

# Collège de France

April 24, 2007

François Maisonrouge

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# AstraZeneca Purchases MedImmune for \$15 bn (USD)

	<u>AstraZeneca</u>	<u>MedImmune</u>
Sales	\$26,475.0	\$1,276.8
R&D Spend	3,902.0	448.9
Net Income	\$6,063.0	\$48.7
Market Value	\$87,287.9	\$14,852.6
Enterprise Value / Sales	3.1x	11.9x
Market Value / Earnings	14.4x	305.0x

Source: Company filings dated 12/31/06 and Factset.  
Market data as of 4/23/2007.

# Evolution of Biotechnology

## Modern Biotechnology Era: Early Phase (1970s-mid 1980s)

- 1970 ▶ Restriction enzymes discovered (Arber, Switzerland, Smith, U.S., & Nathans, U.S.)
  - 1972 ▶ Birth of recombinant DNA—first recombinant molecule (Berg, U.S.)
  - 1974 ▶ Cohen & Berg (U.S.) perfect genetic engineering techniques to cut and paste DNA and reproduce the new DNA in bacteria
- 
- 1971 ▶ Cetus founded (Emeryville)
- 
- 1972 ▶ “Berg letter” in Science recommends moratorium on certain rDNA experiments until safety questions are addressed
  - 1974 ▶ NIH forms Recombinant DNA Advisory Committee for oversight of research

| Science

| Business

| Public Policy

# Evolution of Biotechnology

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# Evolution of Biotechnology

## Modern Biotechnology Era: Early Phase (1970s-mid 1980s) Cont'd

| Science

| Business

| Public Policy

- 1975**
  - ▶ Gene sequencing techniques discovered (Gilbert & Maxam, U.S., Sanger, UK)
  - ▶ Monoclonal antibody technology developed (Milstein, Argentina/UK, Köhler, Germany & Jerne, Denmark)
  - ▶ Transfer of DNA strands from separation gel to filter membrane for probing with complementary labeled DNA or RNA strands (Southern, UK)
  - ▶ Two-dimensional gel electrophoresis developed (O'Farrell, U.S.)
- 1978**
  - ▶ Human insulin cloned into E. coli (Genentech)
- 1976**
  - ▶ Genentech founded by Swanson & Boyer (South San Francisco)—modern biotechnology industry is born
- 1977**
  - ▶ Genex founded (Maryland)
- 1978**
  - ▶ First European biotech company founded—Biogen (Switzerland/Netherlands, later moves to Boston)
  - ▶ First Indian biotech company founded—Biocon
  - ▶ Hybritech founded (San Diego)
- 1979**
  - ▶ Centocor founded (Philadelphia)
  - ▶ First French biotech company founded—Transgene
- 1975**
  - ▶ Asilomar Conference agrees to moratorium on genetic engineering research, pending risk evaluation

# Evolution of Biotechnology

## Modern Biotechnology Era: Early Phase (1970s-mid 1980s) Cont'd

| Science  
| Business  
| Public Policy

- 1981** ▶ First transgenic animals produced (mice)
- 1982** ▶ First commercial gas phase protein sequencer (Applied Biosystems)
- 1983** ▶ AIDS virus isolated (Pasteur Institute, NIH, and UCSF)
  - ▶ First genetic transformation of plant cells by Ti plasmids performed (Zambryski et al, U.S.)
  - ▶ Polymerase chain reaction (PCR) technique invented for multiplying DNA sequences in vitro (Mullins, U.S.)
- 1980** ▶ First biotech IPO (Genentech)
  - ▶ First UK biotech company founded—Celltech
  - ▶ Amgen (Thousand Oaks), Calgene (Davis), and Genetic Systems founded
- 1981** ▶ First monoclonal antibody diagnostic kit approved (Syntex)
  - ▶ Cetus, Genetic Systems, and Hybritech IPOs
  - ▶ Applied Biosystems (Foster City), Chiron (Emeryville), Genetics Institute (Boston), and XOMA (Berkeley) founded
  - ▶ First Canadian biotech company founded—Allelix
- 1982** ▶ First rDNA product approved by FDA (Humulin, recombinant human insulin)
  - ▶ First recombinant vaccine for livestock developed
  - ▶ Centocor and Genex IPOs
  - ▶ Genentech and Corning establish Genencor, a joint venture in the industrial biotech space
- 1983** ▶ Amgen IPO
- 1980** ▶ Landmark U.S. Supreme Court decision approves patenting of genetically engineered life forms (Diamond v. Chakrabarty)
  - ▶ U.S. patent for gene cloning awarded to Cohen & Boyer
  - ▶ U.S. Bayh-Dole Act passed, heralding increased commercialization by universities
- 1983** ▶ U.S. Orphan Drug Act enacted
- 1984** ▶ U.S. Hatch-Waxman Act enacted, simplifying approval of generic drugs
  - ▶ Commission on Genetic Engineering

# Evolution of Biotechnology

## Modern Biotechnology Era: Critical Mass (mid-late 1980s)

| Science

| Business

| Public Policy

- 1986 ▶ First field tests of transgenic plants conducted (tobacco)
- 1985 ▶ Second biotech product approved, first product launched by a biotech company (Genentech's Protropin)
- 1986 ▶ First recombinant human vaccine approved by FDA (Recombivax HB)
  - ▶ First monoclonal antibody treatment approved by FDA (Orthoclone OKT3)
  - ▶ First recombinant interferon therapeutic for cancer approved by FDA (Intron A & Roferon A)
  - ▶ First Ernst & Young biotechnology report published
- 1987 ▶ "Black Monday" stock market crash drastically reduces biotech public equity funding
  - ▶ Genentech's Activase approved by FDA, achieves rapid market penetration
- 1988 ▶ First patent for a genetically altered animal—OncoMouse (Leder & Stewart, U.S.)
  - ▶ First UK Ernst & Young biotech report published
- 1989 ▶ Epogen approved (later becomes first biotech blockbuster)
  - ▶ Elan IPO (Ireland)
- 1985 ▶ NIH approves guidelines for gene therapy experiments in humans
- 1986 ▶ U.S. government publishes Coordinated Framework for Regulation of Biotechnology, with regulations for rDNA organisms
  - ▶ India establishes Department of Biotechnology under the Ministry of Science and Technology

# Evolution of Biotechnology

## Modern Biotechnology Era: Commercialisation and Windows (1990-1997)

| Science

| Business

| Public Policy

- 1990**
    - ▶ Human Genome Project (HGP) formally begins (goal: to map, sequence and render accessible human genes by 2005. Anticipated cost: \$3 billion)
    - ▶ First use of gene therapy to treat human patient (4-year-old ADA patient Ashanti DiSilva)
  - 1991-2** ▶ Pioneering research on DNA microarrays (DNA chips)(Fodor and Brown)
  - 1994** ▶ First breast cancer gene discovered (BRCA1)
  - 1995**
    - ▶ STS gene mapping technique discovered
    - ▶ First genome of a free-living organism sequenced (Hemophilus influenzae bacterium)
  - 1996**
    - ▶ First catalog DNA microarray released (Affymetrix)
    - ▶ First mammal cloned from adult cells (Dolly the sheep)
  - 1997** ▶ First artificial human chromosomes created (Athersys)
- 
- 1990**
    - ▶ Roche acquires majority stake in Genentech
    - ▶ First transgenic dairy cow (GenPharm International)
  - 1991**
    - ▶ Noteworthy product approvals drive soaring market caps and financing
    - ▶ Chiron acquires Cetus
    - ▶ Regeneron IPO
  - 1992**
    - ▶ Amgen becomes first biotech company to join the Fortune 500
    - ▶ Vernalis IPO (UK)
    - ▶ First Canadian Ernst & Young biotech report published
  - 1993** ▶ London Stock Exchange eases rules for listing biotech companies



# Evolution of Biotechnology

## Modern Biotechnology Era: Commercialisation and Windows (1990-1997) Cont'd

| Science  
| Business  
| Public Policy

- 1994**
  - ▶ Calgene's Flavr Savr tomato approved
  - ▶ First European Ernst & Young biotech report published
- 1995**
  - ▶ UK's Alternative Investment Market (AIM) opens, targeting emerging companies
- 1996**
  - ▶ IPO window
  - ▶ European biotech booms
  - ▶ Epogen & Neupogen achieve blockbuster status
  - ▶ First transgenic crops: GM soybeans and corn approved for sale, and GM cotton commercialized in U.S.
- 1997**
  - ▶ Internet bubble siphons VC dollars away from biotech
  - ▶ Tools/platforms become alternative business models
  - ▶ Germany's Neuer Markt opens, targeting emerging companies
  - ▶ European biotech booms
  - ▶ First antibody-based therapy for cancer approved (Rituxan)
  - ▶ Monsanto acquires remaining stake in Calgene
- 1990**
  - ▶ European Commission adopts directives on use and release of GMOs
- 1992**
  - ▶ Prescription Drug User Fee Act (PDUFA) enacted
- 1993**
  - ▶ FDA declares genetically engineered foods "not inherently dangerous" and not requiring special regulation
  - ▶ Biotechnology Industry Organization (BIO) created by merging two smaller trade associations
  - ▶ Japan passes orphan drug legislation
  - ▶ Health Care Structural Reform Act in Germany
  - ▶ First German Genetic Engineering Act
- 1995**
  - ▶ European Medicines Evaluation Agency (EMA) established
- 1997**
  - ▶ Food and Drug Modernization Act passed, including PDUFA renewal

# Evolution of Biotechnology

## Modern Biotechnology Era: Genomics Bubbles (1998-2002)

| Science  
| Business  
| Public Policy

- 1998**
    - ▶ Human Genome Project put on “fast track” for early completion
    - ▶ First isolation of human embryonic stem cell lines (Thomson, Gearhart)
  - 1999**
    - ▶ HGP sequences first human chromosome (Chromosome 22)
  - 2000**
    - ▶ “Working draft” of human genome sequence completed
    - ▶ Golden rice developed
  - 2002**
    - ▶ Genomes sequenced for malaria parasite and transmitting mosquito
- 
- 1998**
    - ▶ Celera Genomics formed, with accelerated timeframe to map human genome
    - ▶ First targeted antibody therapy approved for breast cancer (Herceptin)
    - ▶ First therapeutic agent developed with antisense medical technology (Fomivirsen)
    - ▶ First German Ernst & Young biotech report published
  - 1999**
    - ▶ Roche acquires remaining stake in Genentech
    - ▶ Genentech goes public again, selling 20% of shares
  - 2000**
    - ▶ Genomics bubble, inspired by sequencing of human genome
    - ▶ Valuations soar, industry financing at all-time high
  - 2001**
    - ▶ Genomics bubble bursts. Investors shift from genomics & platforms to products
    - ▶ Biotech-biotech alliances outnumber pharma-biotech alliances
    - ▶ ALZA acquired by Johnson & Johnson
    - ▶ Ernst & Young’s biotech report goes global
  - 2002**
    - ▶ Amgen acquires Immunex
    - ▶ European consolidation begins

# Evolution of Biotechnology

## Modern Biotechnology Era: Genomics Bubbles (1998-2002) Cont'd

| Science  
| Business  
| Public Policy

- 1998**
  - ▶ FDA announces human cloning experiments require prior approval
  - ▶ European Union (EU) passes directive on the legal protection of biotechnological inventions
  - ▶ China launches State Drug Administration (SDA, precursor to SFDA)
  - ▶ Orphan Drug Program enacted in Australia
  - ▶ Malaysia establishes National Biotechnology & Bioinformatics Network
- 1999**
  - ▶ National Institute for Clinical Excellence (NICE) inaugurated in UK, introducing “fourth hurdle” for drug approvals
  - ▶ EU bans new GMO foods
- 2000**
  - ▶ EU passes orphan drug legislation
  - ▶ Clinton-Blair statement calls for genome data to be freely available
  - ▶ Singapore launches Biomedical Sciences Initiative
- 2001**
  - ▶ Bush Administration limits federal funding of stem cell research to existing cell lines
  - ▶ China joins the World Trade Organization (WTO)
  - ▶ UK allows therapeutic cloning of embryos
- 2002**
  - ▶ Germany passes stem cells legislation

# Evolution of Biotechnology

## Modern Biotechnology Era: Coming of Age (2003 – present)

| Science

| Business

| Public Policy

- 2003**
  - ▶ HGP completed
- 2005**
  - ▶ First crop genome sequenced (rice, main food source for two-thirds of world's population)
  - ▶ Several Korean stem cell advances revealed as fraudulent
- 2003**
  - ▶ Sharp increase in product approvals
  - ▶ U.S. financing soars (second highest total to date), no IPOs in Europe
  - ▶ Biotech surpasses big pharma in NME approvals for first time
  - ▶ Biogen & IDEC merge to create Biogen Idec
  - ▶ Germany's Neuer Markt closes
  - ▶ Merger of British Biotech and Vernalis (UK)
  - ▶ Chiron (U.S.) acquires PowderJect (UK)
- 2004**
  - ▶ Product success sustained
  - ▶ Financing soars (second highest total to date)
  - ▶ Asian biotech booms
  - ▶ Biocon IPO (India)
  - ▶ First biogeneric product approved (Australia)
  - ▶ First gene therapy approved (China)
  - ▶ First anti-angiogenic drug for cancer approved (Avastin)
  - ▶ Celltech (UK) acquired by UCB (Belgium)
  - ▶ First Swiss Ernst & Young biotech report published

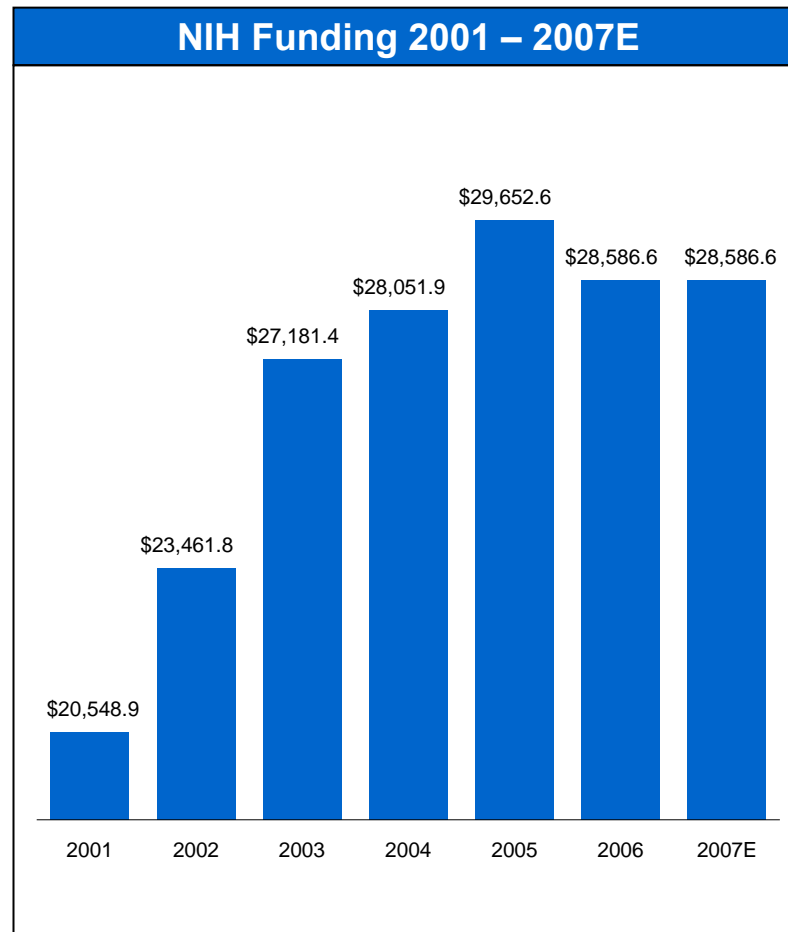
# Evolution of Biotechnology

## Modern Biotechnology Era: Coming of Age (2003 – present)

| Science  
| Business  
| Public Policy

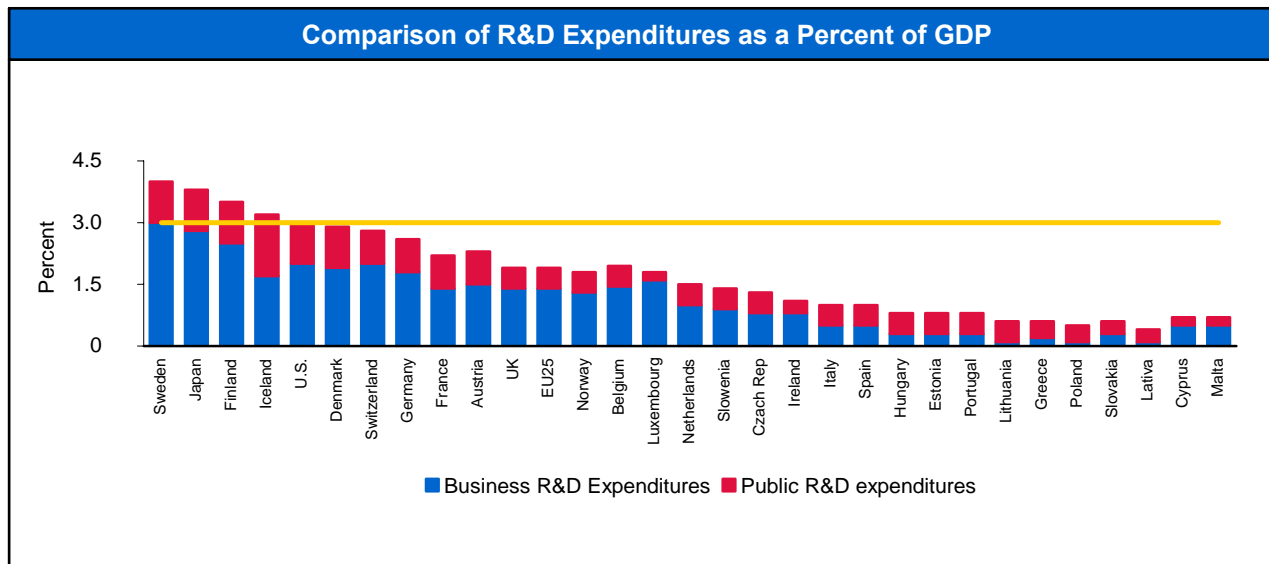
- 2005**
  - ▶ Third year of sustained product success
  - ▶ U.S. industry nears profitability, European recovery in full swing
  - ▶ Financing high, but IPO market cools in U.S. and recovers in Europe
  - ▶ Mergers and Acquisitions soar
  - ▶ Genentech & Amgen enter ranks of ten largest drug development companies by market cap
  - ▶ First drug targeted at a particular race approved (BiDil)
  - ▶ Second biogeneric product approved (Croatia)
  - ▶ Novartis announces bid to increase stake in Chiron to 100%
  
- 2003**
  - ▶ China's State Food and Drug Administration (SFDA) established
  - ▶ European Parliament passes legislation requiring labelling and tracking of GMO foods
- 2004**
  - ▶ California and other U.S. states enact legislation to encourage stem cell research
  - ▶ Safety issues gain visibility, after high-profile product withdrawals
  - ▶ Japan creates Pharmaceuticals and Medical Devices Agency (PMDA)
  - ▶ Germany establishes the Institute for Quality and Cost Effectiveness in the Healthcare System (IQWiG)
- 2005**
  - ▶ India enacts Patents Law
  - ▶ India develops National Biotechnology Development Strategy (Draft)
  - ▶ Malaysia launches National Biotechnology Policy
  - ▶ Bill and Melinda Gates Foundation awards "Grand Challenges in Global Health" grants
  - ▶ Companies prepare for 2006 U.S. Medicare prescription drug benefit
- 2006**
  - ▶ Collège de France - Chaire d'Innovation Technologique - Liliane Bettencourt

# Historical NIH Funding



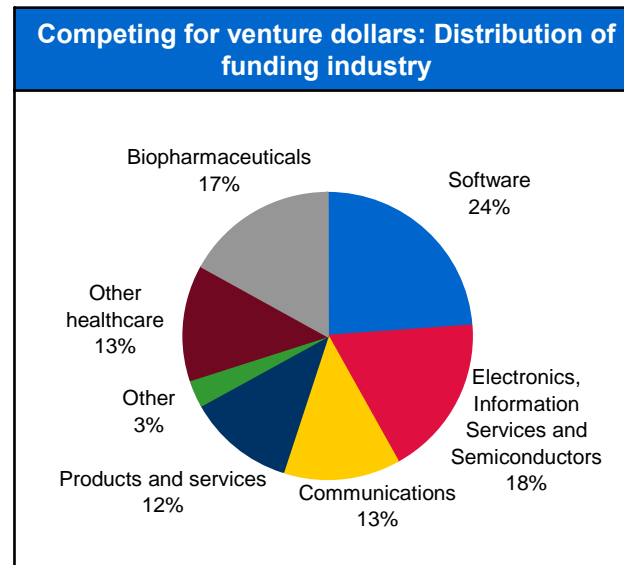
Source: NIH website.

# R&D Expenditures as a Percent of GDP



Source: European Commission, European Innovation Scoreboard 2005

# Funding by Sector





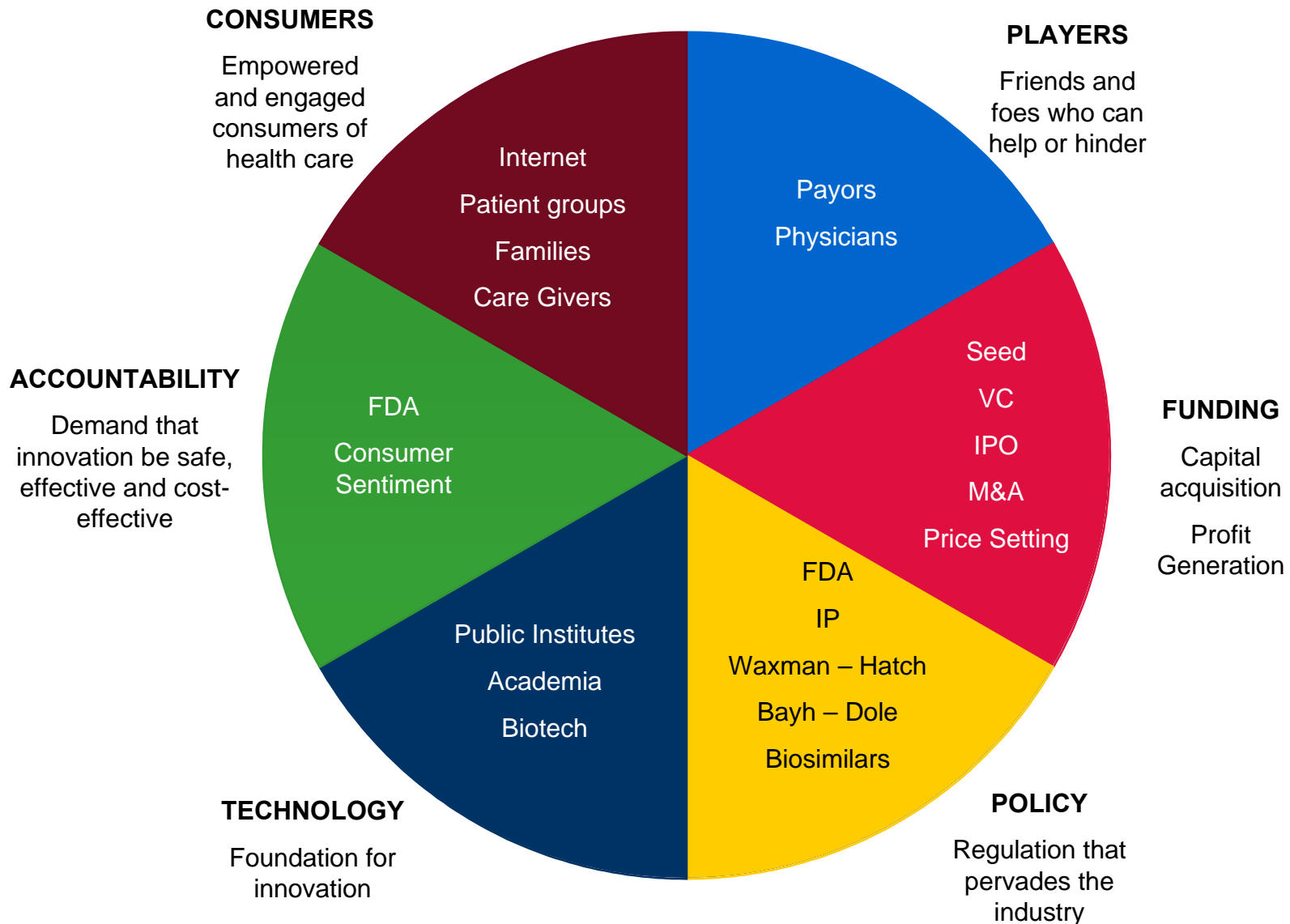
# Decline in R&D from Price Controls

## Estimated Decline in R&D from Price Controls

<u>Drug Prices (Real)</u>	<u>R&amp;D Investment</u>
(10.0%)	(5.8%)
(20.0%)	(11.7%)
(30.0%)	(17.5%)
(40.0%)	(23.3%)
(50.0%)	(29.2%)

Source: John A. Vernon, "New Evidence on Drug Research and Price Controls." *Regulations: the Cato Journal of Business and Government*, Volume 27, Issue No. 3, Fall 2004

# Six Forces Affecting Biotech Success



# Key Success Factors in U.S. Biotech Industry

## National Environment

- ▶ Low and predictable capital gains tax encouraging technology investment
- ▶ Large funding of basic research
- ▶ World-class academic institutions educating scientists

## Entrepreneurial Drive

- ▶ Horatio Alger mentality. No stigma for falling

## Legal and Regulatory Framework

- ▶ FDA
- ▶ IP (protection, plus clear rules for academic institutions and scientists)

## Business Competencies (a majority of which from Big Pharma)

- ▶ Development
- ▶ Manufacturing
- ▶ Sales & Marketing

## Financial Environment

- ▶ Huge health care expenditures
- ▶ Non-centrally controlled prices

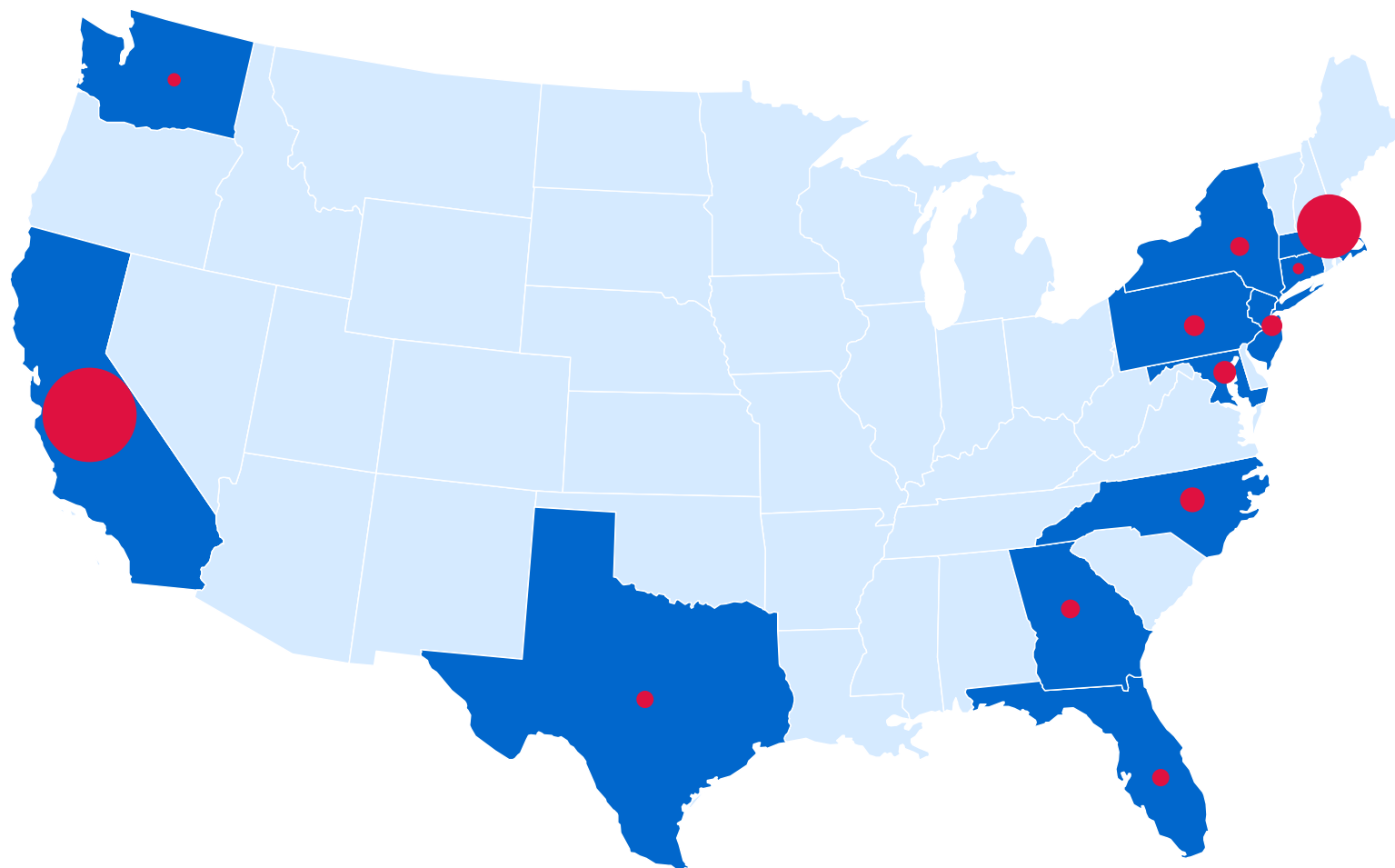
## Physician Support

- ▶ Vocal KOLs

## Consumer Support

- ▶ Vocal special interest groups

# Top U.S. Biotechnology Centers



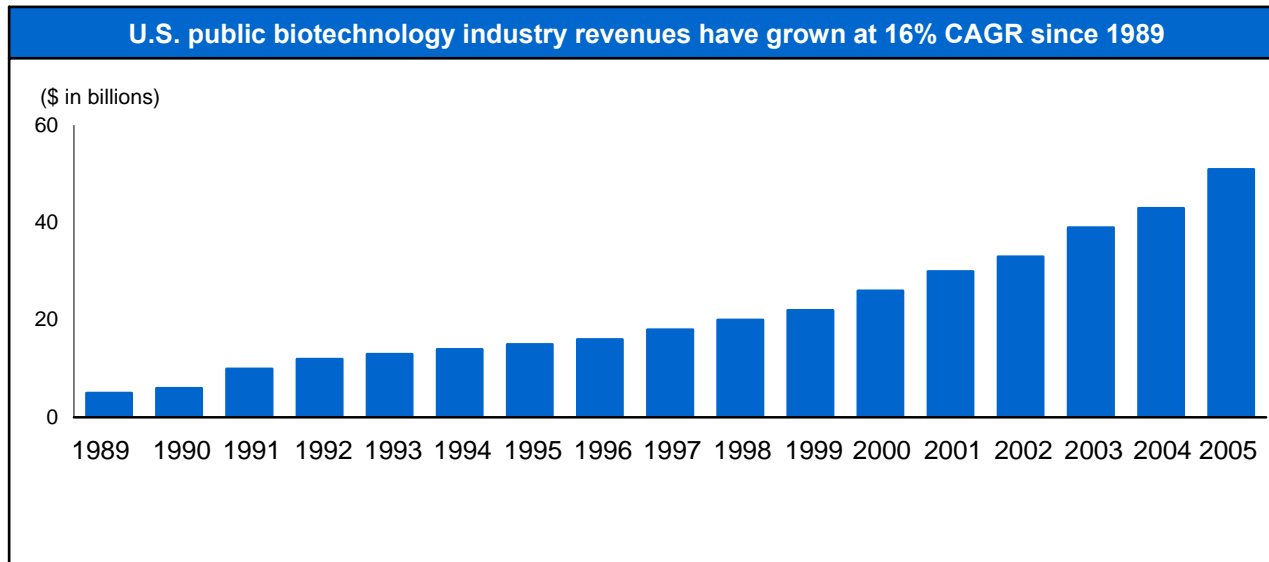
Note: Circle area represents number of biotech companies per corresponding state.

# U.S. Biotech Financial Highlights

**Selected 2005 U.S. biotechnology public company financial highlights**  
**[by geographic area, (\$m), percent change over 2004] (\$ in millions)**

	Number of public companies	Market capitalization 12/31/05	Revenue	R&D	Net Loss (income)	Cash and short term investments	Total Assets
San Francisco Bay Area	67	\$162,261	\$15,431	\$4,284	\$246	\$11,861	\$31,951
	-	53%	25%	5%	(60%)	21%	13%
New England	59	59,582	8,668	3,019	1,194	6,222	24,820
	2%	(3%)	17%	3%	(30%)	(8%)	(2%)
San Diego	37	19,716	2,760	1,073	718	3,431	8,192
	3%	19%	19%	-	(6%)	6%	8%
New Jersey	29	16,946	1,447	737	494	1,950	3,478
	(3%)	38%	21%	(2%)	(16%)	(13%)	(16%)
Mid-Atlantic	19	15,009	1,656	1,080	659	2,578	6,512
	-	3%	(5%)	4%	(10%)	(13%)	(7%)
Southeast	20	6,917	1,441	416	176	1,104	2,970
	-	-	18%	21%	260%	26%	18%
New York State	14	7,333	757	578	296	2,220	3,449
	-	(31%)	(9%)	6%	(18%)	12%	8%
Midwest	11	1,914	201	108	135	300	484
	-	(11%)	(12%)	(18%)	(2%)	(6%)	(3%)
Pacific NW	15	4,036	162	435	537	819	1,245
	(6%)	(22%)	(19%)	(27%)	(35%)	(26%)	(26%)
Los Angeles / Orange County	11	99,917	12,511	2,414	(3,521)	6,005	30,190
	(8%)	19%	13%	(12%)	57%	(2%)	-
North Carolina	10	2,062	469	243	187	334	813
	-	(15%)	(7%)	51%	(38%)	(2%)	(9%)
Pennsylvania / Delaware Valley	11	6,894	1,421	944	488	1,307	3,437
	(15%)	11%	18%	29%	20%	(10%)	(2%)
Texas	10	2,240	169	268	219	479	720
	-	(10%)	2%	26%	42%	20%	7%
Colorado	7	2,401	281	132	132	621	862
	-	9%	59%	11%	(24%)	26%	19%
Utah	2	1,653	106	184	206	392	504
	-	(3%)	50%	(5%)	(1%)	(15%)	(14%)
Other	7	1,466	309	61	(36)	182	527
	17%	(33%)	27%	(61%)	(128%)	(18%)	5%
<b>Total</b>	<b>329</b>	<b>\$410,050</b>	<b>\$47,790</b>	<b>\$15,979</b>	<b>\$2,128</b>	<b>\$39,805</b>	<b>\$120,155</b>
	(1%)	22%	17%	1%	(57%)	3%	3%

# U.S. Biotechnology Revenues

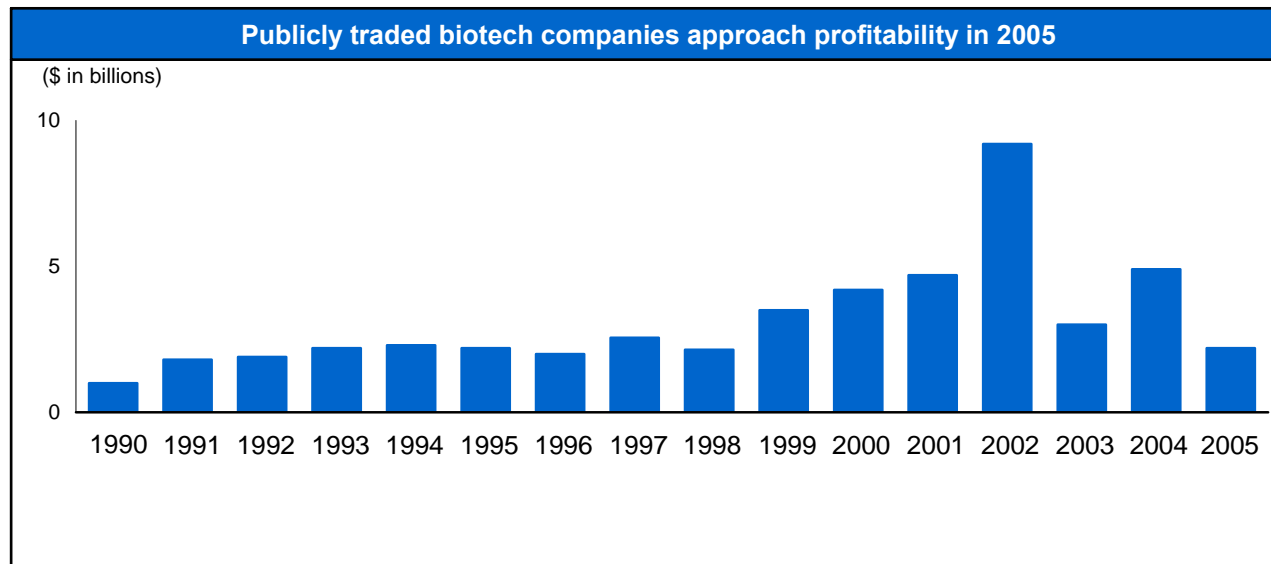


Source: Ernst & Young.

Revenues of U.S. public and private biotechnology companies

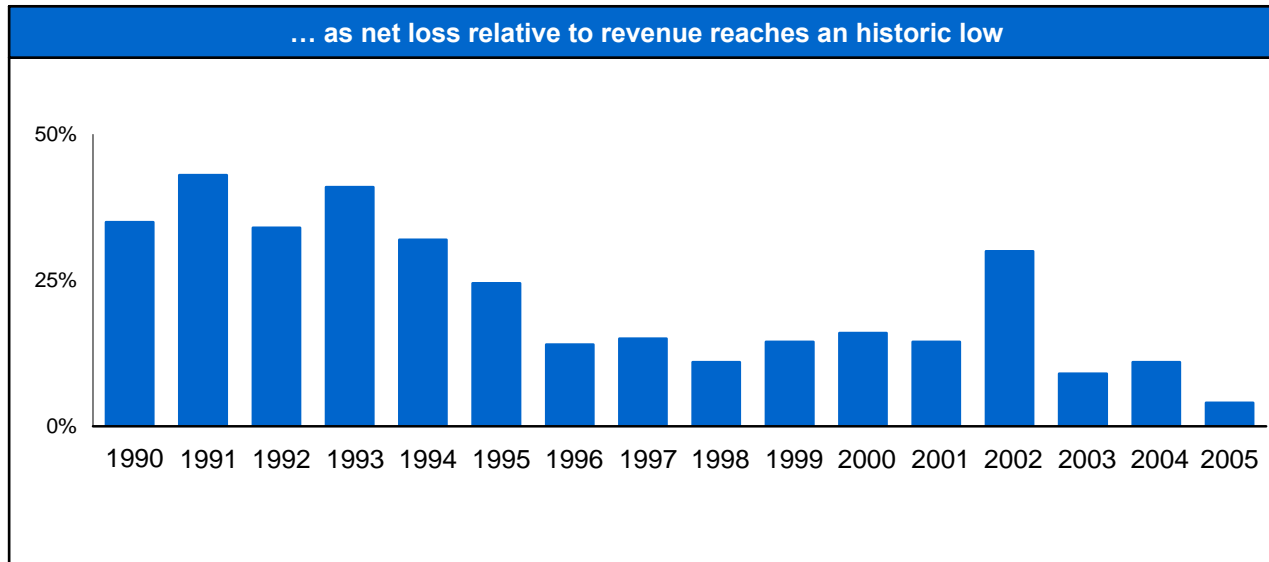
CAGR: Compound Annual Growth Rate

# Publicly Traded Biotechnology Companies



Source: Ernst & Young.

# Net Loss Relative to Revenue



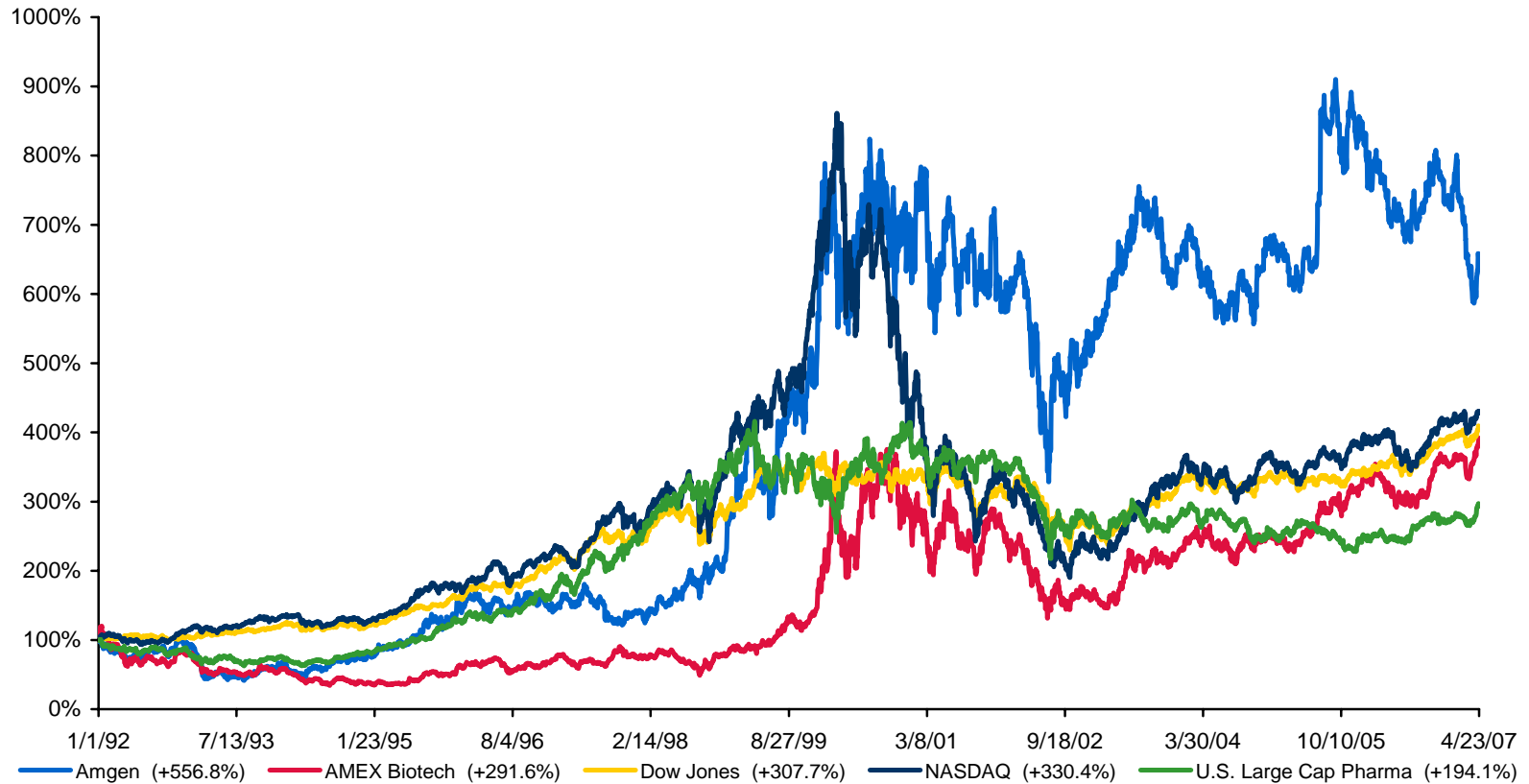
Source: Ernst & Young.



# Biotech vs. NASDAQ, DJIA, and Large Cap Pharma

## Relative Stock Price Performance

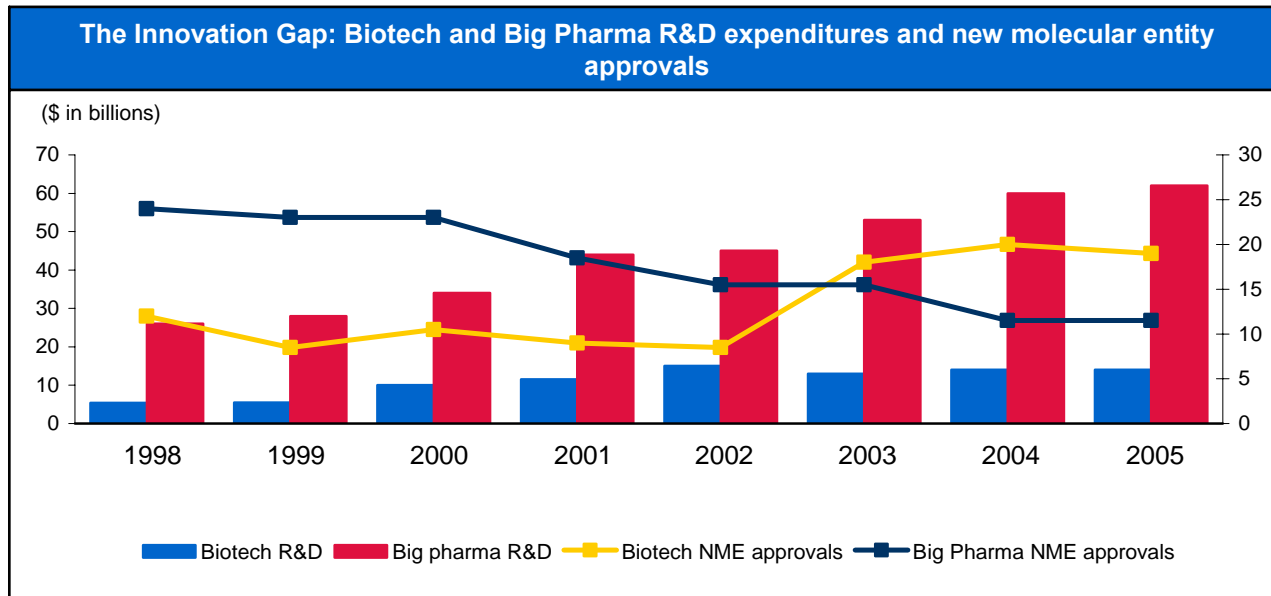
(January 1, 1992 – April 23, 2007)



Source: FactSet.

Note: U.S. Large Cap Pharma includes: ABT, BMY, JNJ, LLY, MRK, PFE, SGP, WYE.

# R&D Expenditures and Approvals

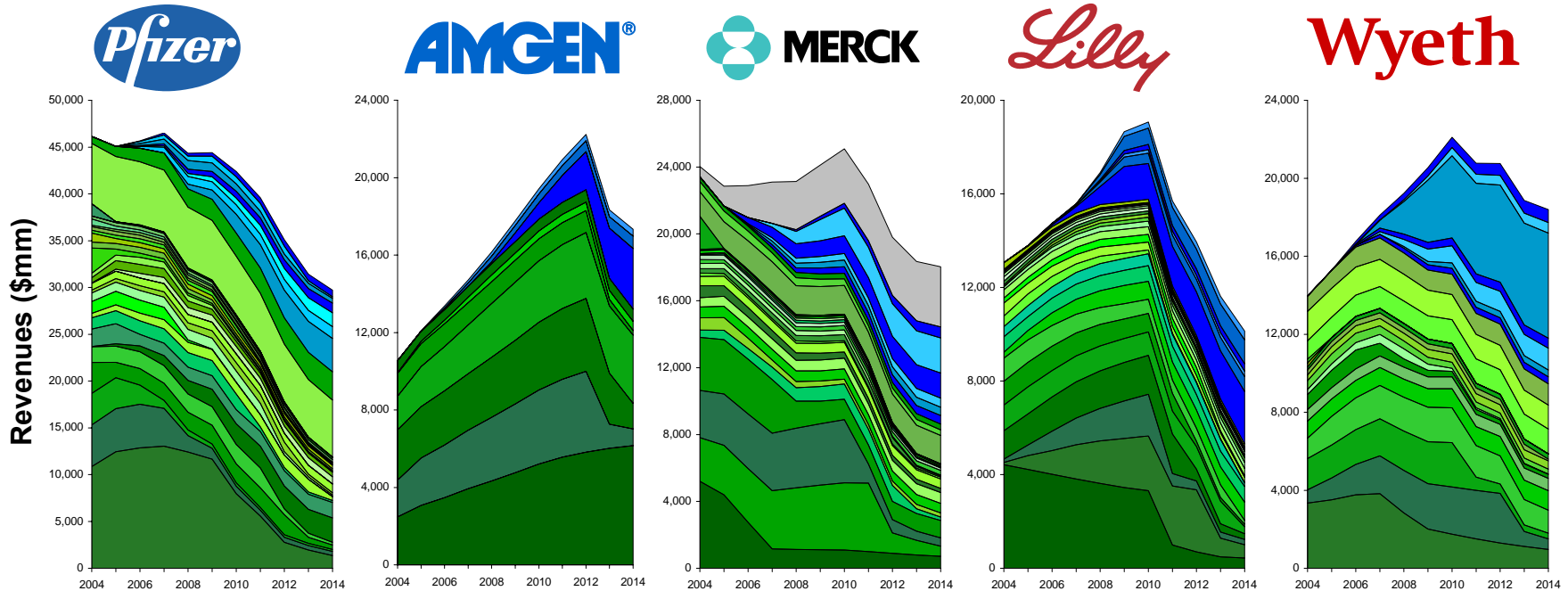


Source: Ernst & Young

Note: Approvals include only new molecular entities and exclude label approvals, new formulations and combinations.

Certain drugs partnered between biotech and big pharma companies are counted in both groups. Big pharma is defined as the 15 largest global pharmaceutical companies by market cap. Companies that do not meet the definition of big pharma and do not meet Ernst & Young's definition of biotechnology are excluded from the analysis. Biotech R&D expenditures including large acquired in-process R&D charges resulting from mergers in some years.

# Many of the Large Pharmas and Biotech Companies Will Face Implications of Finite Patent Lives



Source: Wall Street equity research.