JENNIFER A. TEGFELDT, ESQ.

Jennifer holds a degree in Biological Sciences from the University of California, Davis. Following a several year career as an analytical chemist, Jennifer graduated from Pierce Law in 1985 with the goal of practicing intellectual property law. The IP program, back then, was substantially different than now – Jennifer was the only woman in a class of eight men. She served as an editor to "Idea, the Journal of Law and Technology" almost from the beginning of her legal education. She counts among her most important mentors and guides (as do a number of IP students of Pierce Law), the irreplaceable Professor Bob Shaw, who never saw obstacles, only opportunities.

Jennifer was the first alumnus to be appointed law clerk to a judge of the Court of Appeals for the Federal Circuit. Jennifer served as law clerk to Judge Pauline Newman from 1985-1987, and assisted in such proceedings as Pennwalt, Texas Instruments, In re Thorpe, and the FAA air controller cases.

When her clerkship ended in 1987, Jennifer entered private practice with a small boutique patent law practice and was later recruited to join Fitzpatrick, Cella, Harper and Scinto in the firm's Washington D.C. offices. Her practice focused on patent prosecution and enforcement, appeals, trademarks, copyrights, licensing, and opinion work of all types. Jennifer was very active in the Federal Circuit Bar Association, AIPLA, ITC Trial Lawyers Association, American Bar Association, including gaining Delegate status in the ABA's House of Delegates for the Federal Circuit Bar Association, and the American Inns of Court, Giles S. Rich Inn.

In 1994, Jennifer left private practice to join Genzyme Corporation as one of four attorneys supporting the company. Since that time, the legal team has grown to over twenty patent and corporate lawyers. Jennifer maintains a patent practice, while working closely with the corporate legal team in transactional matters, and in leading legal efforts to develop and put in place collaborations. Within the last year, Jennifer has expanded her "Transactional IP" role in taking on a strategic position in the Business Development team for the Therapeutics business unit of Genzyme General, a division and tracking stock of Genzyme Corporation. As Director, Business Initiatives and IP Legal Affairs, she continues to pursue her business knowledge as a logical and necessary component of intellectual property management and corporate growth.

Jennifer lives in the Boston area, and her friends know that when the winter weather breaks, she'll most likely be out on the water exploring the coast in her sailboat.

# BIOTECHNOLOGY LICENSING

## A VIEW FROM THE INSIDE

ELEVENTH ANNUAL ADVANCED LICENSING INSTITUTE
PIERCE LAW
CONCORD, NEW HAMPSHIRE
*JULY 15-19, 2002*

Jennifer A. Tegfeldt, Esq.
Director, Business Initiatives and
IP Legal Affairs
Genzyme Corporation
Cambridge, Massachusetts

DISCUSSION POINTS

- THE BUSINESS OF BIOTECHNOLOGY
- FORMS OF COLLABORATION
- DEVELOPING THE PROCESS
- CONTRACTUAL CONSIDERATIONS
- ADDITIONAL THOUGHTS IN CRAFTING A SUCCESSFUL COLLABORATION

# I. THE BUSINESS OF LIFE -- BIOTECHNOLOGY

## An Historical Perspective

Source : 2002 Biotechnology Industry Association, www.bio.org, Time Line of Biotechnology

| | |
|---|---|
| 800 B.C. | Humans domesticate crops and livestock |
| 4000-2000 B.C. | Production of cheese and fermentation of wine (Sumeria, China and Egypt)<br>Babylonians control date palm breeding by selectively pollinating female trees with pollen from certain male trees |
| 500 B.C. | First antibiotic made of moldy soybean curds to treat boils (China) |
| A.D. 100 | First insecticide made of powdered chrysanthemums (China) |
| 1590-1675 | 1590 – Janssen invents the microscope<br>1663 – Hooke discovers the cell<br>1675 – Leeuwenhoek discovers bacteria |
| 1797 | Jenner inoculates a child with a viral vaccine against smallpox |
| 1830-1855 | 1830 – Proteins discovered<br>1833 – First enzyme discovered and isolated |
| 1835-1855 | Scheiden and Schwann propose that all organisms are made of cells<br>Virchow announces "Every cell arises from a cell" |
| 1859 | Darwin publishes the theory of evolution by natural selection |
| 1865 | Genetics begins with Austrian monk Gregor Mendel studying garden peas and discovering that genetic traits are pass from parents to offspring in a predictable way – the laws of heredity |
| 1877-1879 | 1877 – Koch develops a technique for staining and identifying bacteria<br>1878 – The first centrifuge is developed by Laval<br>1879 – Fleming discovers chromatin, the rodlike structures in the nucleus that became known as chromosomes |
| 1902-1915 | 1902 -- The term "immunology" first appears<br>1906 -- The term "genetics" is introduced<br>1915 -- Phages, or bacterial viruses, are discovered |

| | |
|---|---|
| 1920 | Human growth hormone discovered by Evans and Long |
| 1928 | Penicillin discovered as an antibiotic by Alexander Fleming |
| 1944 | Avery et al. prove DNA carries genetic information |
| 1946 | Discovery that genetic material from different viruses can be combined to form a new type of virus, an example of genetic recombination |
| 1949 | Pauling shows that sickle cell anemia is a "molecular disease" resulting from a mutation in the protein molecule hemoglobin |
| 1953 | "Nature" publishes James Watson and Francis Crick's manuscript describing the double helical structure of DNA |
| 1956 | Kornberg discovers the enzyme DNA polymerase I, leading to an understanding of how DNA is replicated |
| 1966 | The genetic code is cracked, demonstrating that a sequence of three nucleotide basis (a codon) determines each of 20 amino acids |
| 1969 | An enzyme is synthesized in vitro for the first time |
| 1971 | First complete synthesis of a gene |
| 1973 | Stanley Cohen and Herbert Boyer perfect genetic engineering techniques to cut and past DNA (using restriction enzymes and ligases) and reproduce the new DNA in bacteria |
| 1976 | First time the sequence of base pairs for a specific gene is determined (A, C, T, G) |
| 1977-1979 | First expression of a human gene in bacteria<br>Recombinant human insulin first produced<br>Human growth hormone first synthesized |
| 1980 | U.S. Supreme Court, in Diamond v. Chakrabarty, approves the patenting of genetically engineered life forms |
| 1981 | Scientists at Ohio University produce the first transgenic mice |
| 1983 | Conception of polymerase chain reaction (PCR), in which heat and enzymes are used to make unlimited copies of genes and gene fragments |

| | |
|---|---|
| 1985 | Genetic markers found for kidney disease and cystic fibrosis |
| 1986 | First genetically engineered vaccine for humans: hepatitis B<br>First anticancer drug through biotechnology: interferon |
| 1988 | Harvard molecular geneticists receive first U.S. patent for genetically altered animal – a transgenic mouse ("the onco-mouse") |
| 1990 | Human Genome Project – an international effort to map all the genes in the human body – is launched<br>First transgenic dairy cow used to produce human milk proteins for infant formula |
| 1994 | First breast cancer gene discovered |
| 1997 | First animal cloned from an adult cell: a sheep named Dolly |
| 1998 | Embryonic stem cells used to regenerate tissue and create disorders mimicking diseases |
| 2000 | Rough draft of the human genome sequence is announced |
| 2001 | Scientific journals publish complete human genome sequence |

**"...anything under the sun that is made by man."**
**Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980)**

- The Possibilities of Biotechnology
  - Agriculture
    - Higher producing and drought and insect resistant plants
    - Better tasting and longer lasting vegetables and fruits
    - Higher productivity animals
  - Therapeutics
    - Gene Therapy
    - Protein Therapies
    - Diagnostics, including genetic testing
    - Improved patient therapy monitoring
    - Cell Therapies
    - Combination Therapies
    - Synergies with "chemical" therapies
  - Discovery
    - Models for disease, cell and animal
    - Screening techniques
  - Manufacture
    - Plant (such as picchia)
    - Insect
    - Mammalian cells (human and CHO)
    - Transgenic animals
  - Environmental uses
    - Hazardous waste clean-up

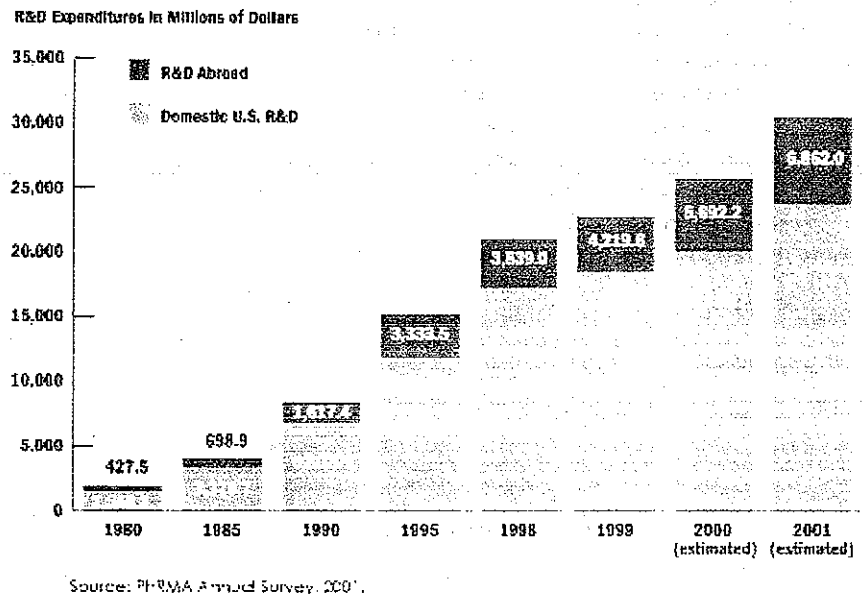
# DRUG DEVELOPMENT IN THE PHARMACEUTICALS INDUSTRY

## Pharmaceutical Industry Profile 2001
## Pharmaceutical Researchers and Manufacturers of America, www.phrma.org

RESEARCH AND DEVELOPMENT INVESTMENT

- In 2001, R&D investment, worldwide, reached $30.5 billion
- 18.7% increase in expenditures from 2000, and triple the R&D expenditure in 1990

Figure 2-1
R&D U.S. AND ABROAD EXPENDITURES, ETHICAL PHARMACEUTICALS, RESEARCH-BASED PHARMACEUTICAL COMPANIES, 1980–2001



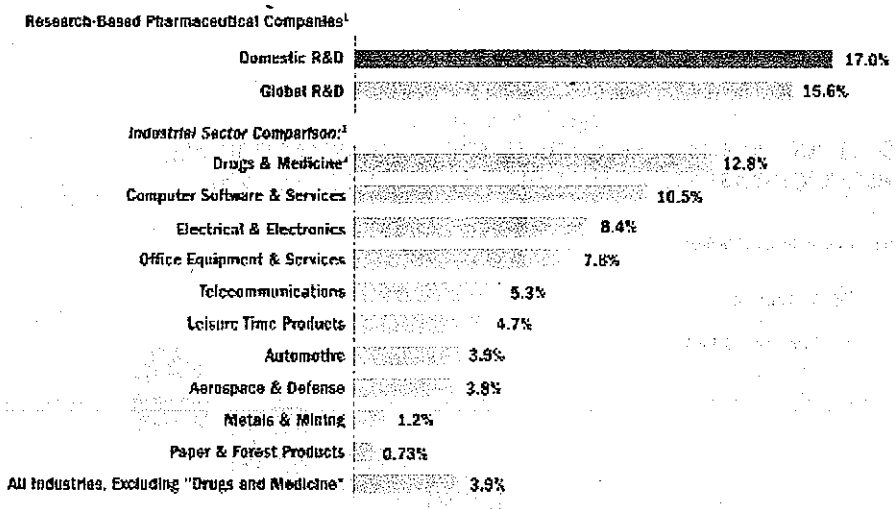

Source: PHRMA Annual Survey, 2001.

Source: Pharmaceutical Industry Profile 2001, Chapter 2, Research and Development – The Key to Innovation, page 12; www.phrma.org

## RELATIONSHIP OF R&D TO SALES

- Greater than three times level of R&D investment in drugs and medicine

**Figure 2-3**
**R&D AS A PERCENT OF SALES, RESEARCH-BASED PHARMACEUTICAL COMPANIES AND U.S. INDUSTRIAL SECTORS, 2000**




1 "Researched-Based Pharmaceutical Companies" based on ethical pharmaceuticals sales and ethical pharmaceuticals R&D only as tabulated by PhRMA.

2 "Standard and Poor's Compustat - 4 digit SIC codes.

3 "Drugs and Medicine" category based on total R&D and sales for companies classified within the "Drugs and Medicine" sector as tabulated by Standard & Poor's Compustat, a division of McGraw-Hill (includes research- and non-research-based companies).

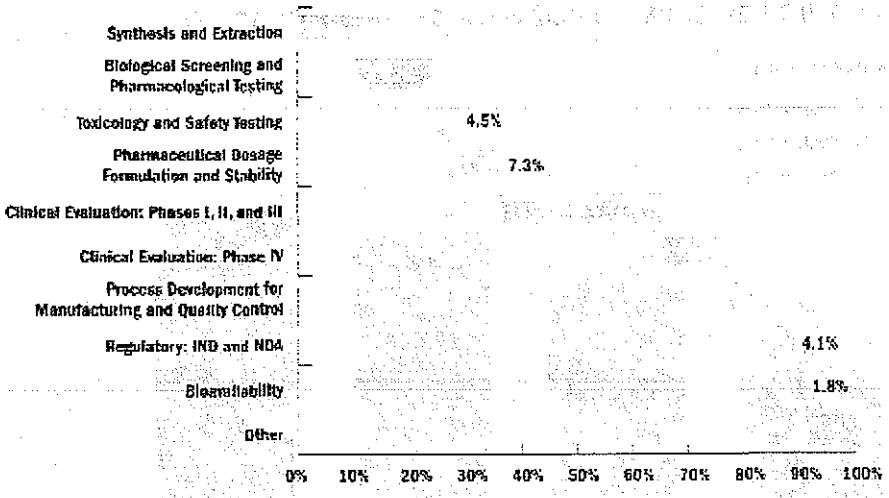
Source: PhRMA, 2001, based on data from PhRMA Annual Survey and Standard & Poor's Compustat, a division of McGraw-Hill.

Source: Pharmaceutical Industry Profile 2001, Chapter 2, Research and Development – The Key to Innovation, pages 13, 15; www.phrma.org

## WHERE THE FUNDING GOES

- 36% spent on preclinical studies
- 29.1% spent on Phase I, II and III studies
- 11.7% spent on Phase IV studies, post approval by the FDA

**Figure 2-4**
**ALLOCATION OF DOMESTIC U.S. R&D BY FUNCTION, 1999**




Note: Totals may not add exactly due to rounding. R&D functions are not exactly sequential in practice.
Source: PhRMA, Annual Survey 2001.

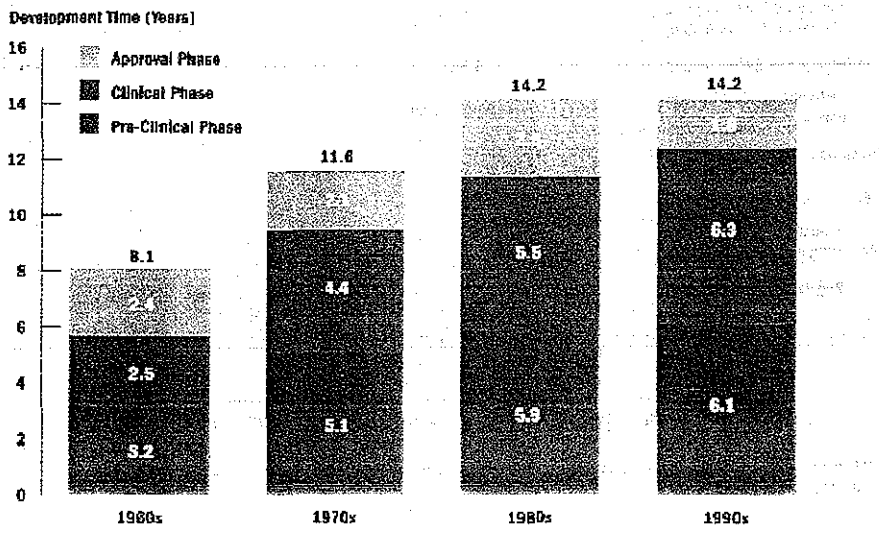
Source: Pharmaceutical Industry Profile 2001, Chapter 2, Research and Development – The Key to Innovation, page 14; www.phrma.org

## OTHER ISSUES BEARING ON COST:

## TIMELINE FOR R&D

- The Developmental Timeline has increased
  - 8 years to approval in the 1960's
  - 14.2 years to approval in the 1990's

**Figure 2-8**
**TOTAL DRUG DEVELOPMENT TIME FROM SYNTHESIS TO APPROVAL**



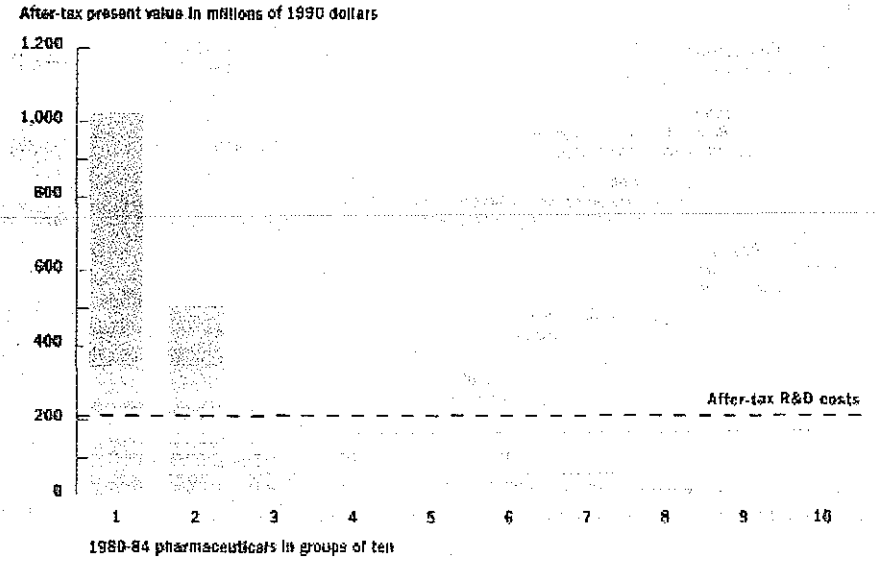

Source: DiMasi J.A., "New Drug Development in U.S. 1963-1999," Clinical Pharmacology & Therapeutics 2001; May; 69(5).

Source: Pharmaceutical Industry Profile 2001, Chapter 2, Research and Development – The Key to Innovation, pages 17, 19; www.phrma.org

## SUCCESS FACTOR FOR DRUG CANDIDATES AND FUNDING OF DEVELOPMENT EFFORTS

- Only three out of ten new drug products or new drug entities (introduced 1980-1984) had returns higher than average after tax R&D costs
- Duke University study also showed that the revenues of 20% of the products provided 70% of the returns
- Companies rely on the success of a few products to support their product development pipeline

Figure 2-9
**ONLY THREE OF TEN MARKETED DRUGS PRODUCE REVENUES THAT MATCH OR EXCEED AVERAGE R&D COSTS**




Note: The drug development cost cited in this chart is after-tax in 1990 dollars for drugs introduced 1980-1984. Based on a separate analysis by The Boston Consulting Group, the pre-tax R&D cost for drugs introduced in 1990 is $500 million.

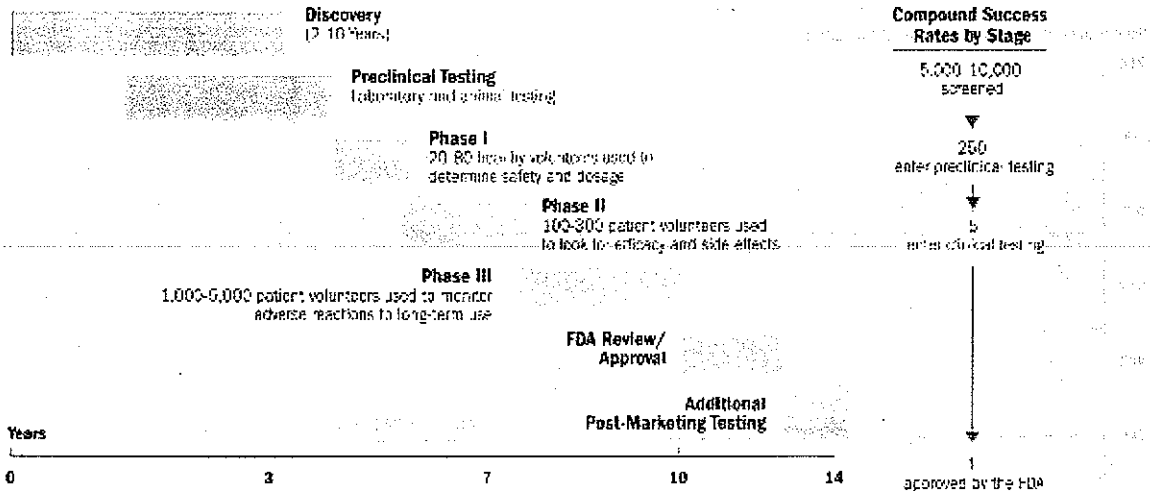
Source: Grabowski, H., and Vernon, J., "Returns to R&D on New Drug Introductions in the 1980s," Journal of Health Economics, Vol. 13, 1994.

Source: Pharmaceutical Industry Profile 2001, Chapter 2, Research and Development – The Key to Innovation, pages 18, 20; www.phrma.org

## LIKELIHOOD OF SUCCESS IN DEVELOPMENT

- One in up to 10,000 compounds ultimately becomes a marketed drug
- Rigorous science at the early stages of development is critical to improving the odds of success

**Figure 3-1**
**COMPOUND SUCCESS RATES BY STAGES**



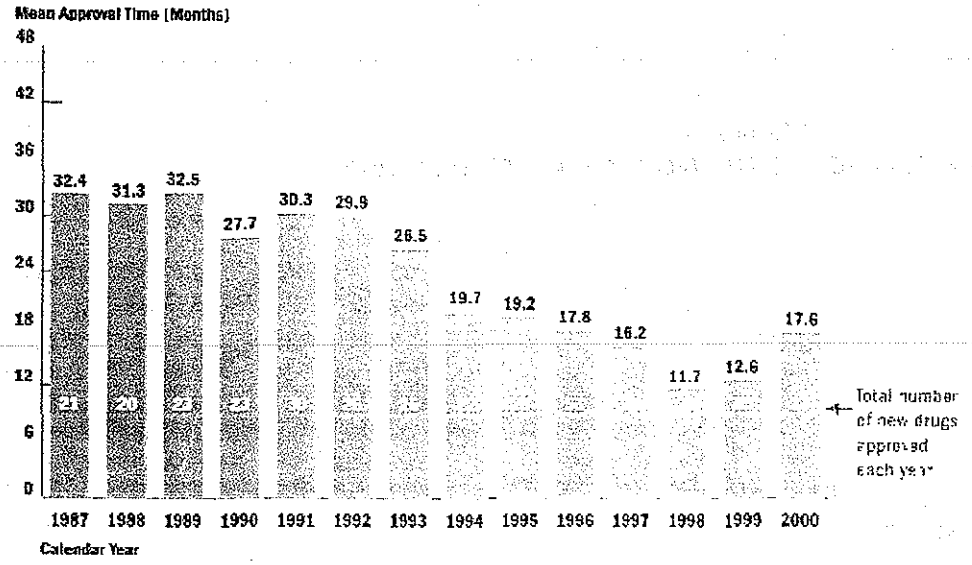

Source: PhRMA, based on data from Center for the Study of Drug Development, Tufts University, 1995.

Source: Pharmaceutical Industry Profile 2001, Chapter 3, Regulatory and Legal Aspects of Drug Development, page 24; www.phrma.org

## FDA REVIEW PROCESS – TIMELINE

- FDA review period reduced by almost half since 1987 due to increased pre-clinical efforts and clinical trials supporting more comprehensive regulatory filings, and FDA efficiency
- Safety is a paramount concern throughout

**Figure 3-2**
**MEAN APPROVAL TIMES FOR NEW DRUGS, 1987–2000**



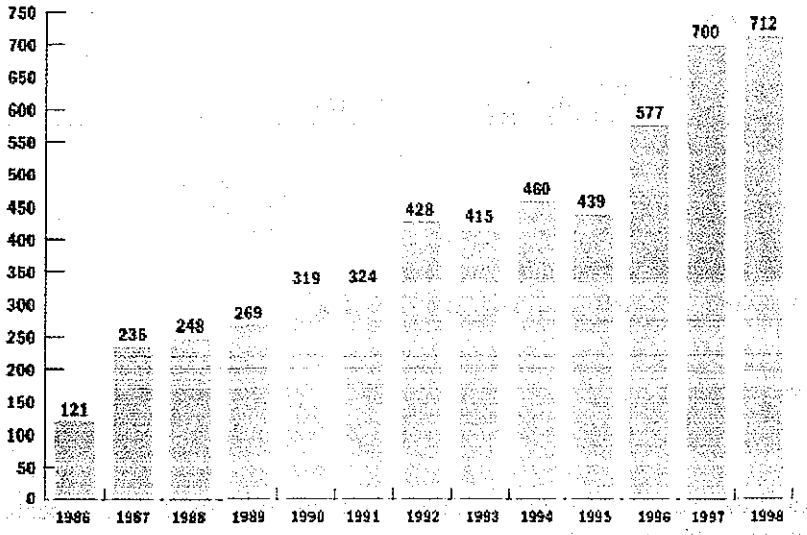

Source: U.S. Food and Drug Administration, 2001

Source: Pharmaceutical Industry Profile 2001, Chapter 3, Regulatory and Legal Aspects of Drug Development, page 25; www.phrma.org

## OPTIONS FOR MEETING THE FINANCIAL CHALLENGE

- Opportunities of success optimized through collaboration
  - Development expertise
  - Regulatory support, national and international
  - Marketing expertise, national and international
  - Capital
- The impetus to form strategic alliances has built nearly seven fold in the twelve year period from the mid 1980's to the late 1990's
- The frequency of mergers and acquisitions (shown in Figure 5-8) have grown annually, and have included larger transactions

Figure 5-7
**INCREASING FREQUENCY OF STRATEGIC ALLIANCES, 1986–1998**




Source: Windhover's Pharmaceutical Strategic Alliances 2000.

Source: Pharmaceutical Industry Profile 2001, Chapter 5, pages 62-63; www.phrma.org

## Figure 5-8
## MERGERS AND ACQUISITIONS IN THE PHARMACEUTICAL INDUSTRY

| | |
|---|---|
| 2000 | G.D. Searle and Pharmacia & Upjohn › Pharmacia Corporation |
| 2000 | Warner-Lambert and Pfizer Inc. › Pfizer Inc. |
| 2000 | Rhone-Poulenc and Hoechst Marion Roussel › Aventis AG |
| 2000 | SmithKline Beecham and Glaxo Wellcome › GlaxoSmithKline |
| 2000 | Centecor and Johnson & Johnson › Centecor acquired |
| 2000 | Knoll Pharmaceuticals acquired by Abbott Laboratories |
| 2000 | Alza Corporation anticipated to be acquired by Johnson & Johnson (subject to Board approval) |
| 2000 | The Liposome Company acquired by Elan Pharmaceuticals |
| 2000 | Pasteur Merieux Connaught › Aventis Pasteur |
| 2000 | Pathogenesis Corporation acquired by Chiron Corporation (non-member) |
| 1999 | Monsanto and Pharmacia & Upjohn |
| 1999 | AHP/Warner-Lambert and Pfizer/Warner Lambert (pending) |
| 1999 | Roche and Genentech |
| 1999 | Warner-Lambert and Agouron |
| 1998 | Hoechst AG and Rhone-Poulenc Rorer |
| 1998 | Sanofi SI and Synthelabo |
| 1998 | Zeneca and Astra |
| 1997 | Hoffmann-La Roche and Boehringer Mannheim |
| 1997 | Nycomed and Amersham |
| 1996 | CibaGeigy and Sandoz |
| 1996 | Elan and Athena Neurosciences |
| 1995 | Knoll and Boots |
| 1995 | Glaxo and Burroughs Wellcome |
| 1995 | Gynopharma and Ortho-McNeil |
| 1995 | Hoechst-Roussel and Marion Merrell Dow |
| 1995 | Pharmacia and Upjohn |
| 1995 | Rhone-Poulenc Rorer and Fisons |
| 1995 | Schwarz Pharma and Reed & Carnrick |
| 1994 | American Home and American Cyanamid |
| 1994 | Hoffmann-La Roche and Syntex |
| 1994 | Pharmacia and Erbamont |
| 1994 | Sanofi and Sterling (prescription drug operation) |
| 1994 | SmithKline Beecham and Sterling (over-the-counter pharmaceutical unit) |
| 1991 | SmithKline and Beecham |
| 1990 | Boots and Flint |
| 1990 | Pharmacia and Kabi |
| 1990 | Rhone-Poulenc and Rorer |
| 1989 | American Home and A.H. Robins |
| 1989 | Bristol-Myers and Squibb |
| 1989 | Dow and Marion |
| 1988 | Kodak and Sterling |
| 1986 | Schering-Plough and Key |
| 1985 | Monsanto and Searle |
| 1985 | Rorer and USV/Armour |

Source: Windhover's Health Care Strategist, 2000.

## II. FORMS OF COLLABORATION

**THE RELATIONSHIP BEGINS...**

- ♦♦ **INTENTIONS AND OBJECTIVES ARE PARAMOUNT**
- ♦♦ **ENSURE THE AGREEMENT MATCHES THE INTENTIONS OF BOTH SIDES – ASK QUESTIONS!**

- CONFIDENTIAL DISCLOSURE AGREEMENTS
  - Purpose: To exchange Proprietary information under obligations of confidentiality
  - Limited term (often five years)
  - Use of the exchanged information only for the purposes of evaluating the contemplated collaboration
  - "Industry standard" format and terms

- MATERIALS TRANSFER AGREEMENTS
  - Purpose: To exchange of materials to conduct specified experimentation
  - Use limited to specified uses
  - Typically requires exchange of resulting data
  - May include a provision permitting publication of results, subject to confidentiality provisions
  - Materials cannot be transferred to third parties, and any unused materials must be returned or destroyed
  - "Industry standard" format and terms

- CONSULTING AGREEMENTS
  - Purpose: To engage a collaborator, often an individual, in the provision of services of mutual interest
  - Term can be one or multiple years, depending on the objectives for the services
  - Should clearly define:
    - The services to be provided by the consultant
    - The time commitment required
    - Payment terms
    - Ownership and use of the consultancy results, and any inventions
  - Typically includes confidentiality provisions
  - Can be used as an adjunct to other forms of agreement, such as licenses or sponsored research agreements
  - If an academic collaborator, be aware of institutional restrictions on scope, time commitment, and rights in intellectual property
  - If the consultant is an employee of an institution, seek institutional approval and sign off

## MORE COMPREHENSIVE FORMS OF AGREEMENT:

- SPONSORED RESEARCH AGREEMENTS
  - Performed under a Research Protocol and Budget
  - Provides for exchange of results obtained
  - Typically includes provisions of confidentiality, and rights to intellectual property developed
  - Often includes publication provisions, if an academic collaborator, subject to obligations of confidentiality
  - Be sure to include a scientific contact within the company to work with the research collaborator
  - Can be developed concurrent with a license or other strategic agreement

**AGREEMENTS WITH INCREASING STRATEGIC IMPORTANCE:**

- LICENSE AGREEMENTS
- COLLABORATION AGREEMENTS
  - Marketing, manufacture, product development, delivery and formulation
- JOINT VENTURE AGREEMENTS
  - Focus on a field defined by product or service
- MERGERS AND ACQUISITIONS
  - Can involve companies of greater/lesser or approximately same size
  - Asset Acquisitions
  - Formation of a new business entity
  - Spin-outs of some or all technology

## III. DEVELOPING THE PROCESS

**A SUCCESSFUL COLLABORATION CANNOT BE BUILT WITHOUT:**

- ♦♦ **DETERMINING THE INTENTIONS OF THE PARTIES IN WORKING TOGETHER, AND**
- ♦♦ **CLEARLY DEFINING THEIR OBJECTIVES**

**CONSIDER:**

- **Relationship defined by Industry**
  - Synergistic technologies
  - Service provider becoming collaborator
  - Advantage of broader collaboration to provide guidance for relationship in the future (such as Master Agreements)
  - Customer/Supplier

- **Relationship defined by Technology**
  - Value of Intellectual Property held, and improvements
  - Anticipated future development of the technology field
  - What other technologies will offer alternatives
  - Is the value in Patents, or driven by trade secrets, copyrights or trademarks

- **Relationship between the Parties**
  - On-going participation of seller
  - Allocation of responsibilities, such as R&D and manufacture, marketing
  - Is the collaboration an entry into a broader future collaboration/acquisition
  - Is "relationship building" a purpose for the collaboration
  - Alliance Management

**ASK:**

**What does the client want at the end of the day?**

**What is important to the deal, and what is not?**

**What makes a good deal a great deal (and when does it go in the other direction)?**

**CLIENT AND COUNSELOR SHOULD UNDERSTAND:**

**How is the collaboration going to move forward, after execution?**

**What is the effect of not thinking through all aspects of the collaboration?**

- **Lengthy and difficult negotiations**
- **Poor future relationships in the future**
- **Project abandoned**

## IV. CONTRACTUAL CONSIDERATIONS

**The agreement must clearly reflect the obligations and rights of the parties and what is important to each**

- Cost
  - Research funding
  - Services funding
  - Option fees for improvements
  - Patent expenses
  - Royalties on earned sales
  - Minimum annual royalties
  - Milestones
  - Patent enforcement expenses
  - Options for fully paid up rights

- Grant clause
  - Exclusive or non-exclusive
  - When can one shift to another
  - Buy-ups or Buy-downs

- Term and Termination
    - Term and patents, pending applications, and trade secrets
    - Termination
        - Unwind provisions
            - Financial considerations
            - Disposition of results
            - Disposition of intellectual property (solely or jointly owned)
            - On-going obligations (such as confidentiality, participation in Intellectual Property Litigation)
        - Termination for cause
        - Termination for convenience

- Due Diligence
    - Development and Milestone Timelines
    - What happens if technical events interrupt the timeline

- Confidentiality and Publications
    - Publications not often issue with companies, but a key issue for academic collaborators
    - Period allowed for removal of the disclosing party's confidential information and patent application filings

- Definitions
    - Test the definitions with a "lay person" reading of the agreement
    - Layering

# DRAFTING THOUGHTS

- **DON'T WRITE AN AGREEMENT YOU WOULDN'T SIGN**

- **IF THE AGREEMENT REQUIRES A LAWYER TO UNDERSTAND IT ...**

## V. ADDITIONAL THOUGHTS

- **Reevaluate the collaboration positioning through the negotiation process**
  - Have the goals or the objectives of the parties changed?
  - As discussions proceed, are there new opportunities for tailoring the collaboration (broadening or narrowing)?
  - Have outside events changed the needs/wants of the parties?
  - Have internal events changed what parties want/need or can afford?

- **Coordinate stacking provisions for royalties**

- **Consider tax implications**
  - **Joint ventures, spin-outs, wind-ups**
  - **International collaborations**
    - **Manufacture on one shore, fill-finish on another**
    - **Customs duties and COGS**

- **The real cost to the collaborator**
  - **In management time**
  - **In consumption of R&D resources**
  - **In consumption of manufacture resources**
  - **In $$ outlay**

**WORK TOWARD A WIN-WIN COLLABORATION**

.....

**GOOD RELATIONSHIPS ONLY GET BETTER**