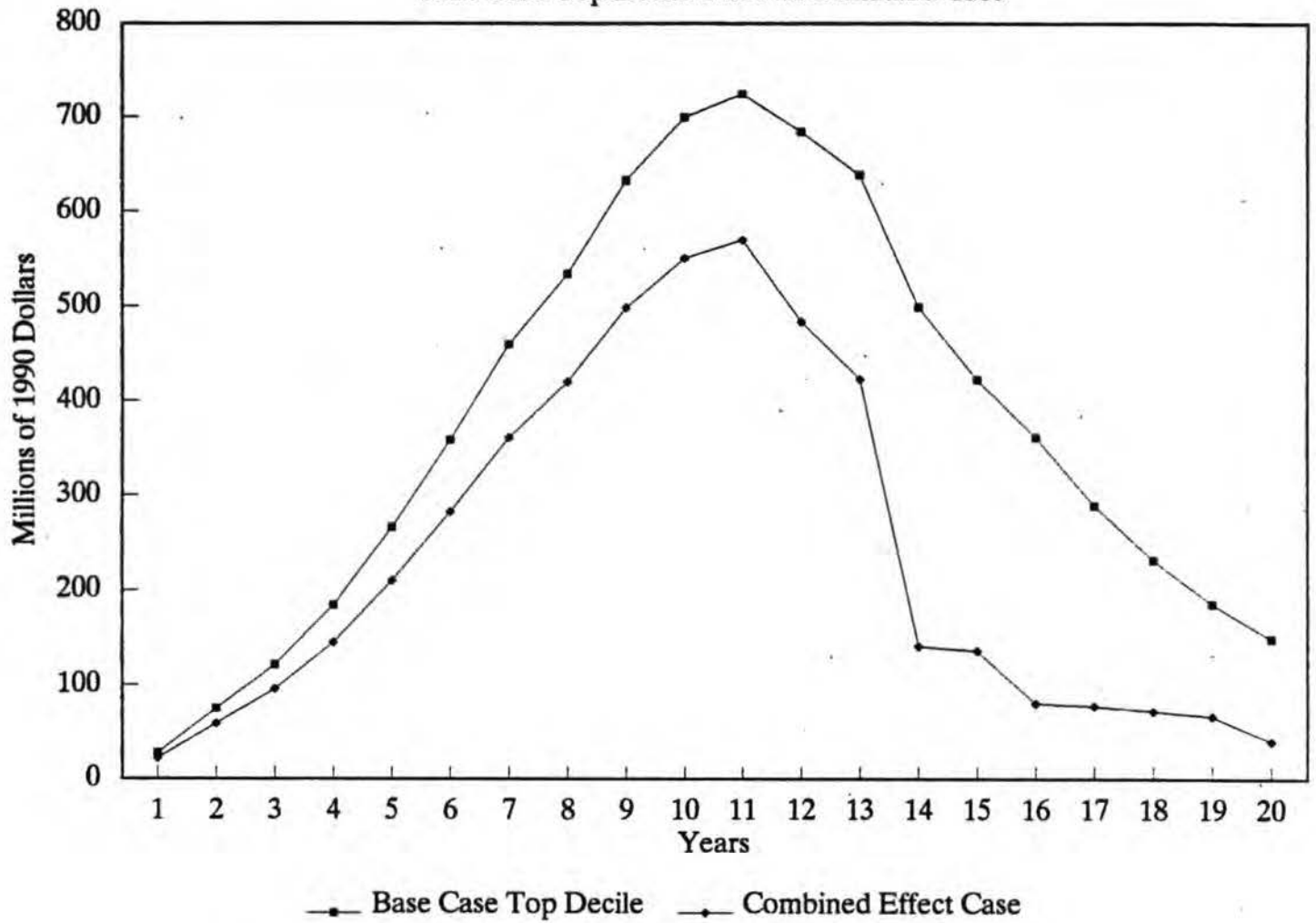


Figure A2

Base Case Top Decile Sales vs. Combined Case



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Price Controls and the Future of Biotechnology: The Results of a Survey

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