



MILLENNIUM EDITION

 **ERNST & YOUNG**

FROM THOUGHT TO FINISH.™

Convergence

The Biotechnology Industry Report

To Our Clients and Other Friends:

Welcome to *Convergence: Ernst & Young's Biotechnology Industry Report, Millennium Edition*. Here, we present an overview of the forces converging to make biotechnology this century's most dynamic force—one positioned to reshape virtually every other industry it intersects and to redefine our lives. From agriculture to chemicals and manufacturing processes, from drug discovery to computer nanotechnology, biotechnology is creating platforms for new products and markets on many fronts.

Biotechnology advances are working to turn into reality what sounded so futuristic in the last century. They are creating a world which, in a sense, is more “living” than ever: Computers are becoming self-regulating; medicines are becoming “intelligent” in their ability to adapt themselves to size, body weight, and metabolism; crop yields are increasing for a growing world population cultivating a finite area of arable land.

These innovations are breathing new life into biotechnology stocks. Already, the new millennium has seen one of the most lucrative periods in the biotechnology industry. In our last report, *Bridging the Gap*, we lamented that the market has not recognized the value being created in the biotechnology industry. That all changed as the year turned, with genomics stocks leading the way to often dizzying heights. Market capitalization of the biotech industry increased 156 percent for the year ending June 30, 2000. The progress made by Celera and The Human Genome Project on a draft map of the human genome triggered an influx of biotechnology into the media and our vocabulary. With it came increasing public interest in the power of biotechnology to improve our lives. As a result, after the market slump of the late 1990s, the maturing technologies of many genomics companies led to an inflow of money into this sector.

In the current market, the average biotech initial public offering (IPO) has raised on the order of \$100 million—easily two to three times more than the average deal five years ago. While this dramatic turnaround has been extremely positive for the industry, the key will be in sustaining investor enthusiasm and returns over the long term. We believe the convergence underway within and outside of biotechnology will lead to a stronger, more diverse, and sustainable industry.

Convergence: Ernst & Young's Biotechnology Industry Report, Millennium Edition explores these industry and market trends. Specifically, this report provides:

- Comprehensive financial data on the biotechnology industry
- Analysis of the latest stock market and equity financial data
- Information on the future of capital markets in light of a growing global economy
- Discussions by the industry's top executives on market trends and the outlook for biotech
- New and exciting developments in technology that have a direct impact on biotech
- News on trends in intellectual property ownership
- An overview of public policy trends, including recent legislation and regulations certain to affect the industry

Most of all, you will learn how biotech is reshaping the marketplace on many fronts. As biotech continues to grow exponentially, those who can leverage this powerful new force will discover unlimited applications and opportunities.

Join us at our Web site at www.ey.com/industry/health and interact with our collection of health and life science knowledge.

The logo for Ernst & Young LLP, featuring the company name in a stylized, handwritten-style script.

Throughout this text we have highlighted concepts and companies that are posted on www.ey.com/industry/health with links and further information. Also, a “ticker” running along some pages draws attention to some recent IPOs of biotechnology companies.

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Letter to the Industry

Carl B. Feldbaum, President,

Biotechnology Industry Organization



The media have called the first
100 years of the new millennium
“the biotechnology century.”
For the biotech industry itself, the first
part of the new millennium has been
nothing short of momentous.

The Drug Pricing Challenge

Three key developments marked this eventful period. The first is the drug pricing issue before Congress. At least six pieces of legislation introduced into the House and Senate in 1999 and 2000 could directly affect drug prices. They represent a greater challenge to research-stage biotech companies than the health care reform debate of 1993–1994.

One aspect of the drug pricing debate is the serious concern that some Medicare beneficiaries lack affordable access to medicines. Also propelling the issue, however, is the opportunistic nature of presidential-year politicking. Our industry, more than any other, wants all seniors—all people—to have affordable access to medicines. The only debate today is *how* to achieve that goal. We have argued that the solution lies in ensuring that seniors have private-sector drug coverage, and not in discounting prices or letting the Health Care Financing Administration—the agency that runs Medicare—control prices.

The biotechnology industry has demonstrated that its drugs and vaccines have the greatest impact on age-related diseases, such as heart disease, various cancers, stroke, and kidney disease. Some of these medicines can lower overall health care costs. In addition, hundreds of drugs currently in late-stage clinical development for age-related diseases will improve the health and quality of life for seniors and reduce the need for hospital and nursing home care. Any legislation involving prescription drugs for our nation’s 39 million Medicare beneficiaries, whose ranks will soon swell with the addition of post-World War II baby boomers, should therefore encourage—not discourage—biotech research and development.

Meeting the Challenge of Public Acceptance

The second critical issue to develop early in the new millennium was a growing public concern about technology. Fear of technology has always existed and promises to continue into the foreseeable future. In 2000, however, criticism from the public reached a level unprecedented in the 25-year history of our industry.

Public concerns are, of course, a consequence of our industry’s progress in applying biotechnology and genomics to improving health care, agriculture, industrial manufacturing, and environmental management. Although agriculture dominates the current public acceptance debate, the antitechnology fervor

it has generated in the U.S. and Europe has implications for other biotechnology applications including health care. Conventional wisdom has held that agricultural biotechnology has a difficult time gaining public support because it lacks obvious consumer benefits. We also saw antitechnology reactions spill over into the fledgling field of gene therapy, however, where the potential benefits for fighting disease are undeniable.

We have a responsibility to ensure access to the medical, agricultural, and environmental benefits of our technology for all nations and their citizens.

A more significant reason for agricultural biotechnology's frustrations may be that it is the first obvious demonstration of biotechnology's ability to change nature. In health care, biotechnology has been tapping the human body's own molecules to treat diseases. What could be more natural? In agriculture, on the other hand, recombinant DNA technology enabled plant geneticists to give plants beneficial traits from other organisms.

Completion of the Human Genome

Two decades of testing and analysis have proven that biotech-derived crops and foods are safe for consumers and the environment. Still, the general public has not embraced agricultural biotechnology, and this wariness may foreshadow the ethical dilemmas certain to be raised by the third momentous development so far in the "biotechnology century"—completion of the DNA sequence of the human genome.

Many have called this feat as significant as landing a man on the Moon. The accelerating search for the molecular causes of diseases and the therapies to counter them is certainly as heart-stirring as that first great image of the Earth suspended in space. The more we learn about our genetic makeup, the more opportunities we have to change it now and for future generations. Our industry must, therefore, focus discussions about decoding the human genome on the potential benefits it presents for health care and the boost it gives to the start-up of more and more innovative companies to develop drugs and vaccines.

Adopting a Set of Principles

At the [Biotechnology Industry Organization \(BIO\)](#), we have initiated a project to encourage companies to incorporate bioethics principles and analyses into their business practices and to make these efforts visible to the public. In 1997, BIO's board of directors adopted a statement of principles for the ethical practice of biotechnology.

The rapid advance of biotechnology and genomics now demands that each company and the entire biotechnology enterprise do more to maintain public confidence. We celebrate the completion of the human genome sequence because of the hope it instills in the hunt for new therapies and cures for our most intractable and devastating illnesses. Whether we find them, however, will depend on maintaining the public's trust that we are using our remarkable new technology to benefit *all* citizens.

The U.S. industry should lead by example, by harnessing our growth potential, emphasizing our ethical sensibility, and remaining united as America's caring, entrepreneurial high-tech industry. This means sharing our progress with developing nations. As the undisputed global biotechnology superpower, we have a responsibility to ensure access to the medical, agricultural, and environmental benefits of our technology for all nations and their citizens.

The Promise of Genomics

William A. Haseltine, Ph.D., Chairman of the Board of Directors

and Chief Executive Officer,

Human Genome Sciences



These are exciting times for the
biotechnology industry,
particularly for those involved in
genomics. Indeed, all pointers suggest
that we are on the brink of
a revolution that will transform
medicine and human life.

The innovations that brought us our current extended life expectancy were introduced in the 19th century, when key ideas in public health—including sanitation, clean water, and clean food—took hold. The 20th century witnessed a second revolution, one that led to improved health through pharmaceutical chemistry. Small-molecule chemicals, created in the test tube or purified from natural sources, have been used for a wide variety of purposes. Such chemistry, along with advances in surgical techniques, has led to the development of medicines that substantially extend life.

Despite this progress, the pharmaceutical industry begins the 21st century in the midst of a little-recognized productivity crisis. The cost of bringing a new drug to market is now close to \$400 million. And despite huge investments in new technology, the rate at which new drugs reach the market has decreased markedly over the past 15 years. It is now far short of what is needed to sustain the sector. The calculations are straightforward: A typical top-tier pharmaceutical company now brings an innovative drug to market only once every 27 months, on average. To achieve a healthy 10 percent annual growth in sales revenues, however, the figure must exceed one new drug every six months. In other words, major pharmaceutical companies must increase their rate of introduction of new drugs approximately five-fold. To make matters more dire, productivity per dollar spent is decreasing even faster than absolute productivity.

One important reason for the slowdown is that drug developers must now be more concerned about drug interactions than they were a decade ago. In the past two years alone, seven major products have been withdrawn from the market because of drug–drug interactions. This could be a damaging trend for the industry. Together with the large number of drugs that will come off patent over the next three years, the productivity crisis provides the principal explanation for the wave of mergers now in progress. But those mergers will not solve the problem.

Genomics to the Rescue

I firmly believe that genomics—the use of large collections of human genes to answer biological questions—is now giving rise to an entirely new class of medicines that could rescue the pharmaceutical sector. These new medicines will use human genes, proteins, and antibodies to regenerate tissues that have been damaged by age, disease, or trauma. Although the drug industry’s old guard has not yet

fully accepted this proposition, many more enlightened pharmaceutical companies are striking partnerships to gain access to genomics expertise.

One important aspect of human genes, proteins, and antibodies is that they have many advantages over conventional drugs based on small molecules. Human molecules pose fewer toxicity hazards, and for that reason alone may be easier to shepherd through clinical trials. It is also easier to identify and test a selection of candidate human-derived drugs in the laboratory than it is to test a range of small-molecule drugs, because far less medicinal chemistry is needed. This will help eliminate expensive testing of drugs that will ultimately fail in patients and healthy volunteers.

uses in development and self-maintenance. Already, companies are developing drugs to regrow blood vessels, rebuild bone, and heal skin wounds. My own company has various clinical trials of such drugs in progress, as do several others. The full impact of this restorative technology will be felt within the next two decades.

The second wave of regenerative medicine will involve implanting tissues grown outside the body. Patients will be given replacement organs made from their own cells to restore damaged organs. Scientists can already build implantable sections of human bladder, blood vessels, trachea, and cartilage in the laboratory. Researchers are even creating segments of new kidney and liver, and I am a

Indeed, all pointers suggest that we are on the brink of a revolution that will transform medicine and human life.

More important, human genes, proteins, and antibodies promise medical benefits far beyond those of conventional drugs. Conventional medicines are like crutches—they compensate for a deficiency, but only for as long as the drug is present. The power of genomics is that we are beginning to understand how the body's manifold components communicate. We are learning how to activate and manipulate the body's own systems for repairing and restoring itself. We can do this because we know the signals the body uses to tell cells to move, differentiate, or die.

Because healthy people naturally repair broken bones, we should be able to use the body's signals to speed and augment the repair process in injuries that are not healing properly. Because the body knows how to repair skin wounds, we should be able to manipulate biological messages to promote healing in wounds that do not heal naturally. Because we know that the body generates new brain cells, there is reason to believe that we will be able to activate that process to effect cures of devastating neurological diseases, such as Alzheimer's and Parkinson's.

Waves of the Future

These novel medicines will arrive in several waves. The first will be based on the substances the body

participant in a project to build an implantable heart outside of the body.

The third wave of innovation will incorporate technologies arising from the remarkable experiments that led to Dolly, the cloned sheep. Cloning resets the genetic clock within cells to make them youthful again. Soon, we will be able to create organs and tissues that are in a crucial sense younger than those of the patient from whose cells they are derived. I call this rejuvenative medicine. By the time this technology is routine, perhaps 30 years hence, I believe we will also see widespread use of implantable medical devices engineered at an atomic scale to be compatible with our bodies. The implications are far-reaching indeed.

Genomics Will Benefit the Biotech Industry

Biotechnology companies that utilize genomics to pursue the development of this new type of medicine will be the principal beneficiaries of these technological trends. Within the medical field, supplying drugs is without doubt the most profitable niche. But there will also be many important opportunities for convergence with other sectors, including companies developing medical devices and drug-delivery technologies.

These areas must make progress in order to maximize the potential of many regenerative and

rejuvenative medicines. As biotech companies' capitalizations have increased, they have become less dependent on nonexclusive technology-sharing agreements with big pharmaceutical firms and more confident in their ability to take drugs to market without giving away the store. Accordingly, I expect to see more, and larger, biotech-to-biotech deals over the next few years.

We can also expect more exclusive technology partnerships incorporating royalty-sharing provisions. My own company recently completed an innovative transaction with [Cambridge Antibody Technology \(CAT\) PLC](#) that exemplifies these features. We not only contracted with CAT for access to its expertise in fully human antibodies, but also provided it with options to develop drugs from proprietary antigens in our collection. If it does so, we can share in the worldwide development of some of those drugs.

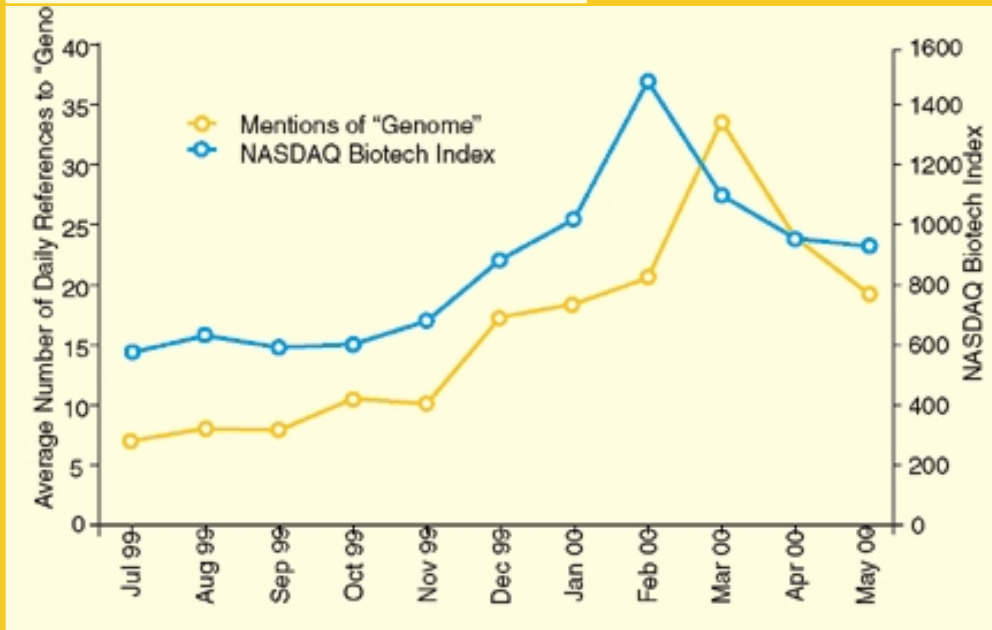
Although human genes, proteins, and antibodies used as drugs will be central to these technological trends and will dominate in the short term, genomics will also benefit and converge with conventional small-molecule drug discovery programs. Genomics provides many new targets for the pharmaceutical industry—molecular structures within the body that chemists collectively try to alter by means of drugs. One important promise of genomics, therefore, is that it may help alleviate the existing pharmaceutical industry's shortage of new blockbuster products and expand the long-term medical horizon.

Because genomics will be central to the development of regenerative medicine, it seems likely that a new genomics elite will emerge. It will comprise integrated biotechnology companies that have all the components in place to create a drug-based revenue stream. Companies providing technology of all sorts for these first movers are likely to benefit as well.

Genomics Will Benefit Patients

Those who gain the most, of course, will be the patients, who as a result of our efforts will live longer and healthier lives. Indeed, there is every reason to believe that longer lives will be an important feature of our future society, provided we can ensure that as many people as possible share in this medical bounty. Life expectancy is already increasing faster than the experts believed likely just a few years ago. We must, however, resist politically expedient efforts to limit pharmaceutical prices. Ill-advised efforts in that direction represent the greatest threat to the bright future I have sketched.

Media Attention on Genomics Mirrors the Stock Market



Source: Ernst & Young analysis

"Mentions of 'Genome'" refers to the average number of articles per day in the Dow Jones Interactive. Selected Publications database that mention the word 'genome.'

"...because of the explosion of press on the sector, we're starting to see more retail people selectively buying these stocks."

—Dennis J. Purcell, page 56

Defining Events in the Biotech Market ...

1 FINANCING

The window opens in late 1999...

- In the last six months of 1999, six companies—including [Maxygen Inc.](#), [Symyx Technologies Inc.](#), and [BioMarin Pharmaceuticals](#)—went public with IPOs that raised over \$478 million, nearly two to three times more than the average IPO issued only a few years ago.
- Between July and December 1999, 16 companies—including [Genentech](#), [Ilex Oncology](#), [Pharmacyclics](#), [ImClone Systems Inc.](#), and [VioPharma Inc.](#)—raised \$3.5 billion in follow-on financing.
- Fifty-three venture-stage financings—most notably [Versicor Inc.](#), [Eos Biotechnology Inc.](#), and [Pharmasset](#)—raised \$640 million in the second half of 1999.

...As investors and the media rediscover biotech...

- Genentech's public re-offering raised \$2.1 billion.
- By the end of November 1999, Biotech indices were 150 percent above the September 4 lows.
- In early 2000, mentions of "genome" in major news media increased 94 percent over December 1999, and this word entered into our common vocabulary.

2 COMBINATIONS AND ALLIANCES

Big pharma-biotech deals further whet investor appetites...

- Pharmaceutical companies continue to look to biotechnology with notable mergers and alliances such as [Warner-Lambert Co.](#) and [Agouron Pharmaceuticals](#), [Johnson & Johnson](#) and [Centocor](#), [Wyeth-Ayerst Laboratories](#) and [Aviron](#), [Merck & Co. Inc.](#) and [Sibia Neurosciences Inc.](#)

...And biotechnology stays within the family.

- Biotech companies using creative mergers, acquisitions, and alliances have strengthened the industry, including those between [MedImmune Inc.](#) and [U.S. Bioscience Inc.](#), [CV Therapeutics Inc.](#) and [Innovex](#), [Millennium Pharmaceuticals Inc.](#) and [LeukoSite Inc.](#)

3 PRODUCTS AND TECHNOLOGY

Biotechnology flexes its muscles with an impressive pipeline of products...

- At the end of June 2000, 283 products were in pivotal trials with cancer, infectious diseases, and neurology studies leading the way.

...And regulators do their part with increased efficacy.

- FDA drug approvals in the first six months of 2000 represented 75 percent of approvals granted during each of the two previous years and included a robust list of products.

... And the Story They Have Told.

...And momentum swings biotech to new heights in the new millennium...

- Nineteen companies—including [Diversa Corp.](#), [ACLARA Biosciences](#), [IntraBiotics Pharmaceuticals](#), [Tanox Inc.](#), and [Charles River](#)—went public in the first half of 2000, raising \$2.2 billion with an average of \$114 million per IPO.
- In the first six months of 2000, 27 follow-ons raised \$7.0 billion. Again Genentech led the way and 26 other companies—including [Celera Genomics](#), [Gene Logic Inc.](#), [Abgenix](#), [Celgene](#), [Medarex](#), [Emisphere Technologies](#), and [Maxim Pharmaceuticals](#)—together raised \$4.2 billion.

- Heralding the continued supply of new biotech companies into the future, 65 companies engaged in 71 private financings to raise \$1.1 billion, with [Rosetta Inpharmatics](#), [Athersys Inc.](#), and [Genaissance Pharmaceuticals](#) raising more than \$40 million each.

...Yet high volatility comes with this territory.

- By June 30, major genome companies declined an average of 54 percent from their March highs.

4 PUBLIC POLICY

Policy-makers show faith and support...

- Congress and President Clinton passed two \$2 billion increases in the 1999 and 2000 National Institutes of Health (NIH) budgets, representing the first installments of a five-year plan to double the NIH budget, dramatically increasing federal support for R&D.
- Legislators adopted a patent-reform bill that allows companies to extend patent protection to compensate for time lost during Patent and Trademark Office delays in reviewing applications.
- Policy-makers also re-authorized the R&D tax credit for five years, the longest extension ever.

...While threatening prohibitive regulations.

- Legislators and the Administration are crafting a Medicare prescription drug benefit that could incorporate, or lead to, some form of price control.
- Proposals for mandatory labeling of biotech foods reached the halls of Congress and the FDA.
- Regulators crafted gene-therapy reform proposals following the tragic death of a 17-year-old clinical trial participant.
- On March 14, 2000, President Clinton and British Prime Minister Tony Blair's joint statement on genetic patents sent shock waves through the market and led to investor confusion.

Convergence: A Technology Explosion

The convergence of formerly distinct industries is occurring at a rapid pace. As convergence continues, the boundaries between the biotechnology industry and an array of disparate market sectors are blurring, leading to a large number of new, hybrid products.

Drawing from this cross-market strength, convergence may ultimately lead to a more sustainable, stable biotechnology market. Further, as the aggregate market capitalization of this convergent biotechnology industry increases, biotechnology companies may play a more prominent role in long-term investment strategies.

In addition to a strong pipeline of human therapeutic products, the biotechnology industry is increasingly interacting with non-traditional sectors such as fine chemicals, semiconductors, information technology, clinical health care, and agriculture. Significant players in these industries are beginning to harness the power of biotechnology. Indeed, many companies are operating in multiple sectors at the same time. The following section provides an overview of these areas of convergence.

Convergence With the Chemicals Industry

Industrial manufacturing processes have traditionally relied upon high-temperature, high-energy noxious chemicals, such as acids, alkali, silicates, and surfactants, which can produce hazardous wastes and excess phosphorus. Enzymatic reactions, however, can safely serve the same role; that is, to bring together reactants to promote the stability of the intermediate state of a reaction.

This biocatalytic approach can be leveraged from living systems and transferred to a variety of manufacturing processes. Enzymes such as lipases, proteases, cellulases, and amylases can be substituted for both noxious and high-temperature, high-energy chemicals. This approach can be applied to a wide range of manufacturing areas, including the processing of grain and the production of detergents, starches, and textiles.

Bringing Biotech to Industrial Processing

Several companies—including [Maxygen](#), [Genencor](#), and [Diversa](#)—have been active in developing biotechnology approaches for industrial processes. Maxygen has focused on molecular breeding technologies, an inherently convergent platform that is widely applicable to many industries, including protein pharmaceutical, agriculture, chemical, and industrial biotechnology.

“This form of recombinant genetics drives high-quality genetic diversity,” says Russell Howard, CEO of Maxygen. Linked to multiple-function assays, genes and gene products can be selected for multiple traits at the same time, and effective

screening can be carried out with relatively low numbers of recombinants. In this manner, live functional screens can be carried out in organisms as diverse as mice or plants. “Defining product opportunities are limited only by the imagination of our researchers,” says Simba Gill, President of Maxygen.

Companies that are developing applications for industrial biotechnology are integrating improvements in the properties of both single enzymes and pathways of enzymatic cascades. Genencor makes use of molecular evolution to improve the properties of proteins and enzymes for specific commercial applications. The company engineers both single proteins and complex metabolic pathways. The assay system used to screen for functional properties is also inherently convergent: For products intended for the industrial, consumer health care, and agriculture markets, the company uses a mouse model of the human immune system to predict the human allergenic potential of these products.

Convergence may ultimately lead to a more sustainable, stable biotechnology market.

In addition to re-engineering known gene products, it is possible to seek out naturally evolved gene products with functions that have been optimized for extreme environments. Diversa accesses genetic material from uncultured organisms found in diverse natural environments, catalogs and stores their genes in gene libraries, and screens these libraries for a variety of activities. The company then enhances gene product function through several techniques, including saturation mutagenesis and genetic reassembly.

New Approaches, New Materials

Symyx takes a highly integrated biotech approach to the creation of new types of materials. After defining the desired characteristics of a potential material, a chemist selects the combination of elements that may fabricate the target material. Using a combinatorial chemistry approach akin to that used in pharmaceutical development, a combinatorial chemistry library is created and tested in highly parallel, high-throughput screening assays.

Sunesis is pursuing “a fundamentally different approach to lead discovery, based on fragment assembly and molecular casting,” according to President and founder Jim Wells. Working with small pharmacophores, Sunesis is recombining these molecular units by linking chemistry and rapid screening of combinations of pharmacophores to identify those that bridge “hot spots,” or critical contact points on a protein. According to James Young, CEO of Sunesis, “we seek to access more refractile and challenging enzyme and protein–protein targets with a class of drug-like molecules that can be advanced to the next stage of drug discovery.”

Convergence With Information Technology

Advances in information technology have brought powerful computational capabilities to biologists’ laboratories, and this has allowed the storage and manipulation of very large scale information sets. In addition, because the blueprint for the human

genome is now available, pharmaceutical and biotechnology companies increasingly leverage the tools and techniques of bioinformatics to find new drug targets. Current research areas include molecular modeling, genomics, proteomics, and physiomics.

Molecular Modeling: Revealing Structural Logic

Many companies are expanding their capabilities in the modeling of individual molecules such as nucleic acids and proteins. Modeling of the three-dimensional structure of a protein based upon its one-dimensional amino acid sequence has proven to be a particularly intractable problem: A direct, predictive relationship between one-dimensional sequence and three-dimensional structure has not been fully described.

In December 1999, **IBM** announced plans to invest \$100 million to build a super computer termed “Blue Gene.” This computer will operate at a clock speed 500 times faster than the world’s currently fastest supercomputer. Blue Gene’s massive computing power will be initially used

to model the folding of human proteins, making this fundamental study of biology the company's first computing "grand challenge" since "Deep Blue" defeated world chess champion Garry Kasparov in 1997.

Genomics:

A Road Map for Finding Drug Targets

Understanding the basis of disease at the molecular level is essential to discovering new therapeutic targets. New tools and products have been created by more than 40 companies to assist drug companies in tackling the genetic basis of disease. **Celera** was a major participant in the effort to sequence the human genome. The company completed a draft of the human genome in June 2000.

Incyte Genomics has developed an integrated genomics-based platform. Incyte's database discovery approach compares partial genes or protein sequences to genes or proteins of known sequence in order to predict their biological function.

Several companies operating in this space are fusing together a suite of interdisciplinary approaches to systematically develop new products and services. **Millennium Pharmaceuticals** has developed an automated high-throughput DNA sequencing approach that allows for the rapid acquisition and data mining of DNA sequence data.

The sequences are grouped into clusters based on their similarities, and a consensus sequence is derived per gene and compared to all other genes and motifs to seek an optimal match. These results are then stored in an annotated database.

Rosetta Inpharmatics has developed a technology platform for assessing the impact of a compound's target activities within any cell type. The company makes use of DNA microarrays, bioinformatics data acquisition and analyses, and a variety of molecular biology techniques to support the expression profiling. This technique has applicability in several markets, including the pharmaceutical, biotechnology, agrochemical, and agricultural biotechnology industries.

Gene Logic has created a set of gene expression database products for the pharmaceutical, health care, and life science industries. Integrating data management techniques with gene expression information, the company can identify the degree to which genes are active in healthy and abnormal tissues.

With the completion of the human genome map, there's been an explosion of data available in both the public and private domain. Several companies are responding by developing data management solutions with integrated computation tools.

IPO: Symyx Technologies Inc. . \$89.2M . November 1999

Biotech at a Glance (\$ in Billions)

	Public Companies			Industry Total	
	1999	Percent Change	1998	1999	1998
Financial					
Sales	\$13.6	13.0%	\$12.0	\$16.1	\$14.5
Revenues	18.8	13.0	16.6	22.3	20.2
R&D Expense	6.9	2.6	6.7	10.7	10.6
Net Loss	3.1	65.3	1.9	5.6	4.4
Industry					
Market Capitalization	\$353.5	156.4	\$137.9	\$353.5	\$137.9
Number of Companies	300	(5.1)	316	1,273	1,311
Employees	114,000	7.5	106,000	162,000	155,000

Sources: Ernst & Young analysis of company financial statement data. Financial data based primarily on financial statements from December 31 of each year. Number of companies and employees as of December 31 of each year. Market capitalization for 1999 and 1998 from June 30, 2000 and June 30, 1999, respectively. Some numbers may appear inconsistent because of rounding.

Silicon Genetics has developed a software package to help researchers locate key genes faster and share results with colleagues more easily. “We are a software company, and our mission is to help research scientists transform gene expression data into more meaningful biological knowledge,” states founder and CEO, Andrew Conway.

DoubleTwist provides bioinformatics services over the Internet. The company’s data warehousing, processing, and mining software assists researchers in the life sciences through an Internet-based interface.

Single genes and their functions have been studied for several decades. With the advent of microarray technology, it is now possible to study large numbers of genes and their expression patterns in parallel. **Affymetrix** produces microarrays of synthetic oligonucleotides bound to surfaces. These allow researchers to perform experiments based upon high-throughput, large-scale gene expression analysis. By comparing the expression patterns of genes induced in normal tissues against those expressed in abnormal tissue, researchers can identify population-based profiles of altered genetic function.

Even traditional technology companies see the market potential brought about by genomics information and technology. Motorola is developing

“biochips” for research and diagnostic applications and its CEO, Chris Galvin, has stated publicly that life science “is too fundamental a technology change for us (Motorola) to not find a way to contribute.”

Proteomics:

Probing the Functions of Gene Products

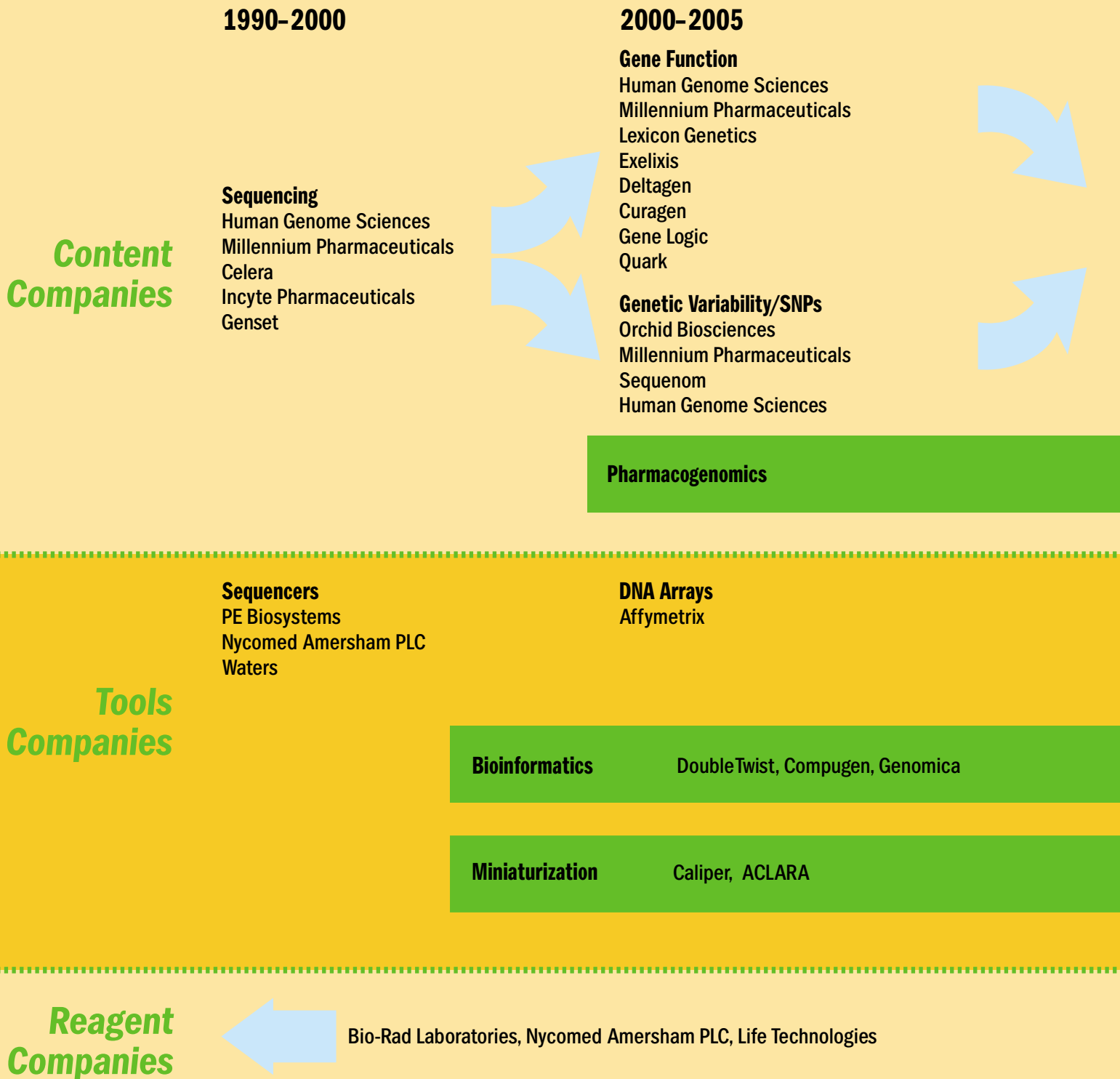
Proteins are produced by genes upon transcription (the transformation of the information in DNA sequences into RNA) and translation (the transformation of the information in RNA into protein). Most disease processes manifest themselves at the level of protein activity, but until recently, high-throughput analysis of proteins was not possible. Proteomics is the field in which the functions of proteins, and their interrelationships, are identified. Also studied is the aggregate role that proteins play in maintaining health and causing disease.

Through a collaboration with **Oxford GlycoSciences**, based in the UK, Incyte Genomics has developed tools for studying proteomics. Oxford GlycoSciences uses its proteomics technology platform in concert with Incyte’s gene expression microarrays and genomic databases to develop a protein expression and sequence database containing annotated protein expression data for numerous tissues.

IPO: Caliper Technologies Corp . \$72.0M . December 1999

While M&A activity reduced the number of companies in the industry, the industry has continued its march toward maturity.

Genomics: The Key Players and Where They Are Leading Us



Source: Credit Suisse First Boston Research.

2002-2010

**Lead Generation/
Lead Optimization**

Vertex
Praecis
Abgenix
Medarex
Protein Design Labs Inc.
Human Genome Sciences
Millennium Pharmaceuticals
MorphoSys
Cambridge Antibody Tech.



2004-2010

**Fully Integrated Drug
and Biotech Companies**

Most biotech and
pharmaceutical companies

CROs

Quintiles
Covance
Parexel

**Fully Integrated Drug
Discovery Companies**

Human Genome Sciences
Millennium Pharmaceuticals

“The technology explosion in the post-genomic era is fundamentally changing the industry infrastructure. Instead of conglomerates that can do it all from genetic research to product marketing, the biotech industry is now a matrix of supply chain relationships along the drug discovery process, with increasing reliance on technology alliances and partnerships.”

–Alex To, Head of Biotechnology Research Group, Credit Suisse First Boston

Variagenics
Millennium Pharmaceuticals
Genaissance Pharmaceuticals



High-Throughput Screening

LJL Biosystems
Aurora Biosciences
Evotec
Molecular Devices

Structural Bioinformatics



Invitrogen, Qiagen, Sigma Aldrich



Celera recently raised \$983 million in capital, and a significant amount of this money is being invested in proteomics research and development. More than 40 companies worldwide are actively engaged in proteomics research and development, and the trend is accelerating as the needed tools become cheaper and more widely available.

Physiomics:

Mapping Metabolism Molecule by Molecule

Physiomics is the study of physiology at the molecular level. By integrating information from a variety of fields—including genomics, proteomics, cell biology, genetics, and biochemistry—companies have begun to simulate living cells, the human body’s metabolic pathways, and whole organs, by using computational and mathematical models.

Physiome Sciences has developed a computational modeling system that integrates mathematical tools, annotated biological databases, and an extensible markup language (XML)-based modeling language. The XML standard allows for the efficient transfer and migration of information across potentially disparate information systems. Using this standard, the company creates computer models of biochemical pathways, cells, organs, and organ systems.

Entelos has developed a computer-based disease-simulation system to serve as a quantitative

model of human physiology. This approach assists researchers in testing hypotheses in “virtual experiments” and in organizing scientific and clinical data.

**Convergence With Health Care:
Post-Genomic Medicine**

The mapping of the human genome in the year 2000 stands as a hallmark in the history of science. As the full genomic sequence nears completion for five individuals (three women and two men), research scientists and physicians are looking to expand the population of individuals whose genomes have been sampled and genotyped, study their genetic diversity, and apply this knowledge to clinical strategies.

Identifying the Genetic Basis of Disease

Several companies—including **DNA Sciences**, **deCode Genetics**, and **Framingham Genomics**—are pursuing strategies to identify the genetic basis of particular diseases among well-characterized patient populations. This information will help identify better clinical management and therapeutic approaches for these patients.

For example, the strategy of DNA Sciences is “to recruit patients both on-line, through **DNA.com**, and off-line, through relationships with care providers, and to build an infrastructure to support a fast and cheap genotyping capacity for

Taxes Generated by the Biotechnology Industry, 1999

Type of Tax	Taxes Collected (\$ Millions)		
	Federal Taxes	State Taxes	Local Taxes
Individual income tax	\$3,351	\$649	\$61
Corporate income tax	914	112	10
Social security taxes	2,331	—	—
Sales and use taxes	—	628	133
Excise taxes	74	288	61
Property taxes	—	—	896
Other taxes	173	222	55
Sub-totals	\$6,843	\$1,899	\$1,216
Total Taxes			\$9,958

Source: Ernst & Young LLP, *The Economic Contributions of the Biotechnology Industry to the U.S. Economy, May 2000.*

these patients,” according to the CEO of [DNA Sciences](#), Hugh Rienhoff.

The impact of this approach may be helpful in the early diagnosis and patient-centered treatment of a wide variety of diseases, particularly those in which the diagnosis was difficult to make, the clinical course was impossible to predict, or the choice of medicines was random. In addition, increased patient awareness of potential diseases and the impact of lifestyle on disease progression can be an important incentive for making healthy choices.

Improving the Design of Clinical Trials

Drug discovery is inherently risky: The failure rate in clinical trials for new, innovative chemicals approaches 90 percent. And that failure rate is costly; clinical trials can cost more than \$100 million per trial. Accordingly, several emerging technologies may help researchers make important decisions at an early stage of development.

[Surromed](#) is currently developing novel proteomic and metabolite profiling techniques to measure and monitor thousands of distinct molecular species found in blood, saliva, and other biological fluids. These technologies will provide detailed phenotypic data for individual patients. The resulting phenotypic profiles—in conjunction with a proprietary, Web-based, electronic medical data capture tool—will enable the discovery of novel

biological markers that indicate the presence and progression of disease. “Longitudinal studies may reveal previously undetected disease markers with significant predictive value and novel therapeutic targets and strategies with significant pharmaceutical and medical value,” stated Gordon Ringold, CEO of Surromed.

The contract research industry is leveraging information technology to improve the efficiency and effectiveness of the clinical trial process. For example, [Quintiles](#), has made substantial investments in electronic commerce in general, and in informatics in particular. The company invests in bringing these technologies to bear on health care-related services, specifically the added operating efficiency that Web-based services can create. To that end, Quintiles has recently made a significant investment in [Healtheon/WebM.D.](#)

Quintiles CEO Dennis Gillings states, “the recruitment of patients is probably the greatest rate-limiting step once we have moved into the clinical trials process.” Historically, patients have been recruited through their doctors, not directly by the company. The Internet allows companies to recruit patients directly, however, and these patients can then be referred to local physicians participating in the trials.

IPO: Maxygen Inc. . \$110.4M . December 1999

While much attention is given to the potential of the biotechnology industry, currently the industry makes substantial contributions to the U.S. economy.

Mass-Customizing Drug Therapies

Historically, drug treatments have been designed by studying the responses of patient populations. Because each individual patient has both a unique genetic makeup and a unique lifestyle, however, certain drug products and therapeutic protocols work well in some patients and poorly in others. Fueled by advances in both biotechnology and information technology, the rapid development of therapeutic approaches for individuals is now possible for certain diseases and drug products.

Virologic has developed a therapy guidance technology to rapidly determine the susceptibility and resistance of an individual patient's physiology to antiviral drug therapies. The company has developed a rapid phenotypic drug susceptibility assay for HIV that measures an infected patient's resistance to antiretroviral drugs, such as reverse transcriptases and protease inhibitors. This assay is used by physicians to design therapeutic strategies for individual patients.

Health Care and Information Technology: An Ideal Pair

The traditional information technology infrastructure that supports most health care environments is based on noncompatible software, hardware, and data formats. Eliminating the manual, error-prone, and

time-intensive business processes currently in place would greatly increase the overall efficiency of the health care market. For this reason, many companies are developing business strategies that seek to migrate to an electronic channel-based commerce and communication system.

The rapid development of communication protocols, new switching and routing technologies, and significant improvements in hardware infrastructure all support electronic channel migration strategies. In particular, exponentially expanding public access to the Internet allows for increasing numbers of both individuals and companies to participate in the information economy. Increased mass data storage devices allow for the efficient management of and quick access to large amounts of on-line data. Exponentially increasing data bandwidth capacities are fueling the exchange of data on a scale unique in human history. Finally, authentication and encryption technologies allow for the creation of secure environments in which customers may eventually place their trust.

Taken together, these technological and strategic factors provide both the means and the motivation for a significant migration toward a digital commerce environment. This migration is taking place within three distinct market segments: community, connectivity, and commerce sites.

IPO: Tularik Inc. . \$97.3M . December 1999

Ernst & Young Survival Index

	1999		1998		1997	
	Number of Companies	Percent of Total	Number of Companies	Percent of Total	Number of Companies	Percent of Total
More than 5 years cash	76	25.2%	75	23.7%	101	30.9%
3-5 years cash	29	9.6	23	7.3	30	9.2
2-3 years cash	30	10.0	38	12.0	46	14.1
1-2 years cash	59	19.6	76	24.0	68	20.8
Less than 1 year cash	107	35.5	105	33.1	82	25.1
Total Public Companies	301		317		327	

Sources: Company financial statement data, Ernst & Young.

Survival index skew analysis indicates the number of years of cash that companies have on hand based on current spending levels. Estimates are based on fiscal year-end numbers. Some numbers may appear inconsistent because of rounding.

Community Sites: Building Virtual Societies

Community sites seek to build virtual societies of patients with similar issues and concerns, and often link these patients to physician specialists who then communicate with them through electronic mail and chat rooms. The health care information available on community sites is often delivered across multiple specialty areas, updated regularly, and typically derived from a mixture of both proprietary and publicly available sources. Aggregating and updating content from many different sources, community sites often organize this information so it can be easily queried and read by customers seeking detailed information on disease states, symptoms, treatments, diet, fitness, lifestyle, or medical equipment and supplies. The prevalence of these sites will have a profound impact on the marketing of pharmaceuticals to doctors and patients.

The communities themselves are often composed of both patients and physicians who speak among themselves, as well as members of other virtual communities. For-profit community sites include accenthealth.com, americasdoctor.com, beansprout.com, cancerfacts.com, drdrew.com, drkoop.com, drspock.com, healthcentral.com, healthhero.com, healthstream.com, selfcare.com, smarttalk.com, intelihealth.com, medcast.com, medconnect.com, mediconsult.com, medscape.com,

onhealth.com, and salu.net. In addition, there are thousands of private Web sites developed by individuals and nonprofit organizations that can complement or compete with the for-profit community sites.

Connectivity Sites: Streamlining the Flow

Connectivity sites are now being implemented to improve and integrate the currently tepid information exchange among patients, physicians, pharmacies, labs, hospitals, vendors, and payers. Communication among these individuals is based on paper forms, phone calls, and redundant data entry. Patients, physicians, and information personnel would all benefit from an efficient and effective flow of digital information. Improvements would be seen in payment claims, eligibility checks, formulary checks, prescription orders, lab test orders, and results reporting. To this end, companies are developing digital data management, procurement, and fulfillment processes that greatly streamline the central information network for the health care environment.

Connectivity sites include abaton.com, caresoft.com, Healtheon/WebMD.com, pointshare.com, skila.com, and wellmed.com. These focus on medical record management and clinical information for patients. Sites designed for payer-provider communication include asterion.com, claimsnet.com, careinsite.com, idx systems, infocure.com, medix resources, and passport health

IPO: Antigenics Inc. . \$72.5M . February 2000

Biotech companies suffered under the tight equity markets of 1998 and most of 1999. Without the necessary influx of funds more companies found themselves with diminishing cash coffers. This situation was reversed for many, especially in the genomics sector, in early 2000.

communications. Sites focused on the management of clinical data include [Axolotl](#), [iScribe](#), [itrust](#), [knowmed](#), [infominers](#), [masterchart](#), [medicalogic](#), [navimedix](#), [\(a\)outcome](#), [valuemed](#), and [vasona](#).

Commerce Sites: Connecting the Players

Commerce market segments include business-to-consumer (B2C) sites, which cater to the end-users of products and services, and business-to-business (B2B) sites, which focus on business between buyers and sellers in the health care supply chain.

B2C sites have been established to facilitate the on-line purchase of products and services. Customer acquisition and site branding are both critical for the long-term strategies of B2C sites. B2C sites include [drugstore.com](#), [planetRx.com](#), [rx.com](#), and [vitaminshoppe.com](#). These and other B2C sites typically migrate toward one of two strategies: to serve as a broad platform for the on-line purchase of an expanded health products inventory or to focus on a niche market, such as vitamins or therapeutic products based on alternative medicines.

B2B sites have been established to minimize the information inefficiencies in the highly fragmented health care supply chain, which includes manufacturers, distributors, wholesalers, and retailers. A clear and compelling value proposition for both buyers and sellers is essential to induce both parties to participate in electronic transactions on these sites. Examples of sites include [channelpoint.com](#), [neoforma.com](#), and [medibuy.com](#). An expanding class of B2B commerce sites focuses on the sales of laboratory reagents, such as fine chemicals, enzymes, and other laboratory supplies. These sites include [chemdex.com](#), [CheMatch.com](#), [chemnavigator.com](#), [ChemConnect.com](#), [Commerx](#) [PlasticsNet](#), [sciqwest.com](#), and [verticalnet](#).

Expanding the Impact of Agricultural Biotechnology

From start-up ventures to global corporations, many companies have invested in significant R&D programs to greatly accelerate the crop-breeding strides made traditionally by farmers. Food crops—including wheat, corn, and rice—were traditionally bred for hardiness and yield through the slow and laborious crossing of different crop strains. Results of these experiments took years to achieve. Today, the highly refined genomic and genetic engineering of agricultural products is carried out in weeks to months, significantly compressing the breeding cycle.

Altering the Traits of Plants

Several traits are currently targeted for genetic modification, including increased resistance to temperature and moisture extremes, and improved resistance to insects and pests. For example, [Agraquest](#), an agricultural biotechnology venture, is focused on environmentally responsible products and services for pest management. Taking advantage of the diversity found within nature, the company seeks out hardy, high-producing strains of the bacterium, *Bacillus subtilis*, which has naturally high pesticide potency. The company then optimizes the fermentation process on pesticide activity, to formulate significant increases in pesticide activity.

[Exelixis](#) is engaged in research to discover and develop improved drugs that treat a variety of human diseases, as well as the creation of products intended for multiple agricultural markets including optimized insecticides, fungicides, and herbicides. To do so, Exelixis makes use of comparative genomics and the computer-based modeling of signaling networks.

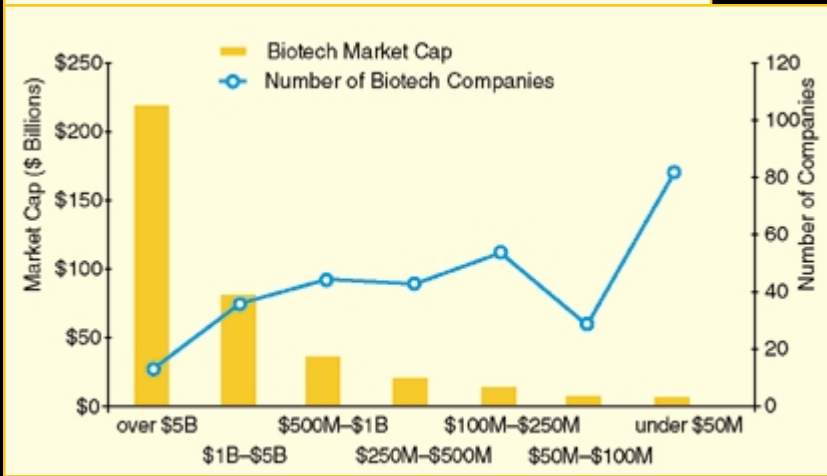
Stated President and CEO George Scangos, “Exelixis has found that, at the tissue culture level, gene function is 80 percent transferable between species.” Accordingly, the company—in an assumption-free process—screens functions across genomes to seek out those genes whose modulation has a desired effect, such as improved insect resistance.

Changing Plant Structures

Commercial crops are also being structurally modified to yield alterations in leaves, stems, branches, roots, or seed structures. These modifications can reduce the energy requirements of plants, further increasing crop yields. In addition, the nutritional content of crops can be substantially enhanced through the adjustment of the relative proportions of molecules such as oils, proteins, fats, and carbohydrates. For example, [Mycogen](#)—a wholly owned subsidiary of the [Dow Chemical Company](#) and an affiliate of [Dow AgroSciences](#)—has developed sunflower seeds with relatively high oleic and linoleic acid concentrations.

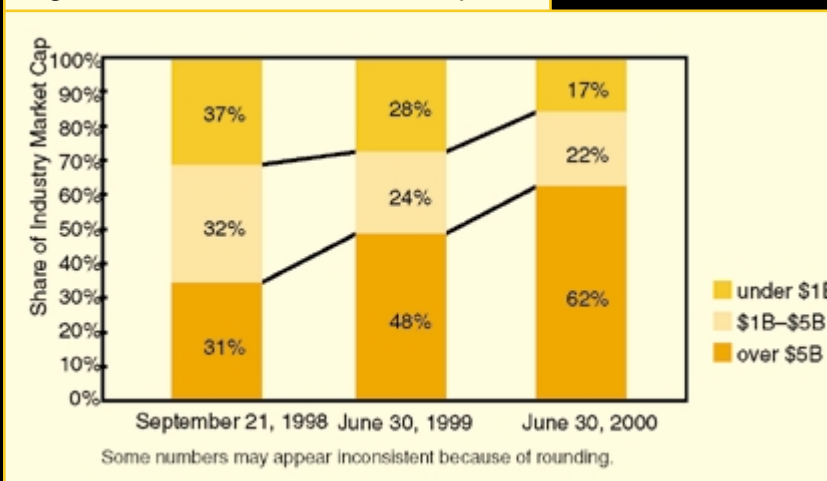
Agricultural biotechnology companies are also leveraging the diversity of nature in their product development strategies. [Phytera, Inc.](#), for example, developed cell culture technologies to create cell libraries for plant species and marine microbes. Phytera will use these libraries to simulate various environmental stresses, to seek out

Large Firms Continue to Dominate Industry Market Cap (6/30/2000)



Sources: Company financial statement data, Ernst & Young.

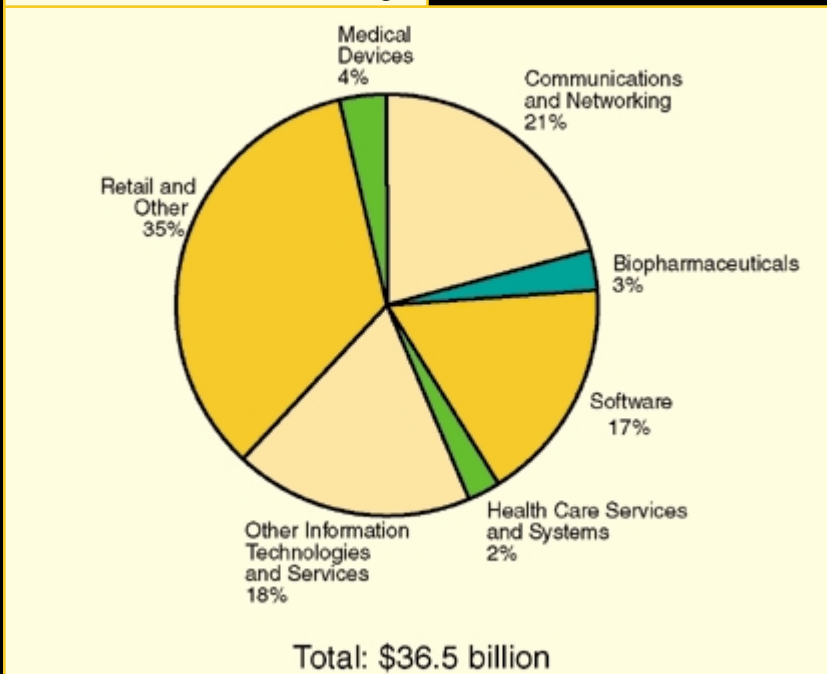
Large Firms Continue to Gain Most Market Cap Share



Source: Compustat

The large-cap biotech companies benefited disproportionately from the stock upsurge, due to investors' desire for more liquid stocks, and the financial and research success at top tier and emerging genomics companies.

Breakdown of 1999 Venture Financing



Source: VentureOne

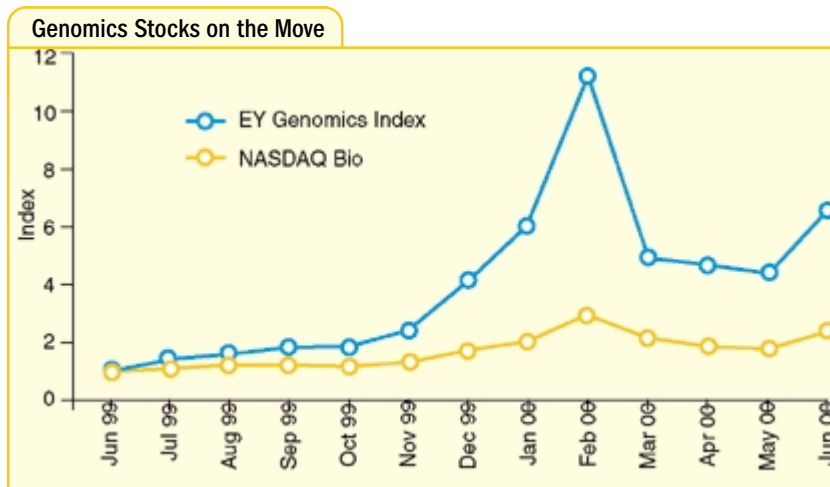
differential gene expression patterns that may correlate with gene function.

Cyanotech works with microalgae technology to produce natural products from microalgae, such as phycobiliproteins. These are fluorescent pigments often used in immunologic diagnostics.

Intercompany collaborations are creating new approaches to developing agricultural biotechnology as well. **Cereon Genomics**, for instance, represents a collaboration between **Monsanto** and **Millennium** to establish an agricultural genomics venture. This venture will bridge technologies such as bioinfor-

matics, expression profiling, and high-throughput screening, and provide leverage among them. With technologies that were the exclusive domain of biotechnology companies developing therapeutic products, agricultural biotechnology companies are rapidly and systematically expanding the pool of knowledge supporting agricultural market development.

This convergence represents the current state of the industry. Convergence is not only redesigning diverse industries in our marketplace, it is also creating a stable and sustainable biotechnology industry.

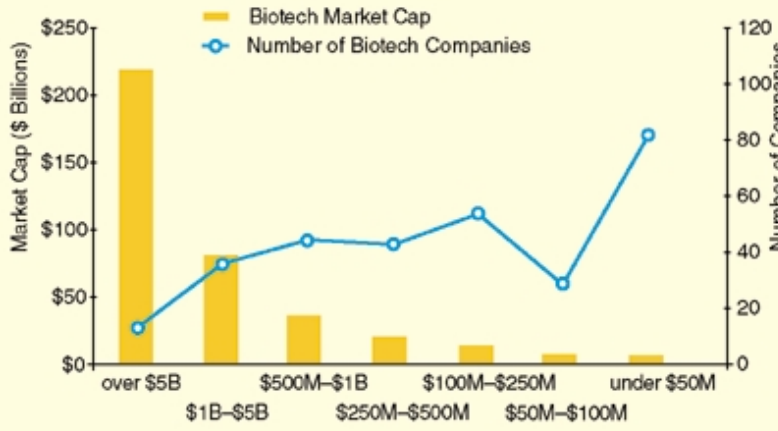


Sources: CBS Marketwatch, Bigcharts Inc. <www.bigcharts.com>. Genomics index constructed by E&Y based on aggregate of market capitalization of selected stocks.

“I firmly believe that genomics—the use of large collections of human genes to answer biological questions—is now giving rise to an entirely new class of medicines that could rescue the pharmaceutical sector.”

—William A. Haseltine, Ph.D.
“The Promise of Genomics,” page 6

Bio Index vs. Blue Chip and Technology Stocks



Source: Yahoo!Finance <www.finance.yahoo.com>

“Biotechnology had been down for a long time, but many of the companies associated with genomics had product portfolios that matured in the clinic over the past several years. They became more interesting, and money flowed into that sector because it was undervalued, on a relative basis, compared with technology. There was an intense focus on the genomics phenomenon, starting with the sequencing efforts by the Human Genome Project and Celera Genomics.”

—Russell Ray, page 54

Strategic Drivers of Convergence

Brian Sager, Ph.D.

Life Sciences Strategy Consultant



In the past year, many companies within the biotechnology industry have been extensively interacting with high-technology companies and utilizing technology originally developed outside of the traditional biotechnology market. This convergence is creating a hybrid marketplace that leverages the strategies, techniques, and business models of formerly disparate markets.

From agriculture to fine chemicals, from drug discovery to health care, companies are migrating and integrating their scientific approaches and business aspirations to create broad platforms for new products and markets. Fueled by—and contributing to—developments in information technology and nanotechnology, these hybrid markets are true bellwethers of the information age, generating enormous quantities of information at multiple scales of time and space.

There are two primary drivers of this industry convergence. First, a market convergence is under way in which companies that had formerly focused on only one market—for example, human therapeutic products—are now expanding into other markets—such as, agriculture. This market convergence is blurring the boundaries of these industries and fueling their rapid collective growth.

Second, a technology convergence is building upon itself in which companies with a technology platform or product for one market are now leveraging that technology in entirely new areas. In this manner, the creativity and innovation that supports individual markets can have an impact on the growth and strategic direction of many other markets.

Taken together, these convergence drivers are restructuring the very architecture of the biotechnology industry.

Mapping the Synergy of Convergence

The convergence spiral shown in “The Dynamics of Industry Convergence” (page 28) illustrates one example of the dynamics of industry convergence. The growing confluence of technology platforms (at the center of this diagram) drive the creation of multiple cross-industry market strategies.

Converging Technology Platforms...

Convergence through the cross-industry spread of technology is rapidly progressing in a self-propagating loop. The biotechnology and chemicals industries are becoming ever more tied together through several technology platforms, including combinatorial chemistry, molecular breeding, and high-throughput screening. Recently, companies traditionally operating with a focus in only one of these industries have begun to extensively use the tools and techniques of the other.

Similarly, biotechnology companies have amassed enormous quantities of data through many lines of research, including genomics, proteomics, and differential gene expression experiments. These data require appropriate management, and pattern detection is critical to extract value from the raw

information. Many developmental efforts have, therefore, been tied to advances in information technology, including the creation of large relational databases and the application of a myriad of artificial intelligence algorithms.

The information technology approaches applied to biochemistry are equally applicable to the fine chemicals marketplace, and companies developing new chemical entities are also organizing their data in large databases with refined analyses programs and multiple, high-bandwidth ports of access. In turn, analyses of the screening data associated with

computational standards, the development of nucleic acid chemistry-based parallel information processing is making significant strides toward commercial applications.

The chemistry and fine chemicals industries are being revolutionized by several approaches borrowed from biotechnology, including molecular breeding, metabolic pathway engineering, and mass fermentation. As a result, the industrial chemicals processing industry is migrating away from high-temperature, high-energy reactions catalyzed by noxious chemicals, toward more environment-friendly, enzyme-

A market convergence is under way in which companies that had formerly focused on only one market are now expanding into other markets.

specific chemical compounds are promoting the design and synthesis of new chemical structures in a broadly systematic manner.

...and Converging Market Strategies...

The synergistically convergent technology platforms of the biotechnology, chemicals, and information technology industries are fueling the application of hybrid technologies across multiple—and formerly distinct—markets. For example, the application and migration of biotechnology products and services to the agricultural market has been building for several years, and recent joint ventures and strategic alliances blur the lines between companies interested in agricultural markets and those interested in pharmaceutical applications.

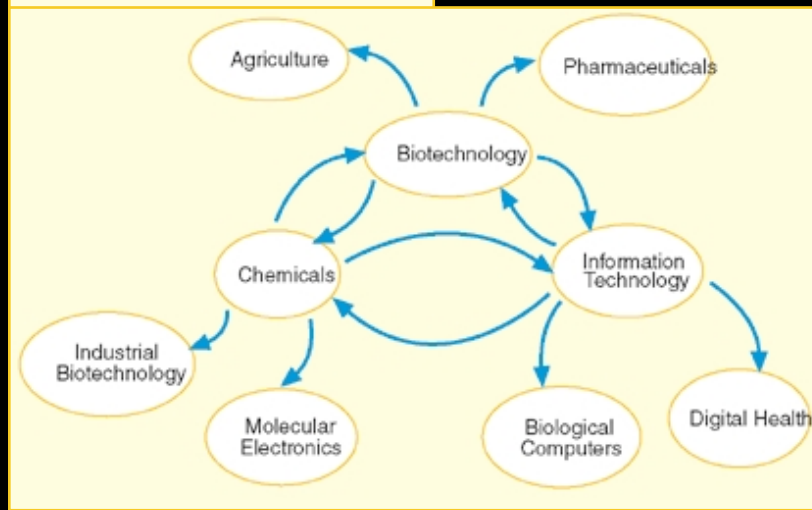
Advances in information technology have catalyzed both the growth of the Internet and the emergence of a plethora of companies bridging the health care and Internet economies. From the creation of community-based, connectivity-based, and commerce-based Web sites focused on the health care market, to the deeply expanded management and analysis of clinical trial data, companies are leveraging information technology platforms as never before. At the same time, the theoretical framework underlying computer science is being used to guide in the design of biologically based computers. While relatively primitive by modern

based chemical production processes. In a different vein, the birth of the molecular electronics industry occurred in part because of advances in the design and synthesis of sufficiently abundant chemical compounds and their screening by use of devices operating at the scale of nanotechnology.

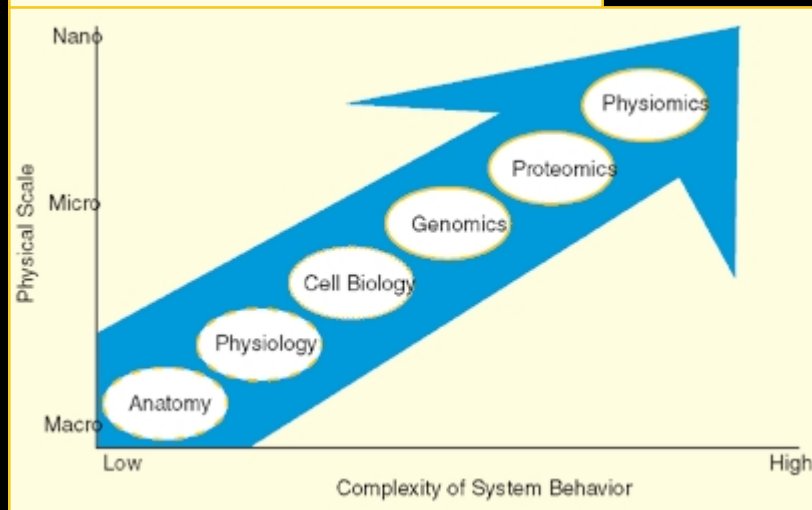
...Lead Toward the Future of Biotechnology

Human therapeutics has historically focused on progressively smaller spatial scales and increasingly complex system behavior (“The Complexity and Scale of the Biotechnology Industry, The Increasingly Complex Science of Human Therapeutics,” page 28). The convergence of technology platforms and the migration of market strategies across multiple industries has broadened this focus, so that modern fields of highly integrated research and development—such as industrial biotechnology, agricultural biotechnology, nanotechnology, and biological computing—span multiple spatial scales and function through multiple levels of system complexity (“The Complexity and Scale of the Biotechnology Industry, Convergence Across Multiple Industries,” page 28). This expanding scope will require the further convergence of mathematical, computational, and physical approaches to support the integrated design, fabrication, and operation of hybrid products that address their respective markets in a responsive and adaptive manner.

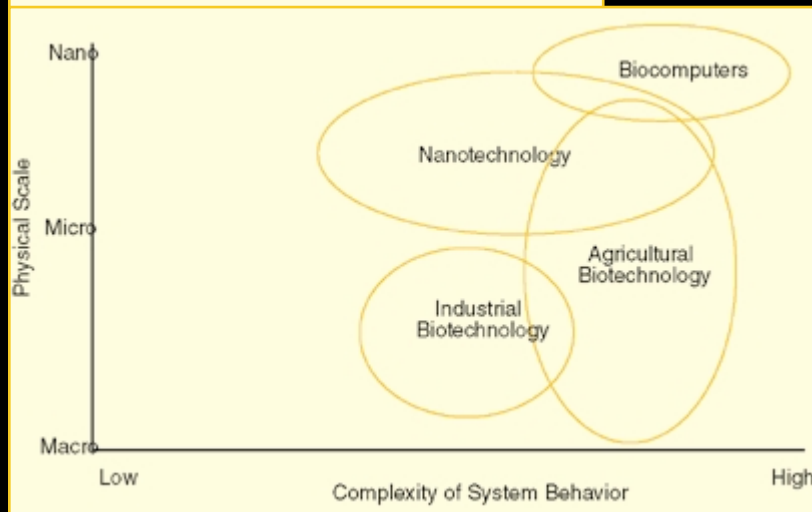
The Dynamics of Industry Convergence



The Complexity and Scale of the Biotechnology Industry: The Increasingly Complex Science of Human Therapeutics



The Complexity and Scale of the Biotechnology Industry: Convergence Across Multiple Industries



Sources: Brian Sager, Ph. D., Ernst & Young, 2000.

Toward the Future of Convergence: Integration of Biotechnology and Nanotechnology

Both nanotechnology and molecular electronics researchers have made use of the technological developments in the life sciences, including the use of enzymes, proteins, and small organic molecules in the synthesis and assembly of very small scale materials. These approaches could lead to new ways to design and fabricate extremely small information-processing and mechanical devices.

Structures That Self-Assemble

Electronic and mechanical devices are continually being designed for increasingly smaller spatial scales. The self-assembly of these devices, therefore, becomes essential to their rapid development and commercialization. Without self-assembly, the reliable and cost-effective manufacture of nanoscale devices would probably be impractical. With self-assembly, however, extremely small devices might be constructed in large quantities for commercial applications.

display is being used to select for peptides that combine to metal nanoparticles. Researchers have also isolated proteins from glassy sponge spicules that have been used to control the synthesis of silicon nanoparticles. These proteins are thought to be involved in building architecturally advanced silicon structures.

Binding Proteins for Specific Materials

Since proteins can dictate growth of a crystal structure, it should be possible to find proteins that bind to specific materials with specific forms. Evelyn Hu and colleagues, at the [University of California, Santa Barbara](#), have used a phage-display-based combinatorial peptide library to select for peptides that can bind to semiconductor substrates. Hu has shown that it is possible to screen for organic peptide sequences that can bind to specific inorganic semiconductor substrates.

In a different approach, Shimon Weiss and colleagues at the Lawrence Berkeley Lab are tagging biological molecules with quantum dots. Ultimately, these researchers seek to engineer proteins and other biological molecules that may be able to specifically

A technology convergence is building upon itself in which companies with a technology platform or product for one market are now leveraging that technology in entirely new areas.

The self-assembly of small devices and molecules currently faces two major challenges. One, physical objects that are extremely different in size must be linked with one another in a predictable manner. To allow for the most general uses of these devices, self-assembled systems are being optimized to be compatible with chemical fabrication taking place in either aqueous or dry environments. Two, commercial availability of production-level volumes of nanodevices requires advances in fabrication that allow for continued control of the design process.

Several researchers are approaching these challenges using biological systems to synthesize composite materials containing both organic and inorganic matter. Working mostly with proteins and peptides, laboratories are developing biomolecular recognition processes that bind or move semiconductor or magnetic materials. In addition, bacterial

interact with—and transfer information among—synthesized inorganic materials.

Molecular Electronics: Less Is More

Since the invention of the integrated circuit in 1958, refinement of microelectronic circuits has progressed at a rapid pace. Gordon Moore, chairman emeritus and co-founder of [Intel](#), observed in 1975 that the number of transistors per chip had doubled each year since 1958. This trend—termed Moore's Law—is still occurring. As circuits have shrunk in size, they have grown in computing power, and this combination has fueled the development of the personal and portable computer industries.

Extrapolating this trend forward, however, by 2012 a circuit would have to shrink to a scale unworkable by current fabrication and control technologies. In addition, even before that size limit is reached, the cost of fabricating such small devices

will have become so high that construction on a mass scale would likely be impractical. Recognizing this approaching barrier, academic researchers and companies are actively engaged in developing chemically synthesized electronic circuits that leverage the properties of individual molecules.

Biological Computers

One potentially intractable computer problem—called the NP-complete—is that computing time grows exponentially with problem size. Leonard Adelman, at the [University of Southern California](#), proposed in 1994 that such problems might be solved using DNA-based computing systems. This approach to biologically based computing makes use of both DNA-based combinatorial chemistry and enzymatic reactions.

Several academic laboratories are rapidly advancing the level of computational complexity represented by the DNA reactions. Because code-breaking can be an NP-complete computational problem, one of the first problems to which this technology may be applied is cryptographic analysis.

The rapid development of self-assembled, molecular-scale information processing circuits and devices is being fueled by the same drivers of technology platform and market convergence that are more broadly impacting the biotechnology industry.

With an increasing pace of convergence, the future products of the biotechnology industry will soon become a market reality.

Convergence Has Its Limits

As companies harness new technologies and expand into new markets, complete convergence is not always achievable. Business units within companies may not be able to share information efficiently. Strategic and operating conflicts can arise as shared resources become scarce. The cost of overall coordination of an extremely large, fully integrated life sciences company (Filsco) may not justify the extended capabilities of such a structure. For example, [Novartis AG](#) and [AstraZeneca plc](#) are spinning out their agribusinesses to form a combined entity, [Syngenta AG](#). This transaction arose from management belief that their pharmaceutical and agricultural business units function better when independent. This belief mirrors the ultimate decision of [American Home Products](#) and [Monsanto](#) to halt their efforts to create a global Filsco.

Rather than grow into enormous, multi-business unit entities, many companies are avoiding these limits of convergence through extensive corporate development. Through cross-market strategic alliances, partnerships, joint ventures, and licensing activities, the sustained reach of the biotechnology industry is rapidly expanding.

IPO: Diversa Corp . \$200.1M . February 2000

Venture Financing

Biotech Deals and Dollars Raised (\$ in Millions)

	Jan.— June 2000	1999	1998	1997	1996	1995	1994	1993	1992
Early rounds	28%	51%	54%	34%	22%	17%	28%	46%	38%
Later rounds	72%	49%	46%	66%	78%	83%	72%	54%	62%
Total number of biotech deals	70	129	145	137	124	94	115	126	133
Total raised in all biotech deals	\$1,010	\$1,530	\$1,251	\$1,080	\$818	\$568	\$679	\$719	\$688
Average Raised	\$14.4	\$11.9	\$8.6	\$7.9	\$6.6	\$6.0	\$5.9	\$5.7	\$5.2

Sources: VentureOne, BioCentury, BioWorld Financial Watch

Some numbers may appear inconsistent because of rounding.

Venture stage funding of biotech firms continues to increase in real terms.

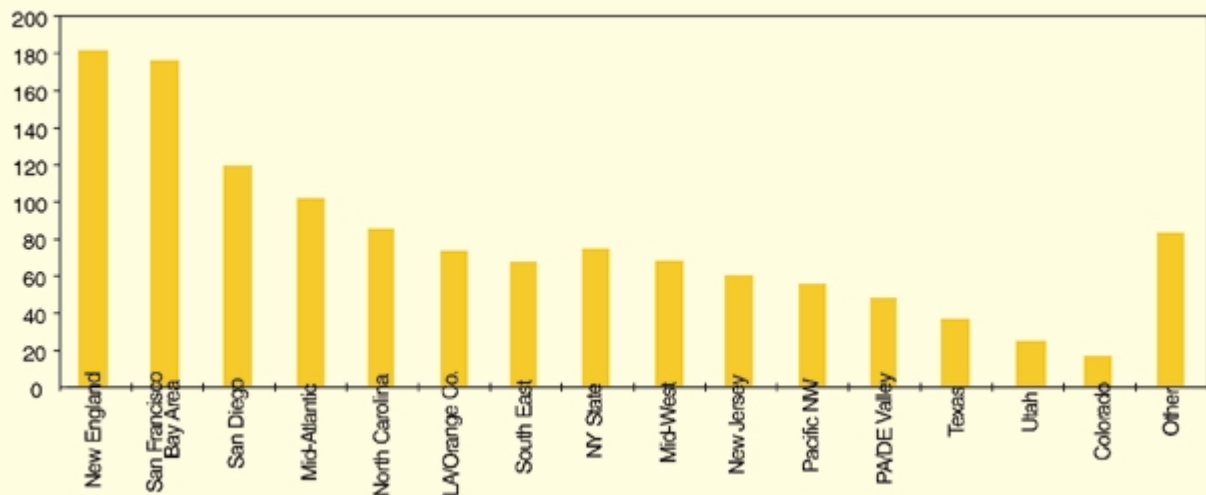
The Merck/Biotech Index—A Comparison

	(\$ in Billions)			Biotech Industry		
	1999	Merck 1998	Percent Change	1999	1998	Percent Change
Total Revenue	\$32.8	\$27.0	21%	\$22.3	\$20.2	10%
R&D Expense	\$2.1	\$2.9	(28)	\$10.7	\$10.6	1
Net Income (Loss)	\$5.9	\$5.2	13	\$(5.6)	\$(4.4)	27
Market Capitalization	\$176.3	\$173.0	2	\$353.5	\$137.9	156
Employees	62,300	57,300	9	162,000	155,000	5

Big pharma companies dwarf the biotech industry in revenue. Still, biotech companies are making significant R&D investments and continue to be an innovation engine for big pharma.

Sources: Company financial statements, Ernst & Young.
Some numbers may appear inconsistent because of rounding.

Census 2000—Counting Biotech (private and public companies by region)



Source: Ernst & Young

Roundtable Discussion:

Biotechnology, Future Directions

The following roundtable—held on June 21, 2000—brought together biotechnology experts to discuss convergence and the future of the biotech industry.

Chen: What will the human genome project advance in our understanding of health and disease? In what way will this impact the development of therapeutic preventive medicine?

Kauffman: In nearly every way. The completion of the human genome project puts us on the threshold of the postgenomic era. In this era, we will learn to understand gene regulatory networks and how they control development from the fertilized egg to the adult. We will also learn how they go awry in conditions ranging from autoimmune diseases, to diseases of cell differentiation, to cancer. We're going to wind up with new modes of treatment for an enormous range of diseases. When we learn how to control gene activity in tissue-specific and cell-specific ways, we can make cancer cells differentiate from malignant to benign behaviors. I would say that will happen in the next 30 years.

Sager: There are at least two ways to approach the question of how the human genome mapping will affect our understanding human disease. The first is to realize that genes and proteins are, of course, not related one-to-one. On the one hand, genes can code for RNA transcripts, which are processed differen-



Moderator:

Leon Chen is a strategy consultant who focuses on the biotechnology and high-technology industries. He received his Ph.D. in Organic Chemistry from the Universite Catholique de Louvain (Belgium) and was a postdoctoral fellow at the Massachusetts Institute of Technology. He can be reached at lyychen@earthlink.net

Participants:

Eric Drexler is chairman of the [Foresight Institute](http://www.foresight.org), a nonprofit educational organization formed to help prepare society for anticipated advanced technology. Eric earned his Ph.D. in molecular nanotechnology from the [Massachusetts Institute of Technology](http://www.mit.edu). He can be reached at www.foresight.org



Stuart Kauffman is a recipient of the MacArthur Fellowship, a co-founder of the Santa Fe Institute, and the chief scientific officer of the [Bios Group](http://www.biosgroup.com), a consulting firm that makes use of complexity theory to help companies improve their business operations. Stuart earned his M.D. from the [University of California, San Francisco](http://www.ucsf.edu). He can be reached at stuart.kauffman@biosgroup.com



Brian Sager leads a national strategy consulting practice focused on the biotechnology and high technology industries. He received a Ph.D. in Biochemistry from [Stanford University](http://www.stanford.edu) and was a Whitney Fellow at [Harvard University](http://www.harvard.edu). He can be reached at bsager@newclassical.com

tially and combined in different ways, and therefore translate to create different proteins.

Second, once proteins exist, they start to behave with each other in highly complex, self-organizing ways, in which they can make modifications on and through one another. For example, if there are 100,000 genes discovered in the human genome, there may be more than one million—perhaps more than 10 million—different protein complexes and discrete, individual proteins interacting with each other. That highly emergent functionality will begin to be approached, I think, when we understand just how nonlinear the relationship may be. This will include a functional proteomics approach, in which the interactions of individual proteins and particular measurements of function will be studied systematically. We will also be looking at the interactions of sets of proteins, and this will ultimately lead to what we might call a physiomics approach. Here, we actually begin to understand metabolic pathways and finally approach the ability to model them effectively *in silico*.

Not all genes code for proteins. As Stuart has pointed out, there are highly complex regulatory networks in cells that are extremely important in the context of disease. After a period of pattern-

lation. That will lead to an even further decomoditization of drugs, because the market will splinter into people who are preferentially treated by a particular molecule or suite of molecules given their specific genotype. If the market is small because the number of people with a particular genotype is small, then there may not be enough of a market to justify the costs of drug discovery.

Drexler: Improvements in instrumentation—which I think will be among the early important applications of molecular devices—will greatly change our sense of how difficult it is to read genes, to sequence genomes. The lack of innovation in gene sequencing technology has been fairly scandalous; we’re still using techniques that don’t apply molecular machinery effectively. Today, we think in terms of large projects to sequence the genome of a single organism, but a bacterium contains about a megabyte of information and can replicate itself, which involves reading and writing all that information, in about 15 or 20 minutes. A device that has as much molecular machinery as a thousand bacteria—which is to say a device that is cheap and can be carried in a pocket—should be able to sequence a human genome in a matter of minutes.

The postgenomic era. In this era, we will learn to understand gene regulatory networks and how they control development from the fertilized egg to the adult.

detection efforts, we’ll be able to articulate and understand the complex suite of regulatory mechanisms and their relative abundance. For example, how many genes are positively regulated and how many are negatively regulated. The ratios of different types of regulatory patterns and motifs will become apparent, and that will provide a focus from a commercial viewpoint. That focus could allow for the effective design of regulatory therapeutics in ways that are attuned to the actual prevalence of different types of regulatory networks in the genome.

Kauffman: There’s a third piece to the question on the genome mapping, I believe. With respect to single nucleotide polymorphisms, we’re going to discover the genetic diversity of the human popu-

Chen: What do you think are the challenges in creating commercial DNA-reading machines such as those you describe?

Drexler: In a lot of these areas, I think the problem is one of culture. We have in hand molecular components that do the necessary tasks, but they need to be integrated into systems, and systems engineering is not something that has traditionally been done by chemists or biologists.

I once asked two chemists at the [Massachusetts Institute of Technology](#) about the largest collaboration they knew of in chemistry. They said it was the synthesis of vitamin B-12, where two professors’ groups collaborated on two parts of the molecule. In engineering, a large collaboration is considered to

ROUNDTABLE DISCUSSION:
BIOTECHNOLOGY, FUTURE DIRECTIONS

be something like the Apollo project. So we can see that the molecular world has a way to go in learning to cooperate in large group efforts.

Sager: There are at least two different challenges in creating commercial DNA-reading machines. The first is an improvement in systems-level product design that fully leverages the power that is available now at the component level. The second is reliable manufacturing to allow a rapid commercialization, which may require interdisciplinary collaborations that don't exist at the moment or are only in the early stages.

Chen: Living organisms, such as bacteria, can be thought of as wonderfully efficient machines. Stuart, how do you see these self-organizing systems being used in hardware-based or information products?

Kauffman: I think about a bacterium swimming upstream in a glucose gradient. We're all willing to say that it's swimming to obtain food, without attributing consciousness to it; it's acting on its own behalf in an environment. I'm going to call a system that acts on its own behalf in an environment an autonomous agent. But then you notice that the bacterium is just a group of molecules, and the question becomes, what must a physical system be so that it can act on its own behalf in an environment?

This definition of an autonomous agent is a self-reproducing molecular system that performs at least one thermodynamic work cycle. But all free living cells fit this definition. They generally

perform work cycles and they reproduce. So, what are the nanotechnology implications of reproducing systems that can build things? What happens if our machines can move around and reproduce?

Drexler: Most obviously, that would give us huge leverage in turning a small amount of capital productive equipment into a large amount in a short time. Design calculations show that molecular manufacturing systems can double their mass in tens of minutes, as with living cells.

Sager: One example of that leverage could be a type of biocomputer. Although this field is in its early stages today, many researchers are working on DNA-based chemical reactions to approach computationally challenging, highly parallel problems. If DNA-based computers compute through DNA synthesis-based reactions, then this system would be a clear example of self-replication in which the physical object is itself replicated and the information derived is a result of that replication.

Another possibility would be a computational fabric that's self-producing, a form of living biomaterial that has very specific properties. Research and development groups are thinking about using these types of materials for very specific applications; for example, changing the color of a fabric based on temperature as a result of some algorithm in the material itself. With both the biomaterial and biocomputing processes, there is the distinct possibility of using self-replication to manifest structure in a fabrication sense and to generate information in an algorithmic processing sense.

IPO: Sequenom . \$157.0M . February 2000

Big Biotech, Bigger Pharma

	Total Revenue (\$ in Millions)	Revenue per Employee (\$ in Thousands)	R&D Expense (\$ in Millions)	R&D Expense per Employee (\$ in Thousands)	R&D Expenditures as Percent of Revenue
Biotech Industry					
Amgen	\$3,433	\$536	\$823	\$129	24%
Genentech*	1,414	364	331	85	23
Biogen	825	611	221	164	27
Genzyme Corp.**	777	201	156	40	20
Alza	763	376	60	29	8
Chiron	684	220	254	82	37
Immunex	559	478	127	108	23
Pharmaceutical Industry					
Merck & Co., Inc.	\$32,762	\$526	\$2,119	\$34	6%
Johnson & Johnson	27,439	281	2,600	27	9
Bristol Myers Squibb	20,199	371	1,843	34	9
Pfizer Inc	16,269	319	2,776	54	17
Glaxo Wellcome	13,566	245	2,049	37	15
Eli Lilly & Co.	9,819	314	1,784	57	18

Drexler: When we improve at molecular manufacturing, it should become possible to make materials that have micron-scale component parts that can move with respect to each other. Each part would contain a significant amount of digital memory, computational function, and the ability to plug into its neighbors and transmit information and power. The net result could be smart materials that can change their shape—change the units they’re displaying on their surface—and actually possess better strength-to-weight performance than we’re familiar with in aerospace materials today.

The most obvious complex self-organizing system that we deal with technologically every day is the human organism, then animals, then plants, then ecosystems, and so on.

Sager: One of the areas in which we’re going to see something develop fast is the designed resistance of genetically engineered foods and the fact that we cannot truly predict the long-term consequences of growing these products. What does it mean for ecosystem stability? We need to look at that, and I would think we should move in that direction quickly.

Regarding genetic privacy, each of us is constantly writing all of our genetic information into skin cells and then leaving them around for others to inspect.

Chen: Concerning systems-level product design, what are the major scientific and technological challenges that might impact self-organizing, systems-based technology products?

Kauffman: Self-organizing is an umbrella term that’s awfully broad. It seems to me that we should find a few specific technological areas that might be positively impacted by bringing them under the rubric of self-organization, then see what we can do with it. The most obvious area with respect to biotechnology products is medicine.

Chen: Eric, what are the major scientific and technology challenges that might impact nanotechnology-based biotechnology products?

Drexler: When I think about the major challenges, they largely look like just work. There are areas in other types of technology, however, in which there are key problems. For example, in fusion power the key challenges are the stability and confinement of the plasma at appropriate temperatures and set densities. In the area of nanotechnology, however, there are many different fronts on which people are making

IPO: ACLARA BioSciences . \$217.4M . March 2000

Net Income (\$ in Millions)	Employees	Market Cap 6/30/00 (\$ in Millions)
\$1,096	6,400	\$72,133
(1,145)	3,880	44,788
220	1,350	9,577
71	3,860	6,304
91	2,030	6,068
161	3,110	8,546
44	1,170	24,746
\$5,891	62,300	\$176,328
4,167	97,800	141,639
4,167	54,500	114,943
3,179	51,000	185,280
2,925	55,273	105,242
2,721	31,300	112,794

Sources: Company financial statement data, Ernst & Young.

Numbers may appear inconsistent because of rounding.

*Genentech incurred \$1.64 billion in special charges for FY 1999.

**Genzyme's market capitalization is the sum of its tracking stocks.

progress, many ways of designing, making, and evaluating things. The tools keep accumulating. I again see the primary challenges as those of developing a systems-building culture that uses tools that presently are in the hands of a non-systems-building culture.

Chen: In what way might these cultures need to change their way of thinking in order to make use of nanotechnology?

Drexler: In terms of learning to use it effectively, I think an appreciation of self-organizing systems will be central. One important thing about the concept of self-organization as a tool in engineering—as a tool in shaping and understanding the world—is that it assumes good and useful results can flow from processes that we don't fully understand, and that better results can be realized by exploiting that potential than by pursuing a rigid step-by-step rational constructive design. One can rationally decide to take one's hands off the system and set up initial systems that let the system shape itself. The incentive to do that grows as the system becomes more complicated, as there is more inside the system to interact with itself, to bring forth novel patterns and behaviors. Certainly, that's what we've been seeing in computers as they've evolved from simple machines without a lot of contents into systems that are virtually worlds in themselves. This is true even more so as we start structuring microscopic amounts of matter with nanoscale precision.

integrate with biotechnology within the next five years. Early examples of this convergence are already in the marketplace.

On a longer time scale, I think there will be an intersection between biotechnology, health care, and electronic commerce business models, for example consumer-focused Web sites where the primary site content is individual genomic data. Certainly, as people attain the ability to rapidly read DNA sequences—and if they could somehow obtain a CD ROM of their individual gene sequences as new discoveries are made—I think it's very likely that individuals would want to see whether or not they have predispositions to specific diseases. I think, therefore, that there will certainly be an intersection between the information technology and consumer genomics areas.

This touches on the genetic privacy issue. If we assume there is genetic privacy in the scenario I just described, then there will be a deep information asymmetry in favor of the patients. Conversely, assuming there is no genetic privacy, there will be deep asymmetry in favor of the health care providers. In both situations, there will be enormous business challenges and ethical implications. There will thus be convergence in the field of ethics and consumer genomics and with these other areas as biotechnology in general becomes more integrated into a variety of different types of products in

IPO: Allos Therapeutics Inc . \$90.0M . March 2000

Chen: In the next five years, what technology platforms or fields of study do you see converging in biotechnology, and why?

Sager: Certainly, biotechnology is designed to be systematic in the sense of leveraging combinatorial chemistry to create compounds that may have therapeutic value, to do high-throughput screening on these compounds, to determine the functionality of the screened compounds, and so forth. These and other technologies that are used now in the biotechnology industry might also be applicable in the long term to the chemical industry, in fine chemicals and in material science, where high-throughput screening and combinatorial chemical processes have not yet become a routine aspect of the core business. I think for that reason that the technology platforms of fine chemicals and material sciences will at least partially

society. I can almost imagine the equivalent of an ISO 9002 certification for ethics; for example, has a product undergone an ethical evaluation prior to launch?

Drexler: Regarding genetic privacy, each of us is constantly writing all of our genetic information into skin cells and then leaving them around for others to inspect. Other people do not yet have the means to read the DNA in the cells, but if I were writing my personal information on scraps of paper and strewing it around the streets, I would not expect privacy.

Chen: We have seen a lot of new technologies and a lot of new start-ups leveraging these technologies. What is the impact of the technology convergence for traditional industries, such as the pharmaceutical industry? How can they leverage this technological convergence?

Drexler: People are quite interested in where the computer industry is going because it's changing so fast. It's an exploding industry. Nanotechnology also seems to be exploding, and it seems clear that the explosion is going to continue because of the payoffs and the technology pathway ahead of us. The momentum is building. In that kind of field, what's important five years from now is not so much what product people are bringing to market as what the expectations are then and what activities people will be using to look at the promise they might see. In other words, if the knowledge in a field is doubling every few years, then what's most important five years from now will probably be the perception that it's an enormous field—one that they have to be involved in and have to put a large fraction of their R&D money into. Therefore, there will be changes in employment patterns, changes in the kinds of instrumentation people buy, and so forth. Many companies are in the business of supplying the R&D chain. Those companies will see tremendous effects from this ramp up, including some of the relatively traditional industries doing instrumentation and such.

Kauffman: There's the persistent problem of milking your established products with good brands, and at the same time migrating value out of those old sacred cows into the new things before they lose their value, which is a very tricky business. It seems that part of what companies have to become good at is

walking the line between transferring value in the right place and time from the mature thing to the new thing.

Then the question becomes, how do you actually do that. I don't have an answer for this. The mature things may just linger for a long time—people still need ball bearings and steel plates. It's fine to hang onto them, as long as you're growing in some of the expanding points of your economy and have some of those under your own roof. You can also form partnerships with other companies that do have these things, where you get some piece of the action in warrants, carries, joint ventures, and so on.

Sager: Certainly developing and tracking interest from investors and collaborators and seeking out joint ventures is critical in these types of areas, whether you're creating a neuropeptide brand or building an electronics firm to grow electronic circuits in a plant. Either way, you'd need to attract the capital markets to the idea and sustain and nurture it long enough for it to come to fruition. I think one challenge is recognizing when these technologies actually become feasible and when their commercialization time line is consistent with investor expectations, especially relative to the types of returns that we've been seeing with both high-technology and Internet-based companies in the recent past. Setting appropriate expectations as to commercialization milestones and technical feasibility is critical in the planning process. This speaks to a need to tightly integrate the business and science sides of any emerging venture.

IPO: IntraBiotics Pharmaceuticals . \$112.5M . March 2000

“With respect to single nucleotide polymorphisms, we're going to discover the genetic diversity of the human population. That will lead to an even further de-comoditization of drugs, because the market will splinter into people who are preferentially treated by a particular molecule or suite of molecules given their specific genotype.”

—Stuart Kauffman, page 33

The Convergence of Biotechnology and IT: Genetics as a Model

Hugh Y. Rienhoff Jr., M.D., Founder,

Chairman, and CEO, DNA Sciences



Jim Clark, Ph.D., Chairman, myCFO



Our shared commitment to DNA Sciences is based on the conviction that information technology (IT) and biology are integral to each other. We believe that IT will learn from and depend upon the processes that biology employs to handle information.

At the same time, IT and technology will interface increasingly with real biology—living things—to collect and deposit information. How will we realize this vision of the future?

Our collaboration begins with a computer scientist's (Jim's) use of computer graphics to represent data and, more important, the products of our imagination—including applications from design engineering to the representation of chemical and biological molecules. [Silicon Graphics](#) represents the first step in our crossing paths. Next, the Internet, a consummate communication tool, entered into the consumer world through [Netscape Communications](#). This event represents in some ways the birth of the Internet. The next step applied Internet tools to the management of health care information and transactions—that is [Healtheon](#), where the two of us met.

Healtheon continues to bring together constituencies from across the health care world. In particular, [Healtheon/WebMD's](#) design empowers consumers with information about and access to previously inaccessible areas of the health care system. DNA Sciences builds on this model by allowing consumer participation in genetic studies that accelerate the discovery process, putting it at the crossroads of Internet technology and the [Human Genome Project](#). We use the Internet's communication power to recruit healthy volunteers and those affected with disease into very large studies on genetics. The goal is to understand all the major genetic variables that contribute to disease. Without the Internet these studies might be very difficult to conduct and take much more time. In this sense, the Internet enables our Big Biology Project, and we are confident that many others will follow.

DNA Sciences' business model extends beyond discovering the genetics of common disease and commercializing related diagnostics and therapeutics. Now, consumers can learn about genetics and, ultimately, take control of their own genetic information in a safe and secure locale. Absent any legislative safeguards prohibiting the misuse of genetic information, consumers—especially healthy consumers—will need a discrete service that can help them identify and manage genetically identifiable disease risks. In fulfilling this need, the company's mission is to serve physician and consumer needs in the area of genetics as this field of medicine moves to the forefront of practice and prevention.

Many of us share the vision that genetics will change medicine forever. But this change will be

impossible without information systems that go beyond Internet and computing technologies. For example, DNA Sciences is working to develop new ways to model and interpret data derived from genetic studies. We are modeling the genome as a series of switches, where each SNP has two (and sometimes three) states and each switch has the potential to interact with other switches. Depending on the configuration of these switches, each genome is programmed to interact with the environment. The sum of these interactions is the state of our health, well-being, and all of our other biological traits. Likewise, gene expression data is demanding new algorithms to make sense of large data sets. Data mining, a practice alien to biologists but common to astrophysicists and consumer data tracking services, will bring insight into what is now a set of confounding patterns. We are only beginning to discover how IT can lend a hand in understanding complex biological systems.

Where is genetics taking us? The first wave of genetics studies single-gene disorders such as hemochromatosis, a condition in which the body avidly absorbs too much iron. The second wave of genetics identifies those genes that contribute significantly to our susceptibility to disease. This

become tractable as a science. Folklore regarding food as medicine will have a rational basis.

We find fascinating the solid consensus among payers, patients, and providers regarding genetics. If genetics can get early surveillance or treatment to a healthy person at risk for disease, if genetics can match the individual with the right medicine, if genetics can provide a better understanding of the progress of disease, all are in favor. Somewhat out of step are those who benefit from the inefficiencies of the current paradigm: empirical treatment and mass prescribing of therapies that do not work for many. This situation will eventually change by regulatory fiat or through a more discriminating marketplace that will not tolerate these inefficiencies.

Where is this going? As we mentioned in the beginning, IT will learn from biology. The high fidelity of biological information systems along within their extremely small dimensions and low energy consumption are a model to the IT world. And the models of how complex, nonlinear processes are managed will be derived from a close inspection and understanding of biological systems. Synthetic cells will perform informatic functions that are in essence cellular computers. They will

The high fidelity of biological information systems along within their extremely small dimensions and low energy consumption are a model to the IT world.

advance allows doctors to speak the language of probability much more: “You are five times more likely to get colon cancer than the average man on the street.” These “predisposition” genes tell us who to watch more closely, who to treat more aggressively, and, ultimately, how the disease comes about and how we might cure or avoid it. Our challenge is to not only understand how to use existing diagnostics and therapeutics for each individual but also use that knowledge to devise new interventions and prevention.

Genetics has even more to offer. To some extent, the subtle effects of our environment—mostly our nutrition and the ubiquitous microbes around us—can be studied only once we have established what genetics contributes to those interactions. The tremendous range of responses that the human population shows to diet will, for once,

have many of the same features as semiconductors but will be made of biological parts and operate in that netherworld interface between electronics and biology. These cells will be programmable and perform many of the functions that chips do.

The other side of that coin will be the ability to program real cells. The time will come when we can influence the function of the human body with information from the outside. More powerful embodiments of this ability will require synthetic cells that serve as the interface—cells that we make and influence but that can communicate with natural cells.

All of these technologies invoke the need to protect individuality, protect confidentiality, and celebrate the sanctity of life. Not surprisingly, technology is helping to achieve this while in the process of transforming us. We are lucky to be living in such fascinating times.

Interview: A Perspective from the Pharmaceutical Industry

The following interview—held on June 26, 2000—sought the pharmaceutical industry’s perspective on today’s converging marketplace. An executive from one of the world’s largest pharmaceutical companies shares his thoughts on trends driving convergence as well as the public’s acceptance of continued innovation.

Devitt: Let’s start by discussing what you think keeps pharmaceutical industry executives awake at night.

DiMarchi: I think two concerns most consume pharmaceutical executives: How can we lessen the cost of true innovation? And, how do we know that the environment will provide an opportunity to achieve an acceptable financial return? If I can be perfectly frank, the central issues pertain to ignorance about the industry.

The financial cost of delivering pharmaceutical innovation continues to increase. Over the past decade, the industry has experienced significant growth in R&D investments as measured as a percentage of sales. This increased expense occurs despite the introduction of very powerful enabling technologies. A big part of the cost is embedded in the empirical manner in which we deliver innovation. Clearly, pharmaceutical research today is far more scientific and rational than it has ever been. Nonetheless, human biology is incredibly complex, and there’s much to be learned regarding the molecular basis of disease.



Participants:

Blake Devitt is an audit partner with Ernst & Young in Indianapolis, Indiana. He specializes in the life sciences industry, with over 15 years of experience working with [Eli Lilly and Company](#) and [Guidant Corporation](#).

He serves on the firm’s Global Partner Group, which focuses on servicing the firm’s top clients.



Richard D. DiMarchi, Ph.D., has served as Group Vice President, Research Technologies and Product Development, at [Lilly Research Labs](#) since 1998.

He began his career at Lilly in 1981 as a senior scientist and, over the years, has served in many capacities, including Director of Biochemistry, Executive Director of Diabetes, and Vice President of Endocrine Research and Clinical Investigation. His academic work includes the publication of more than 80 scientific communications and submissions. He holds 48 U.S. and European patents and applications.

As we experience unprecedented scientific progress in the laboratory, we seem to be regressing in the political environment. The change in public opinion is rooted in what's perceived to be an unacceptably high cost of scientific innovation. A lack of appreciation for the process of pharmaceutical discovery has resulted in a large number of individuals seeking some form of drug price relief. We hear the pharmaceutical industry compared in unfavorable terms to the tobacco industry. While that comparison is completely inappropriate, we must educate a skeptical audience or face the consequences of price controls and regulations that could severely hamper our ability to deliver innovative medicines.

ability to create drug candidates against the drug target. We typically screen a million chemical entities to eventually identify one drug candidate. In finding the one success, there are 999,999 rejects. We have yet to develop the technology that allows a systematic analysis of the failures to guide the refinement of those candidates that hold further promise.

As for target validation, IT has revolutionized how homology searches, based upon primary sequence, are conducted. We seek to similarly utilize higher-order structure to guide homology searches more intelligently. We need additional technologies to solve the structural space problem. As we begin to

The emergence and convergence of pharmaceutical and information technologies provide the greatest basis for optimism in the face of these increasing cost pressures.

Devitt: How is IT creating a converged marketplace?

DiMarchi: It's occurring throughout the pharmaceutical value chain. Starting at the far end, IT is dramatically diversifying how we reach patients. The Internet provides an opportunity to interact with patients in real time. Technology allows the message to be personalized for a single individual—an incredible advance, since there is appreciable patient heterogeneity within most diseases. The ability to reach patients and deliver an individualized message is something that was previously near impossible for the more common diseases.

In the middle of the value chain, IT is accelerating the pace at which we convert data, which are accumulating at unprecedented speed, to help us make informed decisions. The biotechnologies are clearly creating the information, but the informatic technologies are changing how we collect and analyze the data. The seemingly simple act of sharing information electronically (through the Internet and intranets) is facilitating the conversion of the data to information, and thus informed decision-making.

In the discovery realm, there's a steady stream of integrated technologies directed at the two central obstacles to progress: drug target validation and the

understand the laws of protein folding more fully, we'll be able to select targets more efficiently and streamline the chemistry required to convert early chemical leads to drug candidates.

Devitt: What opportunities are being created by the power of IT?

DiMarchi: Fundamental to the application of any and all technologies is the drive to deliver innovation at lesser and lesser cost. It's getting exorbitantly expensive to find truly innovative molecules while, simultaneously, there have been significant increases in marketing costs. The number of sales reps that call upon physicians has reached the point of saturation. When R&D and selling costs simultaneously escalate, it's clear that the financial structure of the business is moving in an unfavorable direction. The emergence and convergence of pharmaceutical and information technologies provide the greatest basis for optimism in the face of these increasing cost pressures. More innovative drug targets and improved methods in drug candidate discovery coupled with less labor-intensive means for marketing pharmaceuticals are emerging on the horizon of this industry.

Devitt: What synergies do you see occurring between the pharmaceutical and biotechnology industries now and in the future?

DiMarchi: Let's start with the announcement regarding the sequencing of the human genome. This is, clearly, one of those milestones that we had to pass to get to where we want to be: more personalized medicine and greater proficiency in drug discovery. However, our enthusiasm is tempered by the simple fact that today we don't know how many genes are in the human genome. The estimates range from as few as 40,000 to as many as 150,000 genes. The scientific immaturity of this field characterizes the environment in which significant R&D investments directed at drug discovery are made.

Human biology is incredibly complex. These bold claims about what can be achieved with the human sequence data available today need to be tempered by the complexity of converting this data to improvements in medicine. It's not a question of *if* we'll get there, it's a question of *when* we'll get there. The question of when has an enormous impact on investment return, and thus on the willingness to invest. Consequently, we need to function in two worlds, using the more proven but inefficient technologies of today while simultaneously inventing more powerful methods. In this regard, envision where a pharmaceutical company that had not participated in the DNA revolution that has surrounded us for at least the past 20 years might reside today.

The biotechnology industry has largely focused on discovery and existed in a symbiotic relationship with the larger pharmaceutical industry, which provides drug development and commercialization expertise. This historical arrangement is evolving, with pharmaceutical companies developing early-stage discovery capabilities and biotechnology companies developing downstream capacity. Also, the recent infusion of additional capital finances into the biotechnology industry provides an opportunity for risk sharing that didn't exist previously. This could facilitate a more balanced relationship than the ones we have historically experienced.

Devitt: How should we properly leverage intellectual property (IP) to encourage high-risk research and development and maintain healthy market competition?

DiMarchi: IP is an uncertainty that exists in the industry as we know it today. Sizable investments are being made even though it's unclear how patent applications that relate to gene sequences without biological proof of function are going to be reviewed.

The pharmaceutical industry is rather atypical among high-tech industries in that the value of an asset usually increases until the point of patent expiration. The ever-quickening emergence of technology should bring shorter life cycles. Will we find ourselves antiquating our own discoveries

IPO: Exelixis Inc . \$136.0M . April 2000

Sales of Top-Selling Drugs Grow Dramatically

Drug	Developer	Marketer	Indication	1998 Sales (\$ Millions)	1999 Sales (\$ Millions)
Epogen	Amgen	Amgen	Anemia	\$1,380.0	\$1,760.0
Procrit	Amgen	Ortho Biotech	Anemia	1,363.0	1,505.0
Neupogen	Amgen	Amgen	Neutropenia	1,120.0	1,260.0
Humulin	Genentech	Eli Lilly	Diabetes	959.2	1,087.5
Engerix-B	Genentech	SmithKline Beecham	Hepatitis B	886.7	540.0
Intron A	Biogen	Shering-Plough	Hairy cell leukemia, Kaposi's sarcoma, and Hepatitis C	718.0	650.0
Kogenate	Bayer Biological	Bayer Biological	Hemophilia A	428.5	403.4
Genotropin	Genentech	Pharmacia	Growth failure	395.1	460.8
Avonex	Biogen	Biogen	Multiple sclerosis	395.0	621.0
ReoPro	Centocor	Eli Lilly, Centocor	Cardiac ischemic complications	365.4	447.3
Total				8,010.9	8,735.0

Source: Med Ad News, July 1998

with better medicines at a point prior to patent expiration? This would certainly change the value equation of pharmaceutical R&D. It will become imperative to maximize the value of the asset immediately upon launch. There's likely to be significant pressure exerted on the development process to deliver timely drug submissions that have regulatory labels supporting immediate commercialization. This could constitute an incredible challenge for the industry that doesn't get the appropriate attention.

Devitt: Today, President Clinton mentioned the threat of unethical uses for genetic information in his remarks on the mapping of the human genome. How can the industry respond to the public's concerns?

DiMarchi: These are significant issues. President Clinton was referring to the potential for inappropriate use of this information to deny individuals access to insurance and certain jobs, as well as other forms of discrimination. There's potential for misuse of this information, and it's something that needs to be carefully managed as this information is collected.

Furthermore, we should recognize that the ability to diagnose risk will probably precede the ability to deliver effective therapy. We are likely to repeatedly confront the dilemma that currently surrounds individuals who find themselves with a

diagnosis of increased risk of a disease, such as breast cancer. Being BRCA1 positive doesn't definitively determine that someone will get breast cancer. However, it does increase the odds significantly. In the absence of more effective pharmaceuticals, does one immediately resort to a mastectomy? These are the sorts of tough issues that are going to emerge.

A big concern that I maintain relates to my early comment regarding ignorance. There could emerge significant animosity for those who have provided the information, in having been the messenger of this problem, as opposed to someone who is enabling the eventual solution.

Devitt: Any final thoughts on how convergence is shaping the future?

DiMarchi: Only the fact that it's the convergence of multiple technologies that is driving us forward. One need look no further than the drug delivery industry to see evidence of this phenomenon. Recombinant DNA technology has provided proteins in virtually unlimited quantities. Simultaneously, the advances in particle science are delivering fine particles necessary for successful drug delivery. Lastly, mechanical devices are available through advances in engineering technology. So, you see advances on all three fronts converging to a point where it appears likely that noninjectable presentations will be commercially feasible.

IPO: Lexicon Genetics Inc . \$220.0M . April 2000

“The biotechnology industry has largely focused on discovery and existed in a symbiotic relationship with the larger pharmaceutical industry, which served to provide drug development and commercialization expertise. This historical arrangement is evolving with pharmaceutical companies developing early-stage discovery capabilities and biotechnology companies developing downstream capacity.”

—Richard DiMarchi, Eli Lilly, page 42

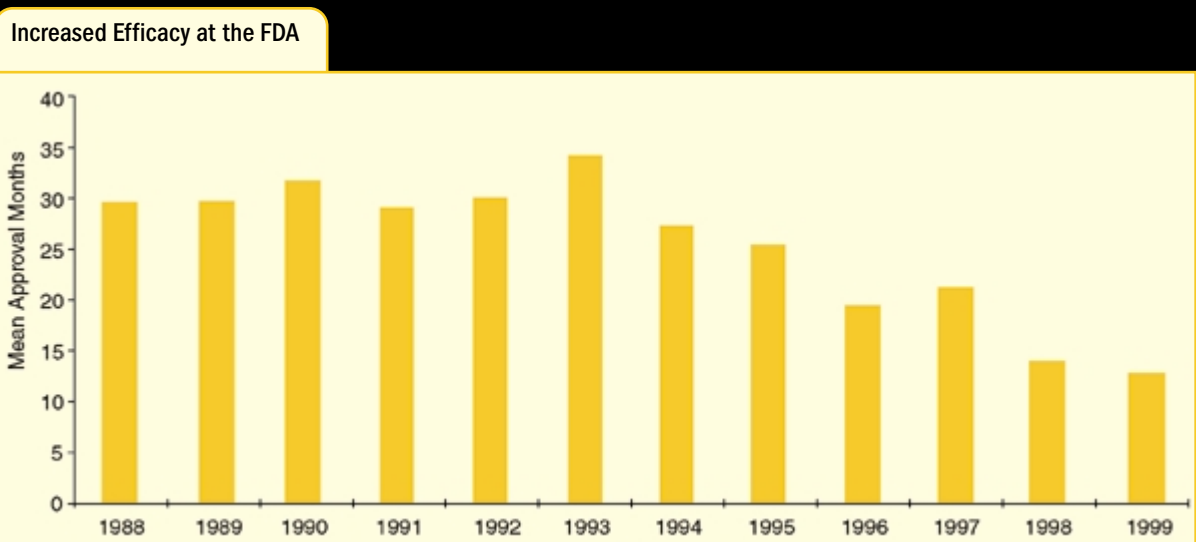
The Product Pipeline: Progress and Potential

While the media focuses on the promise of genomics and drug discovery, the biotechnology industry moves further into the commercialization phase in the clinical world and at the FDA's door. In 1999, the FDA approved 33 products (33 were also approved in 1998, a record for the industry), and 25 products were approved in the first half of 2000. Although we have not seen blockbuster products since 1998, such as **Immunex's** Enbrel and **Genentech's** herceptin MAb, significant progress was made and numerous notable products were launched. **Alza's** ditropan xl for overactive bladder and **BioChem Pharma's** Zeffix for chronic hepatitis B were approved and hit the market during the period. In addition, **QLT's** Visudyne for macular degeneration also moved into commercialization.

The Pipeline Is Accelerating...

After several years of record product approvals, the pipeline is robust with over 280 products in pivotal stage clinical trials, including many promising new products moving closer to the finish line. **AutoImmune's** Colloral for rheumatoid arthritis, **Inhale's** pulmonary delivered insulin for diabetes, and **Coulter's** Bexxar for non-Hodgkin's lymphoma are all in late stage clinical trials. The pipeline is on the verge of explosion driven by the rapid technological advances in the drug discovery toolbox that is dramatically increasing the number of new targets and compounds.

IPO: Packard Bioscience Co . \$108.0M . April 2000



Source: Food and Drug Administration

Continued advances in FDA efficacy are beneficial not just to biotech companies but also to consumers.

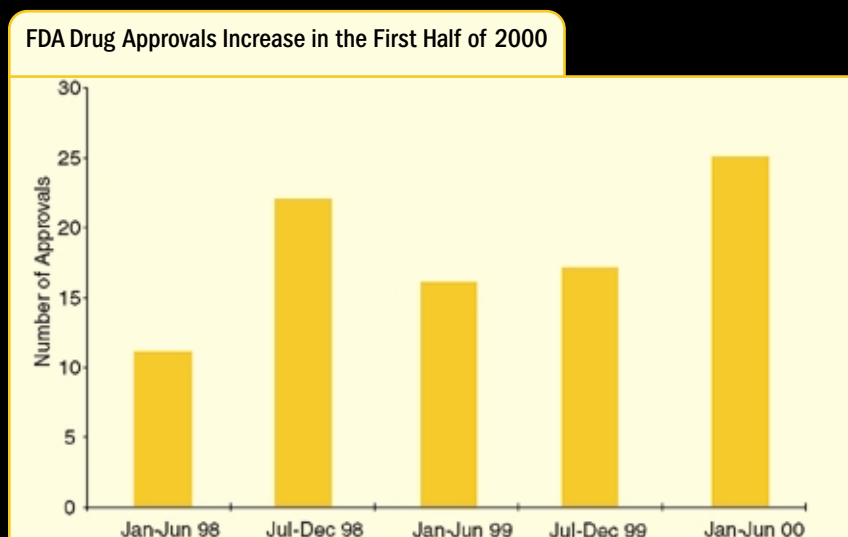
...But Not All the News Is Good News.

The headlines serve as a harsh reminder of the difficulties of taking products through clinical development and the regulatory process. For example, **Biogen** halted certain of its Phase II trials of Antova, including its transplantation and MS trials due to thrombo-embolic events seen in some of the trials. ISIS fell more than 60 percent after it announced

its pivotal trial of ISIS 2302 for Crohn's disease did not demonstrate efficacy. Toward the end of 1999, a FDA advisory committee voted that Gilead's Preveon for HIV failed to demonstrate safety and efficacy. Gene therapy companies were rattled by the publicized deaths of several patients in gene therapy trials, which raised questions about the safety and regulation of such trials.

After several years of record product approvals, the pipeline is robust with over 280 products in pivotal stage clinical trials, including many promising new products moving closer to the finish line.

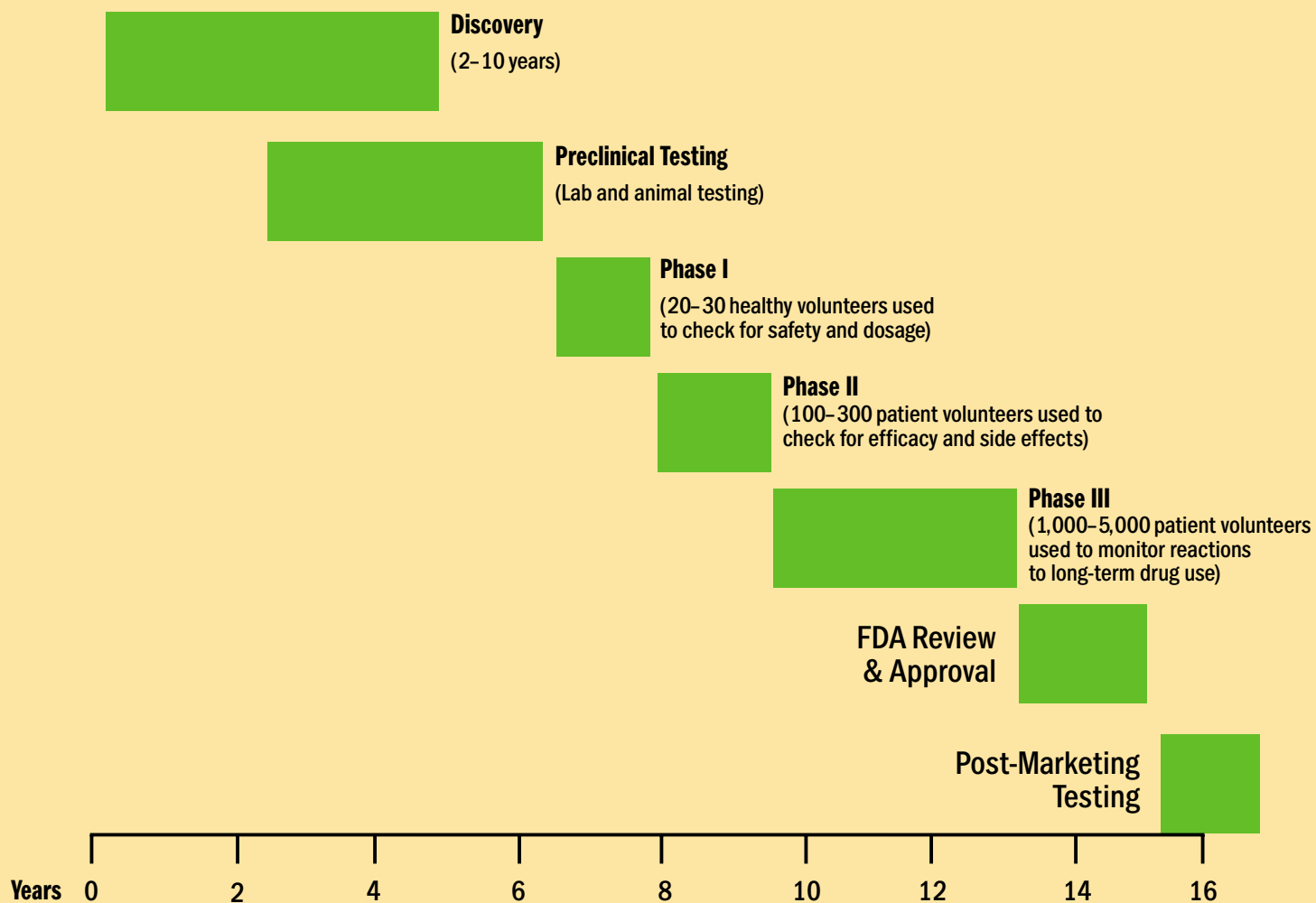
IPO: Praecis Pharmaceuticals Inc . \$92.0M . April 2000



Source: BioCentury

As biotech firms continue to push more drugs to the market, substantial revenue growth is expected.

Overview of the Drug Discovery Process



Source: Ernst & Young



250 lead candidates
in preclinical
testing



5 drug candidates
enter clinical testing;
80% pass Phase I



30% pass Phase II



80% pass Phase III



One drug approved
by the FDA

Strategic Alliances: Leveraging the Tools of Drug Discovery

Strategic alliance deals between pharmaceutical and biotechnology companies—and increasingly among biotechnology companies—have continued at a strong pace.

Although they have always been seen as validating a biotechnology company's science and product candidates, strategic alliances are equally critical for large pharmaceutical companies. More than ever, big pharma relies on biotechnology innovation as a key driver of product development.

The need to maintain or improve historical revenue growth rates and the significant pressure caused by lapsing patent rights for blockbuster products have caused U.S. pharmaceutical companies to triple their R&D budgets in the past decade. According to [PhRMA](#), the industry spent an estimated \$26 billion on R&D this year. An increasingly significant portion of this spending is going outside of the pharmaceutical firms to sponsor research and technology access in biotechnology companies.

In the past, strategic alliances have been predominately product deals. In these transactions, the pharmaceutical company obtained the license to a product candidate developed by a biotechnology company and agreed to fund or continue clinical development. In exchange, it obtained marketing and manufacturing rights in one or more territories. As the biotechnology industry has matured, emphasis has been placed on developing products to a later stage prior to partnering, and/or retaining greater rights to capture more of the value of the end product. Transactions such as [Aviron's](#) license of its intranasal influenza vaccine [FluMist™](#) to [Wyeth-Ayerst Laboratories](#) exemplify this type of transaction. In addition to significant cash payments and milestones, Aviron retained the right to manufacture [FluMist™](#), which has completed Phase III clinical studies, and co-promote the product in the United States.

In addition to licensing clinical stage products, technology access agreements have grown in importance. Under these, a pharmaceutical company obtains access to technology or tools useful in the drug discovery process on a non-exclusive basis. Both pharmaceutical and biotechnology companies are motivated to access cutting-edge technologies, which have the potential to vastly increase the speed and efficiency of the drug discovery process. For example, companies such as [Abgenix](#) and [Medarex](#) have licensed their proprietary technologies for generating antibody product candidates to numerous biotechnology and pharmaceutical companies. This has helped them generate significant payments and the potential for continued royalties, while retaining the rights to use the technology to advance their own

antibody-based pharmaceuticals. Novel technologies have converged in synergistic pairings of drug discovery companies such as Abgenix's transaction with [Human Genome Sciences](#) and Mederex's deal with [Eos Biotechnology](#). These deals marry powerful discovery technologies with the hopes of discovering therapeutic leads that can be jointly developed or partnered.

Many pharmaceutical companies have aggressively sought access to technologies that complement their own internal drug discovery initiatives. [Pfizer](#) has entered into technology access agreements with companies such as [Affymetrix](#), [ArQule](#), [GeneLogic](#), [Incyte Genomics](#), and [Maxygen](#), to obtain access to discovery platforms

[Tularik](#) and [Japan Tobacco](#) entered into a novel agreement in which Japan Tobacco will obtain access to Tularik's gene regulation platform for the discovery of products for treating metabolic diseases in exchange for funding research and development in a separate Tularik subsidiary. The two parties will share profits from any drugs developed, and Japan Tobacco has the option to buy the subsidiary at specified times. In perhaps the largest deal of its kind to date, [Novartis](#) agreed to pay [Vertex Pharmaceuticals](#) up to \$800 million for the discovery and development of drugs which target kinases. In addition to significant sums for research and license fees, under certain conditions, Vertex will have co-promotion rights in Europe and the United States.

The biotechnology industry has been known for its creativity in structuring alliance transactions to access capital and expertise resident in pharmaceutical companies.

and information. Similarly, [Roche](#) has agreements with [Affymetrix](#), [Caliper Technologies](#), [deCode Genetics](#) (of Iceland), [Incyte Genomics](#), and [Tularik](#). As integration of these technologies and programs present challenges of their own, [Aventis](#) chose to align with [Millennium Pharmaceuticals](#), which has assembled an integrated set of discovery technologies. Aventis will pay up to \$500 million—including a \$250 million equity purchase—for access to Millennium's discovery platform in the inflammation area.

Since its inception, the biotechnology industry has been known for its creativity in structuring alliance transactions to access capital and expertise resident in pharmaceutical companies. The creativity of these structures continues in an environment of increasingly retained rights and non-exclusive technology transfers. In combination with pharma's need to keep its pipeline full, these deals will fund the development of proprietary therapeutics and diagnostics as well as drive sustainable growth in the industry.

Convergence and Creativity Continue

Strategic alliances have defined the biotechnology marketplace, and this trend continues into the new millennium. As the industry faces the challenges of market volatility and realizes its vast potential, biotech companies continue to respond with innovation and creativity particularly through creative alliances.

[CV Therapeutics](#) (CVT) and [Innovex](#)'s May 1999 agreement to market the chronic stable angina product Ranolazine is unique in its balance risk mitigation and returned products rights. Breaking from traditional methods, such as finding a pharmaceutical partner or marketing the product solely on their own, CVT created a risk-sharing arrangement with [Innovex Inc.](#), a contract sales organization within [Quintiles Transitional Corp.](#)

Under the alliance, [Innovex](#) will hire and train a sales force to launch and promote Ranolazine, as well as provide post-launch marketing and sales services. In return, CVT will pay [Innovex](#) between 25 percent and 33 percent of revenues from the product. In return, CVT's Senior Vice President and Chief Financial Officer Dan Spiegelman believes, "partnering with [Innovex](#) on a risk-sharing basis will allow CVT to retain most of the profits from the sales of Ranolazine, if approved, while minimizing the financial risk typically associated with launching a company's first product." At the end of the agreement term, [Innovex](#) will transfer the sales force to CVT, which will pay royalties for specified periods.

Review of Stock Market Activity and Equity Financing

Stock Market Performance

The biotechnology industry's stock market performance has improved significantly since our last report. During the second half of 1998, the Asian financial crisis had depressed U.S. stock market prices, particularly lowering small cap and technology stocks. Although the biotech sector is usually immune to the fluctuations of foreign economies, investors seemed to have grouped the sector with other declining small-cap and tech-laden sectors. As a result, biotech indices lost a third of their value between May 1998 and September 1998.

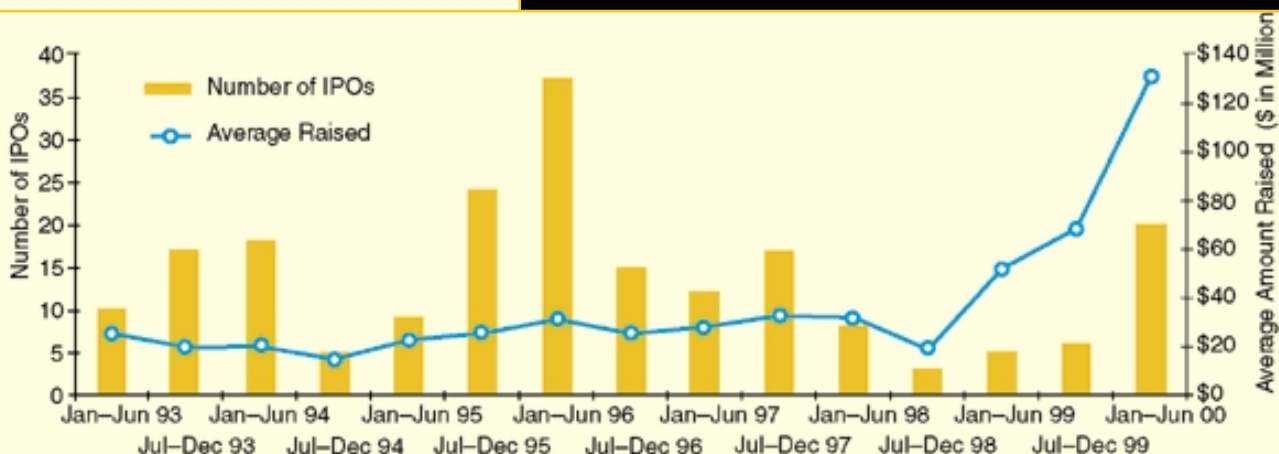
In the last quarter of 1998, the market climate began to improve, and the biotech indices followed the NASDAQ on a bumpy but respectable climb. The industry began to attract investor attention as Wall Street attention focused on a series of favorable fourth-quarter sales reports. Combined with forecasts of rapid sales growth among companies such

as [Idex Pharmaceuticals](#) and [Genentech](#), the backbone for the stock gains was formed that propelled the biotech indices into 1999.

Driven by renewed investor interest in technology companies, both the biotech indices and the NASDAQ posted gains through 1999, with the biotech indices outperforming the NASDAQ as the sector fundamentals improved. For example, the market for biotech equity financing gradually warmed. Although the financing market remained limited through the first half of 1999, [Abgenix Inc.](#) and [Cerus Corp.](#) managed successful follow-on offerings, both of which rewarded investors with price gains and encouraged further investment in the biotech industry. At the same time, the consolidation trend continued. The sparse equity financing environment motivated some biotech companies to collaborate in order to survive, and several attention-grabbing acquisitions and mergers were completed. Big pharma deals like [Warner-Lambert Co.](#)'s acquisition of [Agouron Pharmaceuticals](#) and marketing agreements such as the [Wyeth-Ayerst Laboratories-Aviron](#) collaboration stimulated investor appetite for biotech stocks. Institutional money also moved into the sector, as the perceived potential for returns in other health-related sectors diminished.

Key events sparked new investors to biotechnology in the latter half of 1999. Genentech's July 1999 IPO and news of the complete mapping of chromosome 22 brought media attention and momentum investors to the industry. By the end of

1999 Brings a Window of Opportunity for IPOs



Sources: BioCentury, BioWorld Financial Watch

“What changed compared to the IPOs in the last window is, surprisingly, the relative size and valuation of companies. In the current window, the average IPO has been on the order of \$100 million, which is easily two to three times larger than the average deal of five years ago....The appetite for these stories has certainly been robust, and it has allowed companies in this cycle to raise substantially more capital in their initial public offering, at valuations well beyond expectations.”

—Russell Ray, page 54

November 1999, the biotech indices had increased an amazing 150 percent above the September 4 lows. As the year ended, the biotech upswing shifted into overdrive. Pulled by biotech returns, and perhaps pushed by corrections in Internet stocks, momentum investors began to pour money into biotech stocks. The equity markets also improved, and new IPOs and follow-ons yielded premium returns to investors. The expanding media focus on genomics further aroused investor interest in the industry, and biotech stocks rocketed into the new millennium and into March, reaching levels 600 percent of the September 1998 lows.

In early March, biotech stocks began to slip with profit-taking on the NASDAQ. On March 14, President Clinton and British Prime Minister Tony Blair publicly stated that genomic information should remain in the public domain. Although their statement reinforced the right to patent commercial inventions based on genomics, investors misperceived the statement and sold off genomics stock in abundance. The sell-off extended into the rest of the biotech industry, and as the NASDAQ continued to slide, the biotech sell-off turned into a flood that lasted more than a month and consumed 50 percent of the March 6 index highs. In April, the NASDAQ stabilized, allowing biotech stocks to regain their footing. Soon, favorable first quarter earnings reports again prompted investor investment in biotech stocks, and by mid-July the NASDAQ Biotechnology index was back up to 78 percent of its March high.

Financing

Equity financing typically is closely tied to stock market performance: Strong investor returns in biotech stocks attract new equity financing to the industry. Conversely, weak returns increase the amount of funding from non-equity sources.

July 1998–June 1999

Accordingly, the equity markets were barren during the tepid stock performance of the second half of 1998. Only two companies—Abgenix Inc. and [Colateral Therapeutics Inc.](#),—undertook IPOs in the second half of 1998, raising \$39 million, an average of \$19.5 million per offering. The scarcity of biotech IPOs reflected a general IPO dearth in most industries, as investors preferred investing in established Blue Chip stocks rather than the riskier IPO markets. In spite of stock market improvement, the IPO market remained sluggish during the first half

of 1999, and only five companies went public, most notably [Invitrogen Inc.](#) and [Vaxgen](#). The five IPOs raised \$207 million, which, at an average of \$41 million per offering, was twice the average of the previous half year.

The follow-on market saw similar activity. Only two companies—[Coulter Pharmaceutical](#) and [Anesta Corp.](#)—engaged in follow-on offerings in the second half of 1998, raising a total of \$125 million. During the first half of 1999, five companies raised \$157 million through follow-ons, most notably [Cerus Corp.](#), [Abgenix Inc.](#), and [Trimeris Inc.](#)

With the option for fundraising through IPOs or equity follow-ons virtually nonexistent, biotech companies had to turn to other alternatives. Financings such as debt and convertible stock offerings were an integral aspect of some companies' survival through the second half of 1998 and into the first half of 1999. For example, [Ariad Pharmaceuticals](#) raised \$5 million in November 1998 through a convertible preferred stock offering as a private placement, which boosted its cash coffers to \$20 million. All together, companies used financial instruments like convertible notes 44 times to raise \$787 million in the second half of 1998. Especially notable among these companies were [Sepracor](#) and [Triangle Pharmaceutical](#). In the first half of 1999, these financings grew in importance, especially in the second quarter, with more established companies like [Immunex](#), [IDEC Pharmaceutical](#), and [Humane Genome Sciences](#) completing 81 financings to raise \$1.3 billion, with the most significant dollars coming from convertible debt transactions.

Venture financings rebounded a bit during the public equity dearth of the July 1998–June 1999 cycle. While public markets shrank considerably in scope, venture-stage financings actually increased, raising 13 percent more in real terms than during the July 1997–June 1998 cycle (although representing a smaller piece of overall venture capital pie). In the second half of 1998, 67 companies engaged in 72 venture-stage financings to raise \$640 million. Notable were financings by the Medicines Company, Dyax Corp., Medigene, and Ontogeny Inc., all of which raised over \$25 million. In the first half of 1999, 68 companies engaged in 72 financings to raise \$822 million, with Sequenom, Sensus Drug Development, Idun Pharmaceuticals, DJ Pharma, Bridge Medical Inc., and BioMarin Pharmaceutical together raising over \$25 million of the total, and Advanced Medicine raising a notable \$159 million.

While the cash shortages caused a number of companies to close down operations, more noticeable was the wave of consolidation that the market turmoil accelerated as biotech mergers, acquisitions, and partnerships increased to new levels. Many of these deals were intraindustry, with bigger, more established biotech firms acquiring or negotiating deals with smaller, cash-starved biotech companies. Also of considerable importance was the growing involvement by big pharma looking for product “stories” in the industry. For example Warner-Lambert’s acquisition of Agouron Pharmaceuticals stood out, as did Johnson & Johnson’s acquisition of Centocor. The immediate effect of these huge deals was to draw investor attention to the industry. To a large extent, it was this consolidation trend that set off the market climb of the first half of 1999 and would eventually revitalize the equity markets in the second half.

July 1999–June 2000

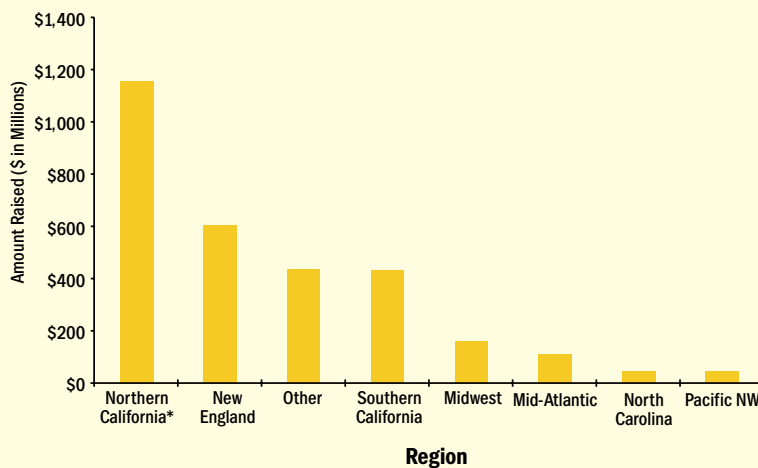
As biotech stocks continued to climb in the second half of 1999, the IPO market picked up. Six companies, including Maxygen, Symyx Technologies, Tularik, and BioMarin Pharmaceuticals, went public, raising \$478 million, an average of \$80 million per IPO. Genentech’s public re-offering which raised \$2.1 billion was also notable. The Genentech deal grabbed media attention, and the significant post-

offering price gains rewarded investors, further increasing investor interest in the industry.

The upward trend in IPO financing continued into the new millennium. Nineteen companies went public in the first half of 2000, raising \$2.2 billion. The average amount raised also continued to surge, increasing to \$114 million from \$80 million during the previous six-month period. Notable IPOs during this period included Diversa Corp., ACLARA Biosciences, IntraBiotics Pharmaceuticals, Tanox Inc., and Charles River. These IPOs and others combined with the financing of the second half to a total of \$2.7 billion in IPO financings in the July 1999–June 2000 cycle, a considerable improvement over the previous cycle’s \$200 million.

Follow-ons also fared much better in the July 1999–June 2000 cycle. Between July and December 1999, 16 companies completed follow-ons, raising an outstanding \$3.5 billion. Although Genentech’s secondary offering accounted for \$2.9 billion, the remaining \$653 million—dispersed among companies like Ilex Oncology, Pharmacyclics, ImClone Systems Inc., and VioPharma Inc.—continued to confirm the rebirth of a healthy follow-on market. The momentum of the follow-on market continued into the first half of 2000, when 27 follow-ons raised \$7.0 billion. Once again, another secondary offering by Genentech accounted for a large portion of the funds, in this case \$2.8 billion, but 26 other com-

**Substantial Regional Variation in IPO Activity
(by Region, July 1998–June 2000)**



*Does not include Genentech’s \$2.1 billion reoffering

Sources: BioCentury, BioWorld Financial Watch

panies—including [Celera Genomics](#), [Gene Logic Inc.](#), [Abgenix](#), [Celgene](#), [Medarex](#), [Emisphere Technologies](#), and [Maxim Pharmaceuticals](#)—together raised \$4.2 billion through follow-ons. At an average of \$160 million per follow-on, the secondary-offering market was well-positioned going into the second half of 2000.

Although the success of the IPO and follow-on markets may have reduced the need for certain types of creative financing, companies still successfully used them through the second half of 1999 and into 2000. In the second half of 1999, companies including [Human Genome Sciences](#), [Transkaryotic Therapeutics](#), [Affymetrix](#), and [Cephalon](#) successfully raised \$1.6 billion through 78 financings with convertible debt deals still leading the charge. The first half of 2000 embodied the explosive growth typical of the rest of the equity market, with \$6.6 billion being raised through 139 financings by companies

such as [Sepracor](#), [Inhale Therapeutics](#), and [COR Therapeutics](#). Together, “other” financings accounted for a third of the \$27 billion raised by biotech companies from July 1998–June 2000.

Venture-stage financing also remained important. In the second half of 1999, 53 companies raised \$640 million through 56 venture-stage financings; notable financings were by [Versicor Inc.](#), [Eos Biotechnology Inc.](#), and [Pharmasset](#). Finally, in the first half of 2000, 65 companies engaged in 71 financings to raise \$1.1 billion, with [Rosetta Inpharmatics](#), [Athersys Inc.](#), and [Genaissance Pharmaceuticals](#) each raising more than \$40 million. Robust public market returns are a key driver of venture state valuations, and a sustainable public market bodes well for younger companies. The explosion of innovative genomics informatics and related technologies will also keep venture capital flowing to the industry.

IPO: Charles River . \$224.0 . June 2000

The upward trend in IPO financing continued into the new millennium. Nineteen companies went public in the first half of 2000, raising \$2.2 billion. The average amount raised also continued to surge, increasing to \$114 million from \$80 million during the previous six-month period.

Roundtable Discussion: Trends in Capital Markets

The following roundtable—held on June 23, 2000—explores trends in today's capital markets and expectations for future markets. These executives shared their views on the overall outlook for biotech and the effect of globalization and other market forces on the industry.

Morrison: We just experienced one of the most lucrative financing periods in the history of the industry. What happened and why?

Ray: The market had been dormant until the appearance last fall of three IPOs—**Maxygen**, **Caliper**, and **Tularik**. Biotechnology had been down for a long time, but many of the companies associated with genomics had product portfolios that matured in the clinic over the past several years. They became more interesting, and money flowed into that sector largely because it was undervalued, on a relative basis, compared with technology. There was an intense focus on the genomics phenomenon, starting with the sequencing efforts by the **Human Genome Project** and **Celera Genomics**. At some point, we will have a wealth of knowledge about the underlying genes of the human genome. With that information, we can expect revolutionary changes in medicine.

What changed compared to the IPOs in the last window is, surprisingly, the relative size and valuation of companies. In the current window, the average IPO has been on the order of \$100 million, which is easily two to three times larger than the average deal of five years ago. It's also important



Moderator:

Scott W. Morrison is an Ernst & Young partner and the life sciences National Practice Leader. With two decades of life science experience, he serves start-ups to multinational public companies in the biotechnology, drug discovery, medical device and health areas.

Participants:

Russell Ray is a managing director and global head of the **Credit Suisse First Boston Health Care Group**, providing strategic and financial advice to life sciences, health care services, and medical device companies. He has successfully completed more than 100 transactions for leading health care companies. Before joining Credit Suisse First Boston, Russ spent 12 years at Deutsche Banc Alex. Brown and its predecessor entities working in health care financing and advisory work.



Dennis J. Purcell joined the Perseus-Soros BioPharmaceutical Fund, LP, as senior managing partner in February 2000. He is responsible for the overall management of the fund, which is dedicated to making private equity investments in the life sciences industry. Previously, Dennis served as managing

director of life sciences investment banking at **Chase H&Q** (formerly Hambrecht & Quist) for over five years, where he was directly involved with over 200 completed transactions and supervised over \$10 billion of financing and advisory assignments in the pharmaceuticals, biotechnology, and medical products industries. Dennis currently serves on the Bioethics Committee of the **Biotechnology Industry Organization**.

that the average pre-money value of the deals that had been completed through the end of May was around \$300 million, versus \$100 million five years ago. The appetite for these stories has certainly been robust, and it has allowed companies in this cycle to raise substantially more capital in their initial public offering, at valuations well beyond expectations.

Purcell: In late 1999, we saw a shift in investing from the Internet to biotech, specifically the genomic sector. Then, we really attracted momentum investors as well as some retail investors. Because of the illiquidity of many of the stocks, it didn't take much for the stocks to really run up. At the same time, we had a number of companies that were able to explain their business plans and their paths of profitability better. And they weren't just one-product companies that were trying to go public. Combine that with the management teams and boards that had been private for a while; they were much better prepared when they hit the public markets.

Morrison: What is the public market outlook for the biotechnology sector over the next couple of years?

Purcell: I think that the market is going to be much more discriminating over the rest of the year. Because of the volatility in the sector, it's very difficult to plan from the time you start to draft a prospectus to when you can get a deal priced. I think companies that embark on going public are going to have to live with that volatility and whatever the valuations might be. The better companies, I believe, will continue to be funded.

Ray: In general, the picture should be pretty bright for the next couple of years. There's a large queue of late-stage products that are going to receive approval during this period, and I would expect the continued success in the clinic and the approval of novel therapies and diagnostics to fuel investor interest.

In addition, the information flow surrounding the human genome sequencing accomplishment will continue. It is my understanding that in the entire history of the pharmaceutical industry, we have focused all drug development activities on about 500 targets. With the 100,000 to 150,000 genes in the human genome, there is clearly a much larger universe of potential drug targets to pursue.

Morrison: How is globalization of capital markets changing the way U.S. biotechnology companies are financed?

Ray: For a U.S.-based company, going outside the U.S. and particularly to Europe has been a proven path. Typically, the amount of money and

percentage of the deals that would be placed outside the U.S. has not been, on average, more than 15 percent to 20 percent of the total offering. That number will go up because there's a significant amount of capital flowing into the venture-backed creation of biotechnology companies in Europe, particularly in Germany.

Globalization also means that there will be more pockets of capital for companies to tap. On balance, however, U.S. companies will still depend on the U.S. markets for their capital, from the public equity markets, simply because of the amount of money that is available for investment in the U.S.

Purcell: We certainly see more of the typical type of transaction being funded out of Europe than we would have two or three years ago. Our experience has been that the larger funds in Europe have a somewhat longer time frame; they are, therefore, more patient investors than we see in the U.S. On the one hand, they don't have to live or die with the volatility that we see so dramatically in the U.S. On the other hand, I think there's an education process occurring, in terms of globalization of biotech. We do see different types of valuations in the U.S. compared with Europe. As we become more global, we must make sure we're all on the same page in terms of the potential risks and upsides of the undertakings. My sense, though, is that we're going to see more investment coming from Europe.

Morrison: Are there new categories of investors entering the biotechnology sector? Who are they and what are their implications for the future?

Ray: What's notable in terms of new investors is the emergence of convertible debt buyers who want to own convertible securities in biotechnology companies. Prior to this market, convertible debt by biotech companies had been somewhat limited to the very, very large companies; to those cash-flow-generating companies that are already capable of supporting the interest payment. In this most recent cycle, however, we've seen a large number of companies that do not make money, but have successfully raised a substantial amount of capital through the issuance of convertible debt securities.

For example, we sole-managed four convertible debt financings between June 1999 and March 2000 for [Human Genome Sciences](#), raising in aggregate \$850 million, and each price was higher than the prior price. There have been several billion dollars raised in this way, much more than in any previous cycle.

Purcell: In addition to the explosion in convertible debt financings, in which many companies raised hundreds of millions of dollars at a time, I

think we're seeing new investors in the market who are reading about the industry and selectively buying stocks. It's the rare day that you don't see a story about biotech on the front page of the news.

Morrison: Do you think the convertible debt market will continue, Dennis?

Purcell: Yes. We're hitting it from both ends of the spectrum. It's really the sophisticated technical people who buy more of the convertible debt securities and have made a judgment that they can buy them in companies that aren't currently generating cash flow. Also, because of the explosion of press on the sector, we're starting to see more retail people selectively buy these stocks.

Morrison: Regarding the class of 2000—those companies that went public in December 1999 and in the first nine months of 2000—is there enough research bandwidth on Wall Street to cover these companies? Or will this be a rerun of the 1990s when many companies became orphaned from an analyst coverage perspective?

Purcell: That's an important issue. We certainly do have an enormous number of companies that have to be covered. In fact, I hear from many people on the Street that even accounts that have bought these companies aren't quite sure what the companies do. It's an education process, and most firms don't have the staff to meet the new needs.

What we're seeing are more co-managers being added to cover this in the hope of buying research. And to a certain degree, that works. Lead managers generally drive the transaction home, however, and

investment banking firms will provide the research sponsorship for the companies that they have committed to financing.

The willingness of firms to cover companies that they did not take public is going to be a function of the bandwidth of their own analysts. Their primary obligation is to support the companies with which that firm has a relationship, as well as those companies that may have gone out with someone else, but by virtue of their performance have demonstrated they are meaningful entities that our investor clients clearly care about. I think you can see, and will continue to see, some broadening of the research sponsorship of companies by analysts who are not involved in the initial public offering.

Morrison: Has there been a large shift in retail versus institutional holdings in the last two windows?

Ray: My general impression is that—with the Internet and the emergence of various forums for retail investors to access information on companies—there may be more participation than in the past from the dot-com trading firms. Obviously, these have a principally retail-based clientele.

As in past markets, however, it is the institutional investor who really determines at what price and at what deal size the company should go public. The retail component, while complementary, is not going to be the driver in subsequently getting the majority of companies financed in their initial public offering.

Purcell: I think there's been a reasonable shift toward retail. Individuals are much more familiar

IPO: Tanox Inc . \$213.8M . April 2000

most investors look to them to provide the bulk of the research.

It is going to be very hard for companies to cover anybody for whom they didn't do an underwriting. It therefore becomes more difficult to get independent research. One of the challenges is that Wall Street hasn't been getting paid very well from research in the biotech sector. If you look at the trading characteristics of companies, and the kind of spreads on trades, they've been steadily decreasing over the last five or six years. Relative shares to co-managers for underwriting have also been decreasing.

Ray: It's difficult to say whether there will be enough bandwidth to cover these companies, because it involves speaking for the firms that took the companies out. Clearly, the responsible

with the sector than they ever were. They know the clinical trials taking place, and they band together into advocacy groups to demand the best treatment. In large part, they are driving treatment options.

This shift has both an up and a down side. Because the science, products, and development are not going to progress in a straight line, we have to avoid the boom-and-bust mentality that shaped the industry in the past 20 years. When we have the inevitable downturns, will the newcomers be long-term investors, or will they sell their stocks first and ask questions later?

Morrison: Large-scale consolidation has been predicted but has never occurred during the history of the biotechnology sector. Will this change in the near term?

Ray: That will be a function of several factors. One is obviously the availability of capital from the public markets and other sources. This will, in large measure, determine whether companies are forced to look at strategic combinations as a way to ensure their survival.

Aside from the capital market-driven aspect of the question, the reason we have not seen as many mergers as predicted is that it's often difficult to address what we call the social issues. That is, what role will the two different management teams from the combining companies play? Frankly, a lot of mergers that make good strategic sense probably did not occur because there was no easy solution to that question.

That being said, there is clearly a premium in the marketplace for the company that has the scale of operations to be a much more viable business. On balance, if one looks to the future, there should continue to be rational combinations of companies with complementary technology, products, and infrastructures.

Purcell: Because of the strength of the industry, I suspect we won't see large-scale consolidation in either 2000 or 2001. Because of the transition that the pharmaceutical industry is experiencing, and because more companies are successful independently owned companies that have market values in

up. The notion of a longer-term business model and what a business model should look like became secondary to whether the short-term stocks were working. We did, however, see a large infusion of companies that were more technology oriented than product oriented.

Ray: In the 1991–1992 cycle, people were obviously drawn to the FIPCO model, which is the fully integrated pharmaceutical model. This is based on the idea that it is reasonable for a life sciences start-up company to pursue a strategy that involves development of all the downstream capabilities—basic R&D through clinical development, manufacturing, and, ultimately, marketing—under one roof. That philosophy was debunked as a viable business strategy for many of the companies from the 1991–1992 class that tried to expend substantial resources to build those kinds of capabilities over a product portfolio that was quite narrow and limited in its maturity.

In the last cycle of the mid-1990s, the business model that people came full circle to accept was more of an outsourcing model. In this we see companies focusing on what they do best and partnering with bigger companies for clinical trials, marketing and manufacturing.

The business model question is particularly meaningful in the genomic space. Are you going to be a genomics provider of data to third parties that

IPO: Genomic Solutions Inc. . \$56.0M . May 2000

excess of \$1 billion, I think some can envision a scenario in which they can go it alone.

If companies can accomplish what they set out to accomplish, one of two things will happen. The drug industry will either have an appetite for approved products, which we have seen over the last couple of years. Or, once a company becomes truly independent and sustainable, the stock market will give it a high valuation. If more of the companies can see their way to independent paths, I don't think we're going to see mass consolidation in the near term.

Morrison: In the last window, did the public markets favor any particular type of business model?

Purcell: No. I think that the public markets in the last window were buying what worked, and what worked were stocks that were being priced and going

then use that information for their own drug discovery? Or are you going to be a fully integrated company that uses that basic functional genomics information to develop your own proprietary therapeutic product portfolio?

Morrison: What trends will keep the public markets active?

Ray: I believe that continued publicity on the fundamental progress taking place in the industry will bring the public markets back. This is what has historically sparked investor interest. On the product side, there is successful commercialization, receipt of FDA approval on launch, and proprietary, novel therapeutic products that improve the care of people. The general excitement that the human genome has created, and the progress we expect, will continue to

keep the spotlight on companies that are doing this exciting work. In doing so, they spark and sustain investor interest. In addition, merger activity that creates companies of scale certainly focuses attention on the potential of marrying complementary technologies and businesses, which would also be a catalyst for investor interest.

Purcell: To a certain degree the public markets of six months ago are doing very well. We have to show continued progress toward the mission and business plan of the company. As long as we do that, we're going to see companies that trade reasonably well. The challenge, of course, is that the science and clinical trials do not progress in a straight line. There are a lot of bumps in the road, and we have to continue to be prepared for those.

Morrison: In the absence of robust public markets, what are the trends in creative financing?

Purcell: Because the window was shut from 1996 until late 1999, more companies have business plans that don't necessarily include going public. They are more used to being private management teams, and their boards are used to the fact that markets can be fickle. Therefore, I think that what we're seeing is companies that are generating and making progress on their business plans and not particularly worried about whether or not they go public. What that means is that there will continue to be private equity available for these companies. I think

that going public as the end game will not be what people think about any more. It will simply be a step in the process, and whether that step is taken in 2000, 2001, or 2002, the important thing is that companies are making progress in reducing risk. And if they do that, sooner or later the value will catch up.

Ray: Even in difficult markets, companies that have developed and made substantial progress can get financed, perhaps at a lower valuation than would have been the case in a hot market. Once public, they can use convertible debt as a financing means. This was clearly used by a large number of companies during the first half of this year. I would expect that instrument to continue to be available to the biggest capitalized, largest market value companies that are making fundamental progress.

Once public, companies can also use PIPE financing—private investment in a public entity—in which companies sell directly to institutional investors stock in a private placement, which is subsequently registered without the benefit of the delays that sometimes come with a publicly filed deal through the SEC (Securities and Exchange Commission). We will also continue to see collaborative financings, with big pharma playing an important role to fund companies that seek to partner with a company that has the infrastructure they lack to manufacture and market the drugs they are developing.

“In general, the picture should be pretty bright for the next couple of years. There’s a large queue of late-stage products that are going to receive approval during this period, and I would expect the continued success in the clinic and the approval of novel therapies and diagnostics to fuel investor interest.”

—Russell Ray, Credit Suisse
First Boston Health Care Group, page 55

A Venture Capital Perspective: The State of the Biotechnology Union

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It would be logical to believe that
the interest in genomics companies
this year was triggered by the race
to complete the sequencing of
the human genome.

In fact, closer scrutiny shows that the strong economy led first to a speculative fever in the Internet world that started to cycle into biotechnology in December 1999. IPOs that had traditionally been priced in the \$100 million pre-money range have more frequently been taken out in the \$300 million-plus range this year. Even as the markets paused for breath in early summer 2000, weak IPOs rapidly appreciated in price.

February/March 2000 saw public genomics companies reach astronomical heights; with several attaining previously unheard of market capitalizations of \$3–5 billion. Perhaps those who have questioned the ability of technology, service, and tool-box companies to provide value to shareholders are finally convinced.

In the meantime, the competition between the public and private programs to sequence the human genome reached its zenith. There can be little doubt that [Celera](#) and its CEO Craig Venter won. In just two years and with less than \$1 billion, Celera achieved what the public program took \$3 billion and 15 years to complete. To be fair, Celera could not have achieved such success without the catalytic affect in the public program. Nevertheless, 0 to \$5 billion in valuation in two years must be a biotech record.

Although the national press seized on the sequencing achievement as the biological equivalent of putting a man on the moon, hopefully it is clearer where genomics is heading than astronautics. In a turn of Churchillian phrase: “Completion of the [Human Genome Project](#) is not the end, or even the beginning of the end; it is but the end of the beginning.”

It is perhaps surprising to some in private financing circles that genomics, which was a hot area 10 or more years ago, has just reached the consciousness of many of the investing public. Fortunately during those 10 years we have had plenty of time to ponder where we go from here. At the beginning of the Human Genome Project, Senator Pete Domenici (R-N.M.) put forth the thesis that it would lead to a cure for human disease in a 50-year period. Getting there from here seems as though it will take a little more time than originally projected.

On one level, the genomic roadmap for drug discovery seems fairly obvious: Find out what all or most of the genes do, find out what are the differences in gene expression between normal and

diseased tissues, work out the pathways of disease, find suitable interference points, and finally, design drugs to uniquely interfere with disease processes. Not surprisingly we have seen functional genomics, gene display companies, and pharmacogenomic companies go public this year.

Despite this roadmap, many troubling questions remain in discovering new drugs through genomic methodology. Protein profiles do not always match gene expression profiles, thus proteomics in its broadest sense may add something

February/March 2000 saw public genomics companies reach astronomical heights; with several attaining previously unheard of market capitalizations of \$3–5 billion.

to the equation. Genomics tells us nothing about protein/protein interactions. Many key disease-initiating gene products may reside in the cellular nucleus and may be difficult or inappropriate targets. Many degenerative diseases may involve more than one pathway and target. Target proteins are often not “druggable” and there is no known *ab initio* method to predict this.

To reward investments in the industry and bring its potential to fruition, the industry must tackle these problems and show that genomics can lead to the discovery of new drugs better, cheaper, and quicker.

Current Public Policy Challenges

Charles Craig

Director of Publications

Biotechnology Industry Organization



It's been both an exhilarating and curious year for the biotechnology industry. On Wall Street, the NASDAQ and American Stock Exchange biotech indices surged to unprecedented heights, plummeted, then jumped up and down frantically, but still remained higher than the previous year's lows.

In Washington, erratic behavior also was on display. Congress and President Clinton soundly endorsed biomedical research with back-to-back \$2 billion increases in the 1999 and 2000 budgets of the [National Institutes of Health \(NIH\)](#). These increases represented the first installments on a five-year plan to double the NIH budget.

Legislators adopted a patent reform bill that allows companies to recoup years of market protection lost during [Patent and Trademark Office](#) delays in reviewing applications. Congress also re-authorized the R&D tax credit for five years, the longest extension ever.

These legislative measures unmistakably encouraged biotechnology's development of new products. NIH support of basic research, for example, is a first step in the discovery of new therapeutic approaches. Without the biotech industry, however, basic research at NIH and universities would never make it out of the laboratory. Biotech companies use these discoveries and invest many times more than the government to create effective medicines for patients.

The Price Control Debate

The votes of confidence from Washington contrasted sharply with the discussions by some members of Congress and the president about imposing price controls on prescription drugs as a means of expanding Medicare beneficiaries' access to medicines. Price controls do not work in a free-market economy, however, and could be counterproductive to the boost Congress gave the industry in other legislative measures.

BIO, whose companies pioneer new therapies and cures—many for age-related illnesses—wants senior citizens to have affordable access to medicines. BIO has consistently advocated ensuring that seniors have affordable private-sector drug coverage, which includes stop-loss provisions to limit seniors' out-of-pocket expenses. In addition to supporting private-sector drug coverage for seniors from the beginning of the Medicare debate, BIO urged Congress to craft a comprehensive Medicare modernization plan that recognizes that biotech medicines have the most impact on age-related diseases and on reducing overall health care costs. But comprehensive Medicare reform—a complex undertaking—fell victim to presidential election-year politics in the 106th Congress. Democrats and Republicans battling for control of the [House of Representatives](#) and the

White House considered the seniors' vote key to victory. They oversimplified the Medicare debate, turning it into an assault on drug prices. Health care reform was reduced to television sound bytes on the cost of drugs.

Among the many factors these sound bytes ignored were the cost savings associated with new biotech medicines, primarily reductions in expensive hospital and nursing home care. A BIO study examined eight illnesses that most often affect seniors: coronary heart disease, stroke, cancer, Alzheimer's, Parkinson's, chronic renal failure, diabetes, and osteoporosis. The combined annual economic cost of these diseases is more than \$660 billion; the vast majority of that amount is spent for hospital and nursing home care.

The study, conducted by PAREXEL International Medical Marketing Services, revealed that biotech medicines on the market have the most impact in treating these conditions and that the drugs and vaccines in development represent even greater promise for improving the health of senior citizens. Researchers also documented per-patient cost savings for some treatments. The report, which examined 20 marketed biotech drugs and 57 in development for age-related diseases, demonstrated that the biotechnology industry's continued innovative drug development is essential for improving the health and quality of life of seniors.

Gaining Public Acceptance

If the drug pricing debate is the most important challenge for the biotech industry in Washington, a close second is gaining the public acceptance of biotechnology in agriculture and gene therapy.

The main legislative concerns on the agricultural front were proposals for mandatory labeling of biotech foods, regardless of whether use of recombinant DNA technology caused any change in the products. BIO supports the strict, science-based guidelines for labels handed down from the FDA. These guidelines alert consumers to nutritional changes or health risks, such as allergic reactions. BIO opposes, however, labeling that merely identifies use of recombinant DNA technology instead of conventional breeding to achieve desired traits in plants and animals. Such labels could lead consumers to assume there are safety differences between foods when none exist.

Labeling, the subject of House and Senate legislation, remained an issue despite scientific reports

confirming that the use of recombinant DNA technology to improve crops is safe for consumers and the environment. The FDA reiterated its support for biotech foods in announcing refinements to its regulatory approach, saying the initiatives were designed to "provide the public with continued confidence in the safety of these foods."

The changes were based on public outreach meetings held in late 1999 in Chicago, Washington, D.C., and Oakland, California. The FDA proposed that developers of biotech foods and animal feeds be required to notify the agency when they intend to market such products. The FDA stated that such a mandate would include requiring specific information to help regulators assess "safety, labeling, or adulteration issues." The consultation process had been voluntary.

Under the proposed rule, the FDA also would issue a letter describing its findings about a product and post the letter to the public on the FDA's Web site. In addition, the FDA said it would draft guidelines to assist manufacturers that want to label their foods to indicate whether they were made with bio-engineered ingredients.

FDA Consultation: Voluntary Versus Mandatory

BIO supported making the approval process for biotech foods more transparent and providing more guidance to the food industry with regard to voluntary claims on food labels. BIO did not consider necessary, however, the FDA's move to make the premarket consultation process mandatory. Numerous independent examinations by authoritative bodies, including the National Academy of Sciences (NAS), have found that the existing regulatory system does a good job of protecting consumers and the environment.

An April 2000 NAS report, *Genetically Modified Pest-Protected Plants: Science and Regulation*, confirmed that foods derived from plant biotechnology are thoroughly tested and safe; the report also pointed out that biotech crops offer significant improvement over traditional agricultural practices.

Another study, conducted by University of Illinois researchers and published in the *Proceedings of the National Academy of Sciences* in June 2000, showed that corn containing a *Bacillus thuringiensis* (Bt) protein toxic to the European corn borer, a destructive pest, posed no threat to black swallowtail butterflies in the field. This study—*Absence of*

Toxicity of Bacillus thuringiensis Pollen to Black Swallowtails under Field Conditions—directly countered a May 1999 [Cornell University](#) laboratory study showing that Bt corn could be harmful to monarch butterflies. The Cornell study brought the European backlash against agricultural biotechnology to the United States, and the battle has since been raging on both sides of the Atlantic.

Gene Therapy Under Fire

More is at stake in this debate than the future of agricultural biotechnology in Europe and the United States. Developing nations can use biotechnology to improve their farming techniques, increase food supplies, enhance nutrition in foods, and improve their citizens' health.

The antitechnology activists, however, have not confined their opposition to agricultural applications of biotechnology. Gene therapy became a target following the tragic death in September 1999 of 17-year-old Jesse Gelsinger, a patient in a clinical trial at the [University of Pennsylvania](#). An [FDA](#) investigation found serious lapses in procedures on the part of the university researchers and halted their studies. Antitechnology activists seized on the tragedy to seek a moratorium on some gene therapy trials. The [NIH](#) rejected that proposal, and [BIO](#) joined patient groups in opposing the moratorium.

The biotech industry supported subsequent initiatives proposed by the [U.S. Department of Health and Human Services \(HHS\)](#) to increase public and patient confidence in all clinical trials of new drugs and biologics. The initiatives focused on informed consent of patients and conflicts of interest by investigators.

HHS already has authority to implement four of the five recommendations:

- Improve education and training of clinical investigators and institutional review boards (IRBs) and their staffs.
- Issue specific guidance on informed consent, clarifying that research institutions and sponsors are expected to audit records for evidence of compliance.
- Require investigators conducting Phase I and II studies to submit clinical trial monitoring plans when applying for [NIH](#) grants. These plans should be shared with IRBs.
- Issue additional guidance to clarify [NIH](#) regulations regarding conflict of interest, which will apply to all [NIH](#)-funded research.

[BIO](#) expressed some concerns with the fifth [HHS](#) recommendation. This would require adoption of legislation giving the [FDA](#) power to levy civil monetary penalties of \$250,000 per clinical investigator and up to \$1 million per research institution for violations of informed consent and “other important research practices.” The [FDA](#), which monitors all clinical trials, already has authority to issue warning letters and impose regulatory sanctions—such as halting studies—to force compliance with agency standards.

Exhilarating Science: Mapping the Human Genome

While Wall Street and Washington struggled with their perceptions of biotechnology, science forged ahead to achieve an unprecedented milestone: completion of a rough map of the human DNA sequence.

The map is a major step in the continuing exploration of the causes of human diseases. The biotechnology industry's discoveries over the past 25 years have been stunning—nearly 100 biotech drugs and vaccines on the market and another 350 in late-stage clinical trials. With a map to guide them, biotech researchers can now accelerate their search for the molecular causes of illnesses and their development of new therapeutic interventions.

But the hard work is just beginning: that is, discovering the function of genes and how they interrelate. In addition to representing the promise of biotechnology, the map represents the power of science, which is certain to generate debate on many bioethical issues, as well as the direction of genetic research. [BIO](#) has always encouraged thorough discussion of these issues in open forums; three important issues under debate in Washington today are discrimination, privacy, and intellectual property.

On the issue of discrimination, [BIO](#) has argued that medical information, including genetic data, should be protected against misuse by insurers, employers, educators, and police. Advances in genetic testing have brought this issue to the fore. People must feel secure that their medical information will not be misused. Otherwise, they will not take advantage of tests that could help them reduce the risk of developing certain diseases as they age.

Privacy is a related issue that demonstrates the dangers of overreacting. Among the reasons genetic information should remain confidential, of course, is to prevent misuse. But medical researchers also need access to patient data to study diseases and develop new drugs to treat them. To achieve this balance between privacy and research, Congress should establish national standards that protect patient anonymity and permit researchers to continue working on new therapies and cures.

Intellectual property, in this case gene patenting, is an issue for which a little explanation goes a long way. Patents are not granted on the raw DNA

Ethics in Biotechnology

The biotech industry has a long tradition of responsible behavior and respect for concerns generated by its research. In the 1970s, when recombinant DNA technology was invented, scientists called for a moratorium on its use until implications of the new technology could be assessed and guidelines for research could be established. The biotech industry was one of the first to support a voluntary moratorium on cloning human beings. It also imposed its own ban on gene therapy research with germ line cells, those that pass genetic information from generation to generation.

Biotech companies must also let the public know that they are conducting business with an appropriate mixture of enthusiasm, caution, and humility.

sequences of genes. A patent is awarded only if the applicant can describe a gene's role in human health or other commercial application. And a patent has no impact on academic researchers not engaged in commercial activity. Such researchers are free to work without obtaining a license.

Without patents, however, there would be no biotech industry and no innovative drug development. Patents enable companies to sell their new treatments and cures for a limited time, free from competition. This gives them the opportunity to earn the money they need to stay in business, pay their employees, and reinvest revenues to develop more new drugs.

BIO and its more than 900 members adhere to a Statement of Principles, adopted in 1997, for the ethical practice of biotechnology. The rapid advance of genetic research now demands more. BIO initiated a project to encourage all companies to integrate bioethics principles into their everyday business practices. Some have already done so by forming bioethical advisory boards to evaluate research projects and hiring consultants to conduct regular classes in bioethics for their employees.

Finally, as genomics fulfills its promise of new therapies and medications, biotech companies must also let the public know that they are conducting business with an appropriate mixture of enthusiasm, caution, and humility.

Securitization of Biotechnology Research Patents

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The biotechnology industry continues to experience unprecedented change, turbulent uncertainty, and unbounded opportunity.

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Driving these diverse forces are the vast expansion of scientific knowledge and intellectual and financial capital devoted to life sciences and biomedical research, which offer great promise to improve human health and quality of life. Also driving these changes are the highly publicized research compliance compromises and failures in informed consent, conflicts of interest, and other critical issues that threaten public trust in both biotechnology research and biotechnology applications.

Perhaps the most important and interesting issue, however, is the establishment of intellectual property (IP) in its various forms as the primary means through which research developments are recognized as new advances, used in further research, and translated into downstream applications in health care and other fields. Real opportunities and real challenges arise in better capitalizing and leveraging this vastly expanding and promising IP array. This is true of many important high-technology fields, but it is especially significant in biotechnology.

Dormant Patents

Most of today's biotechnology patents lie dormant until expiration. Generally, the product or process underlying the patent never reaches the market, and the patent is never transferred or licensed to another potential user. Indeed, according to data compiled by [The Patent and License Exchange](#), well over 90 percent of current patents lie unused on the shelf. The result is that the patent holder never realizes the maximum value of the IP.

Many patents are not transferred to a potential user because of concerns about the commercial use and value of the patent itself, as well as uncertainty about the underlying science. Additional areas of concern are financial and related to regulatory compliance. In market terms, one historical result of this risk and uncertainty has been an illiquid primary market and the nonexistence of a secondary market for IP. Illiquidity correlates closely with market friction and high transaction costs, which restrain value creation in a research organization.

As a result, many patents remain unrecognized or unexamined for lack of effective IP market mechanisms. This is a tragedy, since patented discoveries often represent promising leads to diagnostics, treatments, and cures for diseases—as well other important advances in health and other fields.

A Changing Market

Fortunately, the market is changing. IP transfers today are perhaps most like mortgage transfers of the 1970s, before Federal National Mortgage Association and Government National Mortgage Association mortgage-backed securities swept away old ways and created today's robust, efficient primary and secondary mortgage markets. In these markets, millions of average Main Street investors are linked by Wall Street to the mortgage capital markets through mortgage-backed securities.

Just as with the old ways in mortgages, today's IP transfer and investment transactions exist in an antique world of transaction-by-transaction document development. This system is laborious and expensive, and often includes incomplete and incompletely revealing due diligence, without generally accepted norms for documentation and due diligence. Most important, generally accepted patent validity, valuation, and verification protocols for predicting and rating biotechnology IP investment

By holding participants to basic standards for listing on their exchanges, such markets raise the level of confidence in a given transaction, thus increasing overall liquidity and reducing transaction costs. These standards and conditions of participation can include title services, patent insurance, and relevant third-party assurance that provide a safe harbor "seal of approval" to research organizations and others contemplating a transaction. Valuation metrics as part of the transaction process will also lend a measure of reasonableness to, and will positively differentiate, transactions under consideration.

As primary markets bloom, secondary markets are not far behind. The establishment and accepted use of industry standards for measuring and predicting the risks and returns associated with a given revenue stream allow for pooling of patents into securities tradable on secondary markets and as derivative financial instruments. Not to be overlooked is the fact that the expanding IP marketplace will require evidence of compliance with regulatory

The establishment and accepted use of industry standards for measuring and predicting the risks and returns associated with a given revenue stream allow for pooling of patents into securities tradable on secondary markets and as derivative financial instruments.

reward and risk potentials are not yet in wide use, although many sophisticated buyers and sellers of IP have their own preferred formulas. The net result is a relatively illiquid, undercapitalized market in biotechnology and other technology patents.

New Developments Promise Progress

Fresh breezes and new developments for progress are on the horizon, however. The past year has seen the emergence of recognized exchanges for the trading of IP. The Patent and License Exchange, the [IP Exchange \(IPEX\)](#), and various others have established electronic forums to link prospective buyers and sellers of IP. Furthermore, the Patent and License Exchange will also integrate valuation into the standard process, which will help to solidify trading.

and other requirements as a basic condition of IP transferability. Compliance actions of leading biotechnology researchers and research organizations that conduct and document their research in accordance with recognized best practices will be economically well rewarded for their efforts through higher valuations and more readily transferable IP portfolios.

Similar to what occurred with mortgages in the 1980s, the application of such standards and accepted rules of the game can and will lead to a more robust, liquid market. Just as investment capital flooded into the mortgage market during the 1980s, these developments will attract significant additional capital to research and development institutions in biotechnology and related fields.

The Evolving European Market

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A rapidly evolving European life sciences sector continues to affect every aspect of the biotech industry, from the number of existing companies, to trends in business models, and the state of technology itself.

In this dynamic market, investor favor has returned, propelling the valuation of several companies into the billion Euro group in early 2000. Profitability is on horizon for a number of companies, and numerous biotech products are expected to gain approval.

Based on the experience of the U.S. biotech industry, European companies are striving to achieve significant benchmarks believed necessary for accomplishing sustainability, including the ability to reach significant market valuations, develop a product focus, gain access to technologies capable of producing multiple products, and develop a complete pipeline.

Astounding Growth

The rate at which new companies are being created throughout Europe is astounding, increasing by 173 over the year to 1,351. Germany—where the number of biotechnology companies has risen more than 150 percent in the past three years—can now claim the largest number of European biotech companies. This growth demonstrates the impact of the German government's initiatives to promote the industry. Companies in that country are smaller and have limited pipelines; it remains to be seen whether this novel approach to encouraging start-up companies will generate a sustainable industry.

In Europe, industry revenues have leapt forward over the past year, increasing by about 45 percent to 5.4 billion Euro. This is approximately the level of the U.S. industry seven or eight years ago, with a similar number of companies. While European industry revenues have increased, the total net loss has not changed significantly over the past five years, indicating that—for more mature companies at least—new R&D is being funded largely from increased revenues.

A sizable proportion of the increased revenues comes from alliances with pharma and other biotech. The number of reported alliances doubled in the past two years, to around 240, and early activity in 2000 indicates it shows no signs of abating.

Finance and Markets

Europe's publicly quoted biotech sector had a strong year in 1999, with a particularly robust fourth quarter. The U.K. biotech sector, which represents about two-thirds of the value of European biotech, outpaced the FTSE 100 and the FTSE pharmaceutical and health care indices, which advanced a

modest 8 percent in 1999. The continental European biotech sector did not perform quite as robustly, although there were notable exceptions.

After almost two years of steady decline, the European biotech sector ended 1999 at a worth of approximately 17.8 billion Euro, compared with 10.7 billion Euro at the end of 1998. In the first few months of 2000, the U.K. sector virtually doubled, to 20 billion Euro. [Celltech](#) and [Shire](#) were both lifted into the top 100 companies in the U.K. through a combination of mergers and market sentiment. The return of investor favor propelled the valuation of a number of companies, such as [Cambridge Antibody](#) and [Oxford Glycosciences](#), into the billion Euro group early in 2000.

The London Biotech Index, which measures the stock performance of 15 leading U.K. biotech shares, rose 110 percent during 1999. By contrast,

LSE is at the heart of the effort to create a pan-European alliance of major exchanges that are attractive to multinationals, it has failed to attract non-U.K. companies. There have been attempts to create a pan-European exchange for high-tech, high-growth companies, but the results have so far been muted.

Merger and Acquisition Deals

While merger and acquisition activity has been discussed as a business option for some years now, the first signs that European biotech companies were serious about such activity appeared in 1999.

A number of signatures emerged in the U.S. merger and acquisition activity last year that might help identify the most likely future candidates for acquisition. As many pharma companies are looking to bolster their own pipelines and earnings growth

European companies are striving to achieve significant benchmarks believed necessary for accomplishing sustainability...

the [BioCentury](#) 100 Index, which measures the performance of 100 leading companies globally, saw its value increase by 95 percent. European stock markets for biotech did not turn in quite the same performance as London during 1999. The total market valuations of [EASDAQ](#)-quoted biotech stocks fell from 818 million Euro at the start of the year, to 784 million Euro by the end of the year.

Most of 1999 was quiet for initial public offerings (IPOs). Of the 20 IPOs that closed in 1999, seven took place on European exchanges and involved transactions raising 319 million Euro. The typical European IPO raised less than the average IPO in the United States.

A major challenge facing European biotech companies that want to go public is deciding which market to select. The [London Stock Exchange \(LSE\)](#) has made efforts in the past to evolve as the best place for Europe's high-growth, high-tech companies. But the downturn in the biotech cycle of 1997–1998 has prompted the LSE to take a much more conservative line in terms of company track record. Moreover, only recently have British institutions felt it is safe to return to biotech. While the

potential, it is hardly surprising that nearly all the companies acquired by either pharma or top-tier biotech companies had a product already on the market or in late stage development. Most of Europe's biotech sector is still a long way from fitting the bill as potential prey for predatory pharma companies. They may, however, find themselves being attractive to medium-sized health care companies with ambitious growth plans.

Products and Technology

The Committee for Proprietary Medicinal Products (CPMP)—a part of the [European Medicines Evaluation Agency \(EMA\)](#)—issued ten positive opinions on medicinal biotech products and three on veterinary biotech products. All the products approved emerged from either major pharmaceutical or U.S. biotech companies. These products included [Roche](#)'s prophylactic treatment of acute transplant organ rejection, Zenapax; [Immunex](#)'s rheumatoid arthritis treatment, Enbrel, which is being marketed by [Wyeth Ayerst Europe](#); the Crohn's disease treatment, Remicade, also from Immunex; and [Chiron](#)'s bacterial combination vaccine, Triacelluvax.

European biotech companies have yet to make real headway introducing new biotech medicines into the marketplace. While **Chiroscience** won approval for a long-lasting local anesthetic and **SkyePharma** received FDA approval of DepoCyt, the news was dominated by big name disappointments—including announcements from **British Biotech**, Cortecs (now **Provalis**), **NeuroSearch**, and Vanguard Medica (now **Vanalis**)—that lead products were not developing as hoped.

A number of European companies are moving forward with vaccines, including **Celltech's** Hepagene. **Peptide Therapeutics** began a U.S. Phase II trial comparing its live attenuated yellow fever vaccine Arilvax to **Pasteur Merieux Connaught's** marketed YF-Vax yellow fever vaccine. Sweden's **Active Biotech** and its partner **SmithKline Beecham** completed their Phase III trials of the ETEC vaccine to treat traveler's diarrhea.

Public Policy Forces

Despite supportive words from both the **European Commission** and the leading European governments, biotech received a mixed response from European legislators in 1999.

The European Commission has moved closer to adopting a final set of rules on orphan drugs. As the proposal stands, approved European orphan products would have a 10-year market exclusivity, which

could be reduced if the product is considered too profitable or if a subsequent product is found to be clinically superior. Despite this mixed response, the industry believes the passage of this law will encourage companies to develop drugs against rare disorders, as it has in the U.S.

Although there is some evidence that the **EMEA** has had a successful first five years, many believe that Europe's regulatory system for medicinal products still requires a radical overhaul. The system is considered unduly complex and, in many cases, duplicative of pan-European and national activities.

In what will be considered a landmark decision, the U.K.'s **National Institute for Clinical Excellence (NICE)** recommended that doctors in the British National Health Service should not prescribe Relenza, a neuraminidase inhibitor developed by the Australian biotech company **Biota** and the European pharma giant **Glaxo Wellcome** to treat influenza. The ruling was based on concerns that the cost would place a financial burden on the health system, and that there was not enough evidence to support the drug's use in the most at-risk groups. The possibility that NICE could emerge as a model for other European countries looking for ways to contain their national health bills has concerned the pharma industry. **GlaxoWellcome**, **SmithKline Beecham**, and **AstraZeneca** have

Selected European Financings (July 1999 – June 2000)

	Market	Date	Amount Raised (\$ in millions)
Follow-ons			
Oxford GlycoSciences	London (LSE)	March 2000	\$56.0
Cambridge Antibody Technology Group plc	London (LSE)	April 2000	143.2
Rhein Biotech N.V.	Nmarkt	May 2000	36.8
Karo Bio AB	Stockholm (SSE)	May 2000	22.4
IPOs			
Evotec	Nmarkt	November 1999	\$55.5
Plasma Select	Nmarkt	March 2000	113.5
Actelion AG	Swiss (SWX)	April 2000	139.7
NutriPharma ASA	Oslo (OSO)	April 2000	58.6
GPC Biotech AG	Nmarkt	May 2000	96.1
Pyrosequencing	Stockholm (SSE)	June 2000	115.9

Sources: *BioCentury*, *BioWorld Financial Watch*

warned the British government that NICE's activities could have global repercussions for sales and send damaging signals about the future rewards for innovation.

European campaigners against agricultural and food applications of biotech made huge inroads during 1999, particularly in the U.K. European governments continued to procrastinate over the approval of modified crops, while most British and many European food store chains removed all genetically modified ingredients from their own brand products.

Finally, the next big challenge for the industry will come from xeno-transplantation. Already, European politicians have signaled their concerns about developments that seek to make up for the shortfall in human organ donations by using modified animal parts. European parliamentarians have called for a global moratorium on xeno-transplantation until the technology has been fully tested.

For a comprehensive report on European biotechnology, visit http://www.ey.com/global/gcr.nsf/UK/Ernst_&_Young_Life_Sciences.

The Coming Medicare Marketplace: Breaking Through the Regulatory Barriers to Market Growth

Powerful trends—including aging of the baby boomer population, technological advancements, consumerism, and a strong economy—are overcoming the political obstacles to a Medicare prescription drug benefit. By 2030, the number of Americans 65 years and older will double from today's 33 million to 75 million. Over time, this population will increasingly demand access to state-of-the-art therapeutics. Pharmaceutical and biotechnology firms that anticipate this trend and understand Medicare's coverage process have a competitive advantage in breaking through the barriers to market growth.

The **Health Care Financing Administration (HCFA)**, the organization that administers the Medicare program, determines which products it provides to beneficiaries and at what approved reimbursement rate. National coverage decisions are binding for all Medicare contractors, although local contractors have some discretion in supplementing national decisions and deciding coverage in the absence of national coverage.

The coverage process takes approximately nine to twelve months. Coverage reviews are initiated when HCFA identifies issues such as local conflicts or significant medical advances or when the program receives a formal external request for a coverage decision—generally after the product has been approved by the **FDA**. Formal requests for Medicare coverage must include:

- A description of the product or service and the pertinent Medicare benefit category
- All currently available medical and scientific information on the drug or device
- A description of current studies or trials on the drug or device without disclosing confidential information
- The status of current FDA procedures concerning the drug or device

Within 90 days of receiving the formal request, HCFA either makes a coverage decision or refers the request to the Medicare Coverage Advisory Committee (MCAC). HCFA then receives a coverage recommendation from the committee based on “reasonable and necessary” standards. Included in the recommendation will be a determination of need for additional technology assessment. HCFA announces its decision 60 days after receiving the MCAC recommendation. After a positive coverage decision, the payment change becomes effective within six months after the beginning of the calendar quarter.

Complete information on the Medicare coverage process can be found at <http://www.hcfa.gov/quality/8b.htm>.

Appendix 1: Venture Stage Financing Totals \$3.1 Billion (July 1998 – June 2000)

July 1998		October 1998		February 1999	
BioMarin Pharmaceutical Inc.	\$11.5	Acorda Therapeutics Inc.	\$20.2	Ancile Pharmaceuticals	\$10.1
Ciphergen Biosystems Inc.	13.5	AviGenics	4.0	Arena Pharmaceuticals	17.0
Copernicus Therapeutics	7.6	Bioenergy	1.8	Biostar Inc.	2.1
Cytovia Inc.	2.0	Biolex, Inc.	1.1	Desmos	1.8
Dendreon Corp.	4.7	Cogent Neuroscience Inc.	5.4	Gryphon Sciences	4.4
Esperion Therapeutics Inc.	15.5	FeRx Inc.	7.3	IntraBiotics Pharmaceuticals	23.0
Inhibitex	1.5	Mosaic Technologies	6.0	Pangea Systems Inc.	4.0
Insmed Pharmaceuticals Inc.	14.5	Osiris Therapeutics Inc.	8.0	PHASE-1 Molecular Toxicology	1.0
Metabolex Inc.	8.0	Signature BioSciences	1.0		\$63.4
Myelos	9.6	Third Wave Technologies Inc.	9.5	March 1999	
Nereus Pharmaceuticals Inc.	1.0		\$64.2	ACLARA BioSciences	\$18.0
Paradigm Genetics Inc.	12.0	November 1998		Adolor Corp.	8.5
Situs	10.0	Acusphere	\$5.0	AvMax Inc.	5.0
Vascular Therapeutics	21.6	Acusphere	2.5	Genomica Corp.	13.6
Xcyte Therapies Inc.	12.0	Cepheid Inc.	2.3	Immunicon Corp.	9.3
Zyomyx Inc.	1.0	Dyax Corp.	31.0	Kinetix Pharmaceuticals	8.8
	\$145.9	GenVec Inc.	7.0	Molecular Mining	2.0
August 1998		Illumina Inc.	8.6	Orchid Biocomputer Inc.	16.0
Acadia Pharmaceuticals Inc.	\$10.7	Islet Technology Inc.	1.7	Peptimmune	0.8
Allergenic	5.0	Phase Forward Inc.	8.0	STC Technology	9.2
Chimeric Therapies	13.2	Selective Genetics	4.5	Versicor Inc.	3.8
Cohesive Technologies	6.7	Telik Inc.	10.5	Versicor Inc.	3.0
Consensus Pharmaceuticals	7.0		\$81.1	Zyomyx Inc.	8.5
Dynavax Technologies Corp.	16.5	December 1998			\$106.4
Entelos Inc.	5.8	Afferon	\$0.6	April 1999	
Esperion Therapeutics Inc.	15.0	Biolex, Inc.	1.1	ACLARA BioSciences	\$3.0
Genaissance Pharmaceuticals	10.0	Biopure Corp.	17.9	BioMarin Pharmaceutical Inc.	26.0
Pangea Pharm.	4.7	CytoLogix Corp.	5.4	BioMedicines	12.0
ProdiGene	3.0	Inspire Pharmaceuticals	1.5	BioStratum Inc.	6.0
The Medicines Company	36.0	Memory Pharmaceuticals	10.5	Encelle Inc.	5.0
United Therapeutics Corp.	10.0	Metabolex Inc.	3.0	Genomic Solutions Inc.	6.0
Vinifera Inc.	1.8	Ontogeny Inc.	28.1	Kinetek Pharmaceuticals Inc.	8.8
ViroLogic Inc.	12.6	Pangea Systems Inc.	15.0	LXN	10.2
	\$158.0	Pherin Pharmaceuticals	2.7	Pharmadigm inc.	8.6
September 1998			\$85.8	Rosetta Inpharmatics	9.2
AeroGen Inc.	\$18.0	January 1999		Sequenom	37.0
Chromagen Inc.	5.0	Diversa	\$7.3	Spotfire	6.0
Coulter Cellular Therapies	16.0	DJ Pharma	25.0	Tandem Medical	2.5
Delsys Pharmaceutical Corp.	14.5	EpicYTE Pharmaceutical	4.5		\$140.3
Delsys Pharmaceutical Corp.	3.0	Genesoft	5.4	May 1999	
Deltagen Inc.	11.5	Genoplex	0.8	AtheroGenics Inc.	\$15.9
Inspire Pharmaceuticals	0.9	Idun Pharmaceuticals	30.0	Bridge Medical, Inc	32.5
MediGene	25.7	ImaRx Therapeutics	1.5	Diagnology	1.5
Message Pharmaceuticals Inc.	6.3	Pentose Pharmaceuticals	7.0	Epic Therapeutics	12.5
ReGen Therapeutics	3.5	Regen Biologics	4.0	Kimeragen Inc.	7.5
Southern Biosystems	1.1	Symyx Technologies Inc.	13.0	NitroMed Inc.	11.0
	\$105.5	Zarix Ltd	5.5	Pangaea (now Zycos)	5.7
			\$104.0	Selective Genetics	5.0

Senomyx	1.0	Pharmasset	30.0	NetGenics Inc.	21.3
Xanthon Inc.	8.0	Prometheus	26.5	Orchid Biosciences Inc.	72.0
Xenogen Corp.	11.0	Reprogenesis Inc.	10.5	Periodontix	2.5
	\$111.6		\$133.1	Pharmasset	1.5
June 1999		October 1999		Xanthon Inc.	4.0
Advanced Medicine	\$159.3	Dendreon Corp.	\$10.0		\$216.5
Calydon inc.	10.1	Genomic Solutions Inc.	3.5	February 2000	
Copernicus Therapeutics	0.5	Point Biomedical	4.7	Amplistar	2.6
Galileo Laboratories	11.0	Rosetta Inpharmatics	12.0	Ancile Pharmaceuticals	2.0
Insect Biotechnology	1.8	Sangamo Biosciences Inc.	7.5	Cellomics Inc.	6.5
Medinox inc.	7.4	Senomyx	12.3	Deltagen Inc.	22.5
Molecular Applications Group	2.0	SkeleTech	5.0	Digital Gene Technologies Inc.	22.0
Pharmasset	3.9	UroGenesys Inc.	11.3	Discovery Therapeutics	5.0
PHASE-1 Molecular Toxicology	5.0		\$66.3	Esperion Therapeutics Inc.	5.0
ProdiGene	3.3	November 1999		GeneFormatics	4.0
Protein Delivery	23.0	ICAgen Inc.	\$19.1	Genometrix Inc.	14.1
Protein Design Labs Inc.	23.0	Inspire Pharmaceuticals	12.4	GenoPlex, Inc.	0.1
Sensus Drug Development	25.0	IntraBiotics Pharmaceuticals	25.0	Gryphon Sciences	0.5
Therion Biologics Corp.	10.5	PHASE-1 Molecular Toxicology	1.5	Phytera Inc.	2.0
VitaGen Inc.	10.5	Phase Forward Inc.	27.0	VitaGen Inc.	1.0
	\$296.3	Phytera Inc.	7.1		\$87.4
July 1999		Signature BioSciences	3.0	March 2000	
Adolor Corp.	\$2.5	Versicor Inc.	40.0	3-Dimensional	
AgraQuest	7.0		\$135.1	Pharmaceuticals Inc.	\$17.1
Elitra Pharmaceuticals	16.0	December 1999		AlphaVax Inc.	8.2
Maxygen Inc.	20.0	ACLARA BioSciences	\$5.0	Arena Pharmaceuticals	12.8
Pherin Pharmaceuticals	5.2	Acorda Therapeutics Inc.	5.1	BioStratum Inc.	28.0
Third Wave Technologies Inc.	19.5	Argonex Inc.	9.6	Cepheid Inc.	19.1
Triad Biotechnology Inc.	12.0	Cytovia Inc.	3.0	Ciblex Corp.	1.1
	\$82.2	Inspire Pharmaceuticals	10.0	Ciphergen Biosystems Inc.	28.6
August 1999		Islet Technology Inc.	1.6	Genaissance Pharmaceuticals	60.0
AGY Therapeutics	\$10.0	Mosaic Technologies	4.0	Genomica Corp.	15.0
Arcturus Engineering	5.3	PHASE-1 Molecular Toxicology	5.0	Genteric Inc.	9.0
AtheroGenics Inc.	24.0	Prolinx	4.5	Kosan Biosciences Inc.	24.9
FibroGen Europe Ltd.	15.3	ProtoGene Laboratories	17.0	LifeSpan Biosciences Inc.	13.5
Genesoft	11.4	Structural GenomiX Inc.	7.5	Message Pharmaceuticals Inc.	0.5
Idun Pharmaceuticals	7.4	Sunesis Pharmaceuticals Inc.	25.2	Metabolex Inc.	10.8
Osiris Therapeutics Inc.	5.0	Tanox Inc.	23.7	Oculex Pharmaceuticals	16.0
Variagenics Inc.	19.0	Versicor Inc.	0.5	Rosetta Inpharmatics	41.6
	\$97.4		\$121.7	Seattle Genetics Inc.	30.0
September 1999		January 2000		Spotfire	15.0
AtheroGenics Inc.	\$8.0	Adolor Corp.	\$12.3	Telik Inc.	7.0
Cytokinetics Inc.	20.0	Arena Pharmaceuticals	8.0	Variagenics Inc.	20.0
Desmos	0.5	Esperion Therapeutics Inc.	22.0	Zyomyx Inc.	22.0
Eos Biotechnology inc.	27.0	Genomic Solutions Inc.	8.0		\$400.1
Epigenomics	7.7	Illumina Inc.	28.0	April 2000	
GenoPlex, Inc.	0.6	Insmad Pharmaceuticals Inc.	34.5	AlphaGene Inc.	\$6.5
Gryphon Sciences	1.5	MERIX Bioscience Inc.	1.9	Arena Pharmaceuticals	9.7
Link Technology inc.	0.8	Molecular Geriatrics	0.5	Biolex, Inc.	1.5

Appendix 1 (cont.)

BioStratum Inc.	6.0	May 2000		June 2000	
Cogent Neuroscience Inc.	15.0	Acadia Pharmaceuticals Inc.	\$15.5	Acadia Pharmaceuticals Inc.	\$6.5
Delsys Pharmaceutical Corp.	26.0	Athersys inc.	47.5	Inhibitex	15.0
Exact Laboratories Inc.	32.0	BioNumerik Pharmaceuticals Inc.	12.0	Maxia Pharmaceuticals Inc.	10.3
Nereus Pharmaceuticals Inc.	8.6	Entelos Inc.	14.6		\$31.8
NewBiotics Inc.	6.3	Pharmadigm Inc.	12.0	Total	\$3,180.0
Structural Bioinformatics Inc.	32.6	The Medicines Company	25.7		
Structural GenomiX Inc.	32.0	Xenogen Corp.	30.5		
Xanthon Inc.	12.0		\$157.8		
	\$188.2				

Sources: BioCentury, BioWorld Financial Watch, VentureSource
 Numbers may appear inconsistent because of rounding.

Appendix 2: Follow-on Offerings Raise Almost \$11 Billion (July 1998 – June 2000)

Company	Amount Raised (\$ in Millions)	Offer Date	Company	Amount Raised (\$ in Millions)	Offer Date
Coulter Pharmaceutical, Inc.	\$66.1	July 1998	Abgenix Inc.	521.6	February 2000
Anesta Corp.	59.5	December 1998	Celgene Corp.	250.9	February 2000
Aronex Pharmaceuticals, Inc.	13.1	February 1999	Genzyme Transgenics Corp.	80.5	February 2000
Abgenix Inc.	45.0	March 1999	Maxim Pharmaceuticals Inc.	176.3	February 2000
Cerus Corp.	46.2	March 1999	Aradigm Corp.	46.0	March 2000
Trimeris Inc.	29.4	May 1999	Biopure Corp.	87.5	March 2000
Alliance Pharmaceutical Corp.	23.3	June 1999	Celera Genomics	983.3	March 2000
NeoTherapeutics Inc.	10.8	July 1999	Centaur Pharmaceuticals	21.9	March 2000
Ribozyme Pharmaceuticals	6.3	July 1999	Diacrin Inc.	39.7	March 2000
Pharmacyclics	89.1	August 1999	Emisphere Technologies, Inc.	200.1	March 2000
CV Therapeutics, Inc.	69.0	October 1999	Enzon Inc.	102.4	March 2000
Emisphere Technologies, Inc.	22.0	October 1999	Genentech Inc.	2,819.9	March 2000
Genentech Inc.	2,870.00	October 1999	Maxygen Inc.	145.5	March 2000
Invitrogen Corporation	60.0	October 1999	Medarex Inc.	412.7	March 2000
Magainin Pharmaceuticals	11.0	October 1999	Nanogen Inc.	82.5	March 2000
Vion Pharmaceuticals	11.0	October 1999	Neose Technologies	73.6	March 2000
ViroPharma Inc.	57.0	October 1999	Regeneron Pharmaceuticals	77.4	March 2000
Advanced Tissue Sciences Inc.	15.0	November 1999	SuperGen Inc.	65.9	March 2000
Alexion Pharmaceuticals	47.8	November 1999	Tularik Inc.	65.90	March 2000
BioCryst Pharmaceuticals, Inc.	50.5	November 1999	Avigen Inc.	26.0	April 2000
Ilex Oncology Inc.	58.8	November 1999	Aviron	49.5	April 2000
ImClone Systems Inc.	101.2	November 1999	Corixa Corp.	60.8	April 2000
Progenics Pharmaceuticals Inc.	43.7	November 1999	Cubist Pharmaceuticals Inc.	94.9	April 2000
Gene Logic Inc.	262.0	January 2000	Ribozyme Pharmaceuticals	56.7	April 2000
Vical Inc.	125.9	January 2000	Texas Biotechnology Corp.	62.5	April 2000
			Total	\$10,797.6	

Sources: BioCentury, BioWorld Financial Watch
Numbers may appear inconsistent because of rounding.

Appendix 3: Three Billion Raised in IPOs (July 1998 – June 2000*)

Company	Amount Raised (\$ in Millions)	Offer Date
Abgenix Inc.	\$23.0	July 1998
Collateral Therapeutics Inc.	16.0	July 1998
Albany Molecular Research Inc.	56.3	February 1999
Invitrogen Corporation	45.0	February 1999
Immtech International Inc.	11.5	April 1999
United Therapeutics Corp.	54.0	June 1999
VaxGen Inc.	40.3	June 1999
BioMarin Pharmaceutical Inc.	67.3	July 1999
Biopure Corp.	42.0	July 1999
Synyx Technologies Inc.	89.2	November 1999
Caliper Technologies Corp.	72.0	December 1999
Maxygen Inc.	110.4	December 1999
Tularik Inc.	97.3	December 1999
Antigenics Inc.	72.5	February 2000
Diversa Corp	200.1	February 2000
Sequenom	157.0	February 2000
ACLARA BioSciences	217.4	March 2000
Allos Therapeutics Inc.	90.0	March 2000
IntraBiotics Pharmaceuticals	112.5	March 2000
Exelixis Inc.	136.0	April 2000
Lexicon Genetics Inc.	220.0	April 2000
Packard Bioscience Co.	108.0	April 2000
Praecis Pharmaceuticals Inc.	92.0	April 2000
Sangamo Biosciences Inc.	52.5	April 2000
Tanox Inc.	213.8	April 2000
Genomic Solutions Inc.	56.0	May 2000
Orchid Biosciences Inc.	55.2	May 2000
Paradigm Genetics Inc.	47.3	May 2000
ViroLogic Inc.	35.0	May 2000
Cepheid Inc.	30.0	June 2000
Charles River	224.0	June 2000
Dendreon Corp.	45.0	June 2000
Total	\$2,888.4	

Sources: BioCentury, BioWorld Financial Watch

*Excludes Genentech's reoffering of \$2.1 billion

Numbers may appear inconsistent because of rounding.

Appendix 4: Selected Mergers and Acquisitions (July 1998 – April 2000)

Company	Acquired by or Merged with
July 1998	
International Murex Technologies Corp. (Canada)	Abbott Laboratories
August 1998	
Virus Research Institute Inc. Neurex Corp.	T Cell Sciences Inc. Elan Corp. (Ireland)
September 1998	
Molecular Dynamics Inc.	Amersham Pharmacia Biotech Inc. (Sweden)
October 1998	
NanoSystems LLC (sub. of Eastman Kodak) Penederm Inc. Coral Therapeutics Inc.* Q.E.D. International Inc. Simirex Inc.*	Elan Corp. (Ireland) Mylan Laboratories Inc. HemaCare Corp. Quintiles Transnational Corp. Quintiles Transnational Corp.
November 1998	
Tseng Labs Inc. Chiron Diagnostics Corp. (sub. of Chiron Corp.) Gull Laboratories Inc. Vascular Genetics Inc.*	Cell Pathways Inc.* Diagnostics business of Bayer AG (Germany) Meridian Diagnostics Inc. Humane Genome
December 1998	
Life Technologies Inc.	Dexter Corp.
January 1999	
TheraTech Inc.	Watson Pharmaceuticals Inc.
February 1999	
Advanced Inhalation Research Inc.* Acacia Biosciences Inc.* Oak Grove Technologies Inc.* Valorum-UK (formerly Pharmakopius International, U.K.)	Alkermes Inc. Rosetta Inpharmatics Inc.* Quintiles Transnational Corp. PRA International Inc.*
March 1998	
DepoTech Corp. Sequus Pharmaceuticals Inc. Pacific Pharmaceuticals Inc.	SkyePharma plc Alza Corp. Procept Inc.
April 1999	
ATP Inc.*	PPD Inc.
May 1999	
Agouron Pharmaceuticals	Warner-Lambert Co.
July 1999	
NeXstar Pharmaceuticals Inc. Apex Bioscience Inc.* Aprogenex Inc.* BioChem ImmunoSystems Inc. (diagnostics sub. of BioChem Pharma Inc.) Cytel Corp. Peptimmune Inc.* Vysis Inc.	Gilead Sciences Inc. U.S. subsidiary of VitaResc Biotech AG* (Germany) Vysis Inc. ABX Diagnostics Inc.* (sub. of ABX Diagnostics, France) Epimmune Inc. Genzyme General Applied Imaging Corp.

Appendix 4 (cont.)

August 1999

PolyMasc Pharmaceuticals plc
Scandipharm Inc.*
Sparta Pharmaceutical Inc.
ImuMed Deutschland GmbH
(German unit of Transplant Technologies Inc.)
Innovir Laboratories
(sub. of Nexell Therapeutic Inc.)
Magnetic Imaging Technologies Inc.*
Target Quest*
Target Quest*
Vascular Therapeutics Inc.*

September 1999

Thetagen Inc.*
Androgenics Technologies Inc.

October 1999

Centocor Inc.
EnzyMed Inc.
IntraEar Inc.*
Ribi Immunochem Research Inc.
SynQuest Inc.

November 1999

CombiChem Inc.
RiboGene Inc.
Diatide Inc.

Fuisz Technologies Ltd.
North American Vaccine Inc.
Pentose Pharmaceuticals Inc.*
Sibia Neurosciences Inc.
U.S. Bioscience Inc.

December 1999

Allelix Biopharmaceuticals Inc. (Canada)
JT America Inc.'s 50% interest in
Xenotech Inc. and Xenotech L.P.
Axogen Ltd.
LeukoSite Inc.
Shire Pharmaceuticals Group (U.K.)

January 2000

Heaven's Door Corp.*
Medeva plc. (U.K.)
BioNexus Genomics Inc.*
Discovery Technologies Ltd* (Switzerland)
Shanghai Genecore
Biotechnologies Co. Ltd.* (China)

Valentis Inc.
Axcan Pharm Inc. (Canada)
SuperGen Inc.
Viper Resources Inc.
Ribozyme Pharmaceutical Inc.
Nycomed Amersham Inc. (unit of Nycomed Amersham plc, U.K.)
Dyax Corp.
Dyax Corp.*
GlycoDesign Inc.* (Canada)

New Chemical Entities Inc.*
Genta Inc.

Johnson and Johnson
Albany Molecular Research Inc.
Durect Corp.*
Corixa Corp.
United Therapeutics Corp.

DuPont Pharmaceuticals
Cypros Pharmaceutical Corp.
Schering-Berlin Inc. (U.S. management holding company
for Schering AG, Germany)
Bioval Corp. International (Canada)
Baxter International Inc.
VI. Technologies Inc.
Merck & Co. Inc.
MedImmune Inc.

NPS Pharmaceuticals Inc.
Abgenix Inc.

Elan Corp. plc
Millennium Pharmaceuticals Inc.
Roberts Pharmaceutical Corp.

Procept Inc.
Celltech Chiroscience
Ashni Nutraceuticals Inc.*
Discovery Partners International
Celera Genomics

February 2000

Genetic MicroSystems Inc.*	Affymetrix Inc.
Research Genetics Inc.*	Invitrogen Corp.
Medco Research Inc.	King Pharmaceuticals Inc.
Chiron Technologies Pty Ltd. (aka Mimotopes, Australian subsid of Chiron Corp.)	MitoKor*
Kimeragen Inc.*	ValiGen SA*
BioChem ImmunoSystems Inc. (diagnostics divison of BioChem Pharma Inc., Canada)	Minority shareholder (Not Disclosed) and management group

March 2000

U.S. operations of British Biotech plc (U.K.)	Ilex Oncology Inc.
Small Molecule Therapeutics Inc.*	Morphochem AG* (Germany)
Strata Biosciences*	GeneTrace Systems Inc.
Synergy Pharmaceuticals Inc.*	United Therapeutics Corp.
Verex Laboratories Inc.	PR Pharmaceuticals Inc.*

April 2000

Novopharm Ltd.* (Canada)	Teva Pharmaceutical Industries Ltd. (Israel)
BIO101*	Quantum Biotechnologies
t. Breeders Inc.*	Viacord Inc.*

Source: BioWorld Financial Watch, 1998, 1999, 2000

*Indicates private company

Appendix 5: Number of Pivotal Trials (by Disease Category, June 2000)

Disease Category	Phase II/III / Phase III
AIDS	9
Allergies and asthma	1
Cancer	74
Cardiovascular	15
Cell therapy	1
Cystic fibrosis	1
Dermatology	5
Diabetes	5
Endocrinology and metabolism	8
Gastrointestinal	5
Gene therapy	2
Hematology (including blood substitutes)	17
Hepatitis	8
Immunology/inflammation	6
Infectious diseases (including vaccines)	28
Multiple sclerosis	2
Nephrology and urology	4
Neurology	19
Ophthalmology	5
Osteoporosis	3
Pulmonary diseases	2
Rheumatoid arthritis	3
Sepsis	3
Transplantation	2
Wound healing	6
Miscellaneous	49
Total	283

Source: Goldmans Sachs, *Biotechnology Products*, June 2000

Appendix 6: Regulatory Milestones: Selected FDA Approvals (July 1998 – June 2000)

Company	Product	Indication
Alkermes/Genentech	Nutropin Depot somatropin long-acting recombinant human growth hormone	Treats growth hormone disorders
Alza	Ditropan XL once daily controlled release oxybutynin	Treats urinary incontinence
Alza	Viadur leuprolide acetate titanium implant	Provides palliative treatment of advanced prostate cancer
Andrx	Generic version of AstraZeneca's Prilosec omeprazole	Treats duodenal/gastric ulcers and gastro-esophageal reflux disease
Andrx	Generic version of Elan's Naprelan naproxen extended release NSAID	Treats arthritis
Andrx	Oruvail ketoprofen	Distinguishes between influenza A and B
Bio-Rad	Homocysteine by HPLC assay	Measures homocysteine levels to assess risk of atherosclerotic vascular disease
Bioject	Needleless formulation of Serono's Saizen growth hormone	Treats pediatric growth disorders
Biomatrix	HylaSine viscoelastic gel device	Reduces bleeding during and after sinus surgery and reduces post-surgical scarring and adhesions
Biopool International	Bioclot aPC Sensitivity Kit	Delivers and targets drugs to the lymphatic system and liver
Biopool International	Anti-D blood grouping reagent	Diagnoses canine heartworms
Biopure	Oxyglobin cross-linked hemoglobin	Treats social anxiety disorder
Boston Biomedica	Accurun 106 HIV Antigen Positive Control	Controls for blood supply screening tests
Boston Biomedica	Borrelia burgdorferi IgM Western Blot	Is a homocysteine measuring system
Carrington	Acemannan Hydrogel wound dressing	Provides wound healing and protection
Carrington	Ultrex preservative-free hydrogel	Manages pressure and stasis ulcers, post-surgical incisions, burns, and skin conditions associated with peristomal care
Cephalon	Provigil modafinil alpha adrenergic stimulant	Treats excessive daytime sleepiness associated with narcolepsy
Chiron	RIBA HCV 3.0 Strip Immunoblot Assay	Treats cutaneous lesions in patients with AIDS-related Kaposi's sarcoma
Chiron	HIV-1/HCV transcription-mediated amplification assay	Used with procedures requiring a stent
Cohesion	CoStasis and DynaStat surgical hemostats	Stops or controls active bleeding during general, hepatic, and cardiovascular surgeries
Connetics	Olux clobetasol propionate foam	Treats dermatoses of the scalp
Cypress Bioscience	Prosorba column	Detects crosslinked N-telopeptides of type I collagen (NTx) in serum as a marker for bone resorption
Digene	Hybrid Capture II Chlamydia/Gonorrhea Test	Detects chlamydia and gonorrhea DNA in cervical specimens
Digene	High-Risk Hybrid Capture II HPV test	Detects HPV that causes cervical cancer
Dura Pharmaceuticals	Maxipime cefepime	Is an injectable calcitonin to treat Paget's disease and hypercalcemia associated with malignancy

Appendix 6 (cont.)

Company	Product	Indication
Elan	Nifedipine calcium channel blocker	Used in brachytherapy to treat prostate cancer
Focal GelTex	FocalSeal-L synthetic absorbable surgical sealant Welchol colesevelam non-absorbed lipid-lowering agent	Seals air leaks during surgery Lowers LDL cholesterol in patients with primary hypercholesterolemia
Genentech	TNKase tenecteplase (TNK-tPA)	Treats acute myocardial infarction
Genzyme Surgical Products	Sepramesh Biosurgical Composite	Used in hernia repair procedures
Hemagen	Virgo beta2 glycoprotein antibody kits	Treats ethylene glycol poisoning
Hemagen	Total protein, Albumin, Calcium, and GGT clinical chemistry reagents	Used in HMGN's Cobas Mira analyzer
Hemagen Diagnostics	Clinical chemistry reagents	Used in Cobas Mira, an analyzer developed by Roche
Heska	Perioceutic doxycycline gel	Selects hematopoietic stem cells and removes tumor cells from autologous peripheral blood as part of cancer therapy
Hycor	Anti-Cardiolipin Screen ELISA test	Detects antibodies associated with antiphospholipid syndrome
Hycor	Anti-Cardiolipin IgC, Anti-Gastric Parietal Cell and Anti-Glomerular Basement Membrane ELISA tests	Identifies herpes simplex virus
Hycor Biomedical Immunex	ANA-ELISA Enbrel etanercept soluble tumor necrosis factor receptor	Treats influenza A and B Provides first-line treatment to reduce the signs and symptoms of moderately to severely active rheumatoid arthritis, and to delay joint damage
Integra LifeSciences	DuraGen absorbable implants	Detects hepatitis-C
Layton BioScience	Inversine mecamlamine nicotinic receptor antagonist	Treats Tourette's syndrome and other neurological disorders
Ligand	Targretin bexarotene capsules	Treats cutaneous manifestations of CTCL in patients with refractory CTCL
Ligand	Targretin bexarotene 1percent gel	Treats cutaneous lesions in patients with early-stage CTCL
Ligand Pharmaceuticals	Panretin gel alitretinoin	Are hemostatic agents to help control bleeding in cardiovascular, neurosurgical, and general surgical procedures
LXN	In Charge Diabetes Control System	Manages secondary hyperparathyroidism in patients undergoing chronic renal dialysis
Matritech	NMP22 Test Kit	Diagnoses bladder cancer
Meridian	Premier C. difficile Toxins A and B test	Detects C. difficile toxins
Nabi	Nabi-HB hepatitis B immune globulin	Relieves inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses of the scalp

Company	Product	Indication
Nexell Therapeutics	Isolex systems	Injects insulin
Noven	Transdermal 17(beta)-estradiol delivery system	Determines sensitivity to activated protein C
Organogenesis	Apligraf engineered skin replacement tissue	Treats diabetic foot ulcers
Ostex International	Osteomark NTx Serum test	Uses fusion protein to treat persistent or recurrent CTCC lymphomas that express the CD25 component of the interleukin-2 receptor
PharmaNetics	Heparin Management Panel and Accent system	Manages anticoagulation during cardiopulmonary bypass procedures
PharmaNetics	Low Range Heparin Management Test	Heparin assay for cardiology procedures
Quidel	QuickVue Influenza Test	Identifies gene responsible for methicillin antibiotic resistance in <i>S. aureus</i>
SangStat	Celsior	Treats hypertension
Unigene Laboratories	Forcaltonin	Treats symptoms of menopause
Unimed	AndroGel 1 percent testosterone gel	Treats conditions associated with hypogonadism
UroCor and Mills	I-125 radiation seeds	Used as a prophylaxis for people exposed to hepatitis-B
BioPharmaceuticals	Agenerase amprenavir	Is a test kit that determines exposure to Lyme disease
Vertex		Detects hepatitis-C virus
ZymeTx	ViraSTAT lab tests	

Source: BioCentury, 2000

**Appendix 7: Selected 1999 Public Company Financial Highlights
(by Geographic Area, \$ in Millions, Percent Change over 1998)**

	Number of Public Companies	Market Capitalization (6/30/00)	Number of Employees	Product Sales	Total Revenue
San Francisco Bay	60	\$103,472.8	20,635	\$3,277.6	\$4,529.1
	3%	240%	15%	23%	23%
New England	53	\$58,990.8	18,395	\$2,289.9	\$3,164.2
	-7%	137%	5%	15%	15%
San Diego	30	\$17,768.2	5,236	\$645.5	\$892.0
	-6%	203%	-12%	-25%	-25%
New Jersey	22	\$14,048.1	3,255	\$434.7	\$600.6
	-4%	258%	-6%	15%	15%
<hr/>					
New York State	21	\$8,392.4	1,908	\$177.0	\$244.6
	0%	353%	11%	16%	16%
Pacific NW	18	\$30,582.4	2,839	\$595.3	\$822.6
	0%	131%	12%	50%	50%
Mid-Atlantic	16	\$26,447.9	4,621	\$705.5	\$974.9
	-11%	261%	-3%	19%	19%
South East	15	\$3,298.7	4,663	\$418.2	\$577.9
	-6%	105%	-7%	9%	9%
<hr/>					
Mid-West	12	\$1,101.1	913	\$109.6	\$151.4
	-8%	33%	-15%	9%	9%
Texas	11	\$2,067.4	978	\$59.4	\$82.0
	0%	201%	3%	7%	7%
Los Angeles/Orange County	10	\$76,172.8	22,632	\$3,209.8	\$4,435.4
	-9%	122%	8%	15%	15%
Philadelphia/Delaware Valley	8	\$3,316.5	974	\$61.0	\$84.3
	-27%	-25%	-55%	-80%	-80%
<hr/>					
North Carolina	7	\$3,763.8	25,667	\$1,491.3	\$2,060.8
	-13%	-44%	29%	31%	31%
Colorado	4	\$593.8	232	\$16.6	\$22.9
	-20%	-13%	-69%	-86%	-86%
Utah	4	\$2,420.3	297	\$32.5	\$44.9
	0%	445%	-34%	21%	21%
Other	10	\$1,074.3	851	\$94.0	\$129.9
	-9%	88%	-9%	10%	10%
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Total	301	\$353,511.3	114,095	\$13,617.9	\$18,817.4
	-5%	156%	8%	13%	13%

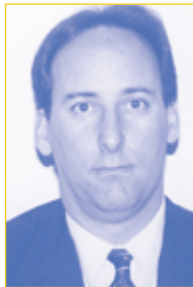
Sources: Company financial statement data, Ernst & Young. Some numbers may appear inconsistent because of rounding.

R&D	Net Income (Loss)	Cash & Short Term Investments	Total Assets
\$2,187.1	\$(2,035.5)	\$4,897.1	\$16,182.2
8%	889%	17%	52%
\$1,480.9	\$(791.6)	\$3,341.2	\$7,279.0
14%	66%	3%	15%
\$526.3	\$(421.4)	\$1,332.9	\$2,508.8
-22%	-21%	13%	-3%
\$214.2	\$(54.7)	\$453.5	\$935.1
-14%	-72%	25%	12%
<hr/>			
\$253.9	\$(192.6)	\$461.2	\$833.4
27%	18%	15%	25%
\$421.8	\$(159.7)	\$975.6	\$1,453.5
17%	66%	102%	67%
\$270.5	\$(47.9)	\$994.6	\$2,014.6
-4%	-73%	43%	25%
\$127.0	\$(142.4)	\$126.7	\$799.4
10%	-5%	-32%	5%
<hr/>			
\$56.6	\$(37.2)	\$142.8	\$271.7
-20%	-70%	-28%	-17%
\$99.8	\$(123.8)	\$168.9	\$253.6
4%	21%	5%	14%
\$917.6	\$1,161.1	\$1,603.0	\$6,056.2
18%	189%	10%	10%
\$123.6	\$(193.1)	\$366.2	\$453.0
-66%	-3741%	-16%	-68%
<hr/>			
\$133.7	\$(2.3)	\$504.2	\$2,314.2
23%	-79%	38%	42%
\$31.2	\$(32.4)	\$54.0	\$100.2
-29%	883%	-61%	-68%
\$50.2	\$(57.0)	\$116.7	\$200.9
1%	29%	-25%	-3%
\$30.5	\$(26.3)	\$64.5	\$222.6
-22%	-32%	-34%	-14%
<hr/>			
\$6,924.9	\$(3,156.8)	\$15,603.1	\$41,878.4
3%	65%	13%	22%

The development of *Convergence: Ernst & Young's Biotechnology Industry Report, Millennium Edition* was a convergence in itself, the work of many dedicated professionals within and outside of Ernst & Young.



Glen T. Giovannetti



Scott W. Morrison

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