iJOBS Workshop: Drug Development in Biotechnology - Agenda

- 9:30 – 9:45AM Introduction and Purpose of the Symposium – Janet Alder
- 9:45 – 10:15 Overview of the Pharmaceutical Industry – Larry Wennogle
- 10:15 – 10:25 Questions/Discussion
- 10:25 – 10:55 Technologies for discovery of new drug candidates – Mary Konsolaki
- 10:55 – 11:05 Break
- 11:05 – 11:35 CNS Drug Development (What is a “drug target”) – Sam Kongsamut
- 11:35 – 12:05PM Clinical Development of a Pharmaceutical Agent for Food and Drug Administration (FDA) approval – Ira Daly
- 12:05 – 12:35 The story of Entresto – Novel therapy for Heart Failure - Randy Webb
- 12:35PM Working lunch will be served
- 1:00 – 1:30 Funding the Pharmaceutical and Biotechnology Industry – Ben Bowen
- 1:30 – 2:00 Break out groups – Attendee will break out into small ~6 person groups to develop a plan to organize a biotech company designed to develop pharmaceuticals.
- 2:00 - 2:30 The long and winding road to a marketed drug – Ron Steele
- 2:30 – 3:00PM General Discussion including answers to questions submitted in advance of the symposium by participants.
- 3:00 – 4:00PM Mixer

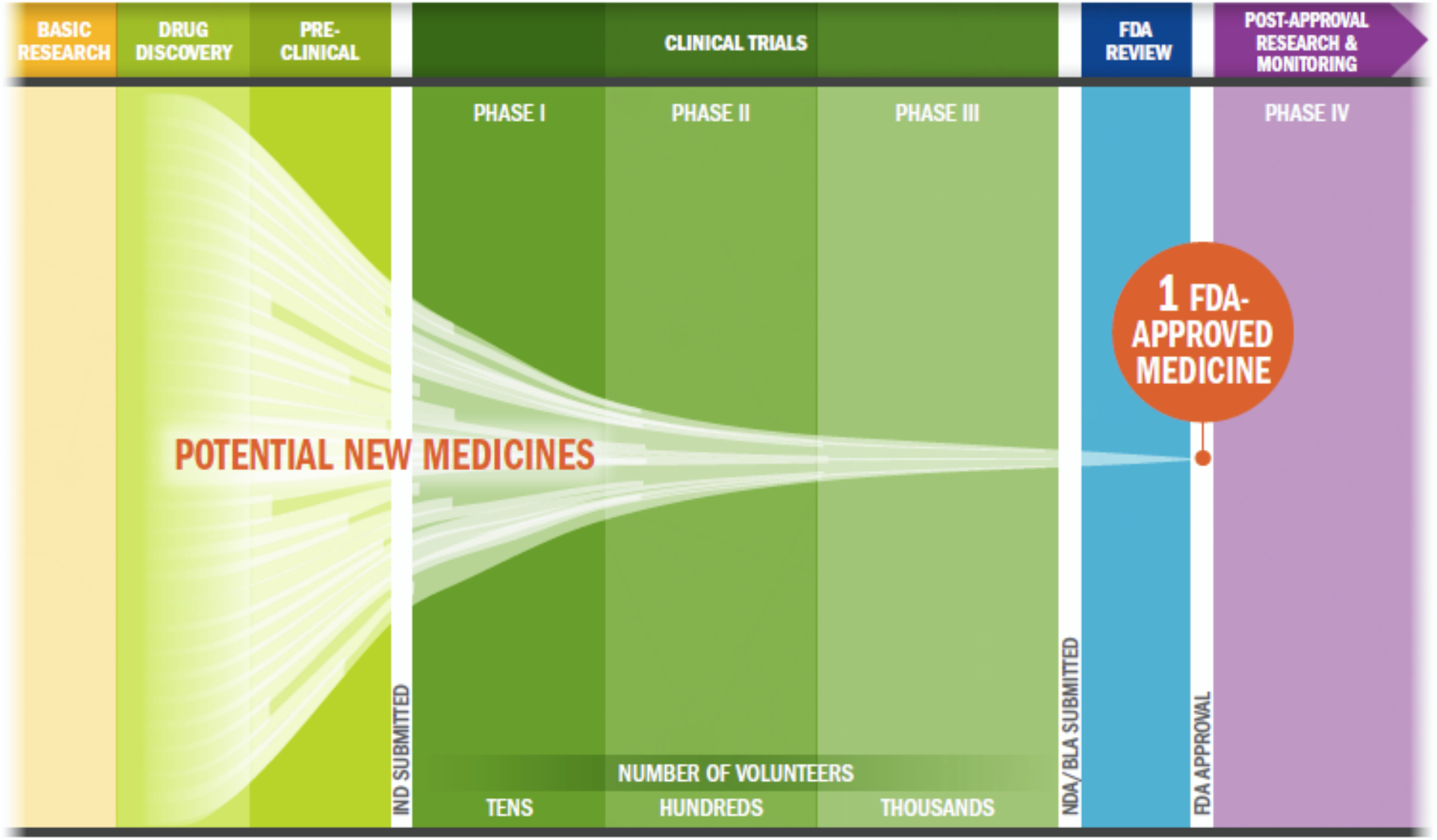
Drug Development in Biotechnology

October 21, 2016
Rutgers University
Piscataway, New Jersey

The Challenge: Odds are against you!

- 11-15 years to develop and win Food and Drug Administration (FDA) approval of a novel pharmaceutical agent
- Estimated costs range … Average cost of $2.6 Billion (PhRMA report) for New Drug Approval (NDA)
  - Central Nervous System drugs generally higher/longer/riskier
- Less than one in ten drugs that enter Phase I clinical development succeed to approval and marketing
- Less than one in two marketed drugs gain back the money used to win approval
- Estimates of how many small molecules are made/screened per novel pharmaceutical agent approved is difficult and depends on the field/prior art

THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



L. Wennogle - Drug Development in Biotechnology - Oct. 21, 2016

Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

Typical IND-enabling Pre-Clinical Toxicology and Safety Studies

Prior to studies in humans, an Investigational New Drug (IND) application must be filed with and approved by the FDA. The FDA has a specific set of in vivo/in vitro studies that must be conducted for IND approval.

- *In vitro*
  - Assay development and validation
  - Dose formulation analyses
- Rat Toxicity
  - Single dose
  - 7 day dose ranging
  - 14 and 28 day toxicity
- Dog/Monkey
  - Maximum tolerated dose
  - 7 day dose ranging
  - No effective dose level
  - 14 and 28 day toxicity
- Genotoxicity
  - Bacterial mutagenicity
  - Chromosome aberration
  - Rodent micronucleus
- Safety Pharmacology
  - hERG inhibition
  - CNS rodent
  - Cardiovascular (telemetry)
  - Respiratory

Larry Wennogle, Ph.D.
Overview of the Pharmaceutical Industry

- Introductory statements and setting the stage for the symposium
- My career in brief
- 30,000 foot view of the Pharmaceutical Industry
  - Markets/revenues/employees
- The challenges
- The changing landscape
  - Historical perspective
- A few words about the legal aspects and patent law

Data Sources

- Pharmaceutical Research and Manufacturing Association of America PRMA
- Center for Disease Control
  - National Center for Health Statistics' (NCHS) Office of Analysis and Epidemiology
  - Package Inserts for approved drugs at Food and Drug Administration (FDA)
- State of New Jersey
- Taganpoint Consultants (Mark Lane)
- PubMed/PubChem
- Google
- WebMD
- Wikipedia

Focus on Biopharmaceuticals

Including:

- Biopharmaceutical Industry
  - Traditional “Big Pharma”
  - Biotech Companies
  - Generic Manufacturers
  - Human clinical trials “industry”

Generally not including:

- Chemical Manufacturing
- Devices
- Clinical Diagnostics

Industry Overview

- Biopharmaceutical sector

Figure 11: Medicines in Development in 2012: Selected Categories

Reflects number of compounds in clinical trials or under review by the FDA.
*Rare diseases are those affecting 200,000 or fewer people in the United States.
SOURCES: Except where noted otherwise, data for listed conditions from: Adis R&D Insight, Wolters Kluwer Health (Accessed 9 January 2012). Data for rare diseases are from: Pharmaceutical Research and Manufacturers of America, Orphan Drugs in Development for Rare Diseases 2011 (Washington, DC: PhRMA, 2011).

Pharmaceutical Research and Development Association (PhRMA) member companies

- Abbott
- Amgen
- Astellas
- AstraZenica
- Biogen
- Bayer HealthCare LLC
- Boehringer Ingelheim
- Bristol-Myers Squibb
- Celgene
- Cubist Pharma
- Daiichi Sankyo
- Dainippon Sumitomo Pfizer
- Eisai
- EMD Serono
- Endo Pharma
- GlaxoSmithKlyne
- Johnson & Johnson
- Eli Lilly
- Lundbeck
- Merck & Co
- Novartis Pharma
- Novo Nordisk
- Otsuka
- Purdue
- Sanofi
- Sigma-Tau
- Takeda Pharma
- Alkermes
- Arena Pharma
- BioMartin Pharma
- CSL Behring LLC
- Depomed
- Ferring Pharma
- Helsin Therapeutics
- Horizon Pharma
- Ikaria
- Orexigen Pharma
- Shionogi Inc.
- Sucampo
- Theravance Inc.
- United Therapeutics
- Vertex
- Vifor
- Vivus Inc.
- Xoma Ltd.

Blue – headquartered in New Jersey, Purple – significant presence in New Jersey

Total Sales by company

Novartis top in total sales in 2014 with $47B

2014 | 2013 | 2012

#	Company	2014 ($m)	2013 ($m)	Growth ($m)	Growth (%)
1	Novartis	47101	47468	-367	-1
2	Pfizer	45708	47878	-2170	-5
3	Roche	39120	39163	-43	0
4	Sanofi	36437	37124	-687	-2
5	Merck & Co.	36042	37437	-1395	-4
6	Johnson & Johnson	32313	28125	4188	15
7	GlaxoSmithKline	29580	33330	-3750	-11
8	AstraZeneca	26095	25711	384	1
9	Gilead Sciences	24474	10804	13670	127
10	Takeda	20446	19158	1288	7
11	AbbVie	20207	18790	1417	8
12	Amgen	19327	18192	1135	6
13	Teva	18374	18308	66	0
14	Lilly	17266	20962	-3696	-18
15	Bristol-Myers Squibb	15879	16385	-506	-3
16	Bayer	15486	14854	632	4
17	Novo Nordisk	15329	14877	452	3
18	Astellas	14099	13508	591	4
19	Boehringer Ingelheim	13830	15789	-1959	-12
20	Actavis	13062	8678	4384	51
21	Otsuka	11308	11226	82	1

Key Points: PhRMA companies

- In the year 2011
  - spent $49B in R&D
- Roughly 78% - domestic
- Roughly 17% of Total Sales

TABLE 1: Domestic R&D and R&D Abroad,* PhRMA Member Companies: 1975–2011

(dollar figures in millions)

Year	Domestic R&D	Annual Percentage Change	R&D Abroad*	Annual Percentage Change	Total R&D	Annual Percentage Change
2011**	$38,529.9	-5.3%	$10,946.0	9.2%	$49,475.9	-2.4%
2010	40,688.1	15.1	10,021.7	-9.6	50,709.8	9.2
2009	35,356.0	-0.6	11,085.6	-6.1	46,441.6	-2.0
2008	35,571.1	-2.8	11,812.0	4.6	47,383.1	-1.1
2007	36,608.4	7.8	11,294.8	25.4	47,903.1	11.5
2006	33,967.9	9.7	9,005.6	1.3	42,973.5	7.8
2005	30,969.0	4.8	8,888.9	19.1	39,857.9	7.7
2004	29,555.5	9.2	7,462.6	1.0	37,018.1	7.4
2003	27,064.9	5.5	7,388.4	37.9	34,453.3	11.1
2002	25,655.1	9.2	5,357.2	-13.9	31,012.2	4.2
2001	23,502.0	10.0	6,220.6	33.3	29,772.7	14.4
2000	21,363.7	15.7	4,667.1	10.6	26,030.8	14.7
1999	18,471.1	7.4	4,219.6	9.9	22,690.7	8.2
1998	17,127.9	11.0	3,839.0	9.9	20,966.9	10.8
1997	15,466.0	13.9	3,492.1	6.5	18,958.1	12.4
1996	13,627.1	14.8	3,278.5	-1.6	16,905.6	11.2
1995	11,874.0	7.0	3,333.5	***	15,207.4	***
1994	11,101.6	6.0	2,347.8	3.8	13,449.4	5.6
1993	10,477.1	12.5	2,262.9	5.0	12,740.0	11.1
1992	9,312.1	17.4	2,155.8	21.3	11,467.9	18.2
1991	7,928.6	16.5	1,776.8	9.9	9,705.4	15.3
1990	6,802.9	13.0	1,617.4	23.6	8,420.3	14.9
1989	6,021.4	15.0	1,308.6	0.4	7,330.0	12.1
1988	5,233.9	16.2	1,303.6	30.6	6,537.5	18.8
1987	4,504.1	16.2	998.1	15.4	5,502.2	16.1
1986	3,875.0	14.7	865.1	23.8	4,740.1	16.2
1985	3,378.7	13.3	698.9	17.2	4,077.6	13.9
1984	2,982.4	11.6	596.4	9.2	3,578.8	11.2
1983	2,671.3	17.7	546.3	8.2	3,217.6	16.0
1982	2,268.7	21.3	505.0	7.7	2,773.7	18.6
1981	1,870.4	20.7	469.1	9.7	2,339.5	18.4
1980	1,549.2	16.7	427.5	42.8	1,976.7	21.5
1979	1,327.4	13.8	299.4	25.9	1,626.8	15.9
1978	1,166.1	9.7	237.9	11.6	1,404.0	10.0
1977	1,063.0	8.1	213.1	18.2	1,276.1	9.7
1976	983.4	8.8	180.3	14.1	1,163.7	9.6
1975	903.5	13.9	158.0	7.0	1,061.5	12.8
Average		11.2%		12.3%		11.4%

*R&D Abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic R&D, however, includes R&D expenditures within the United States by all PhRMA member companies.

**Estimated.

***R&D Abroad affected by merger and acquisition activity.

Note: All figures include company-financed R&D only. Total values may be affected by rounding.

SOURCE: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2012.

TABLE 2: R&D as a Percentage of Sales, PhRMA Member Companies: 1975–2011

Year	Domestic R&D as a Percentage of Domestic Sales	Total R&D as a Percentage of Total Sales
2011*	21.1%	16.7%
2010	22.0	17.4
2009	19.5	16.8
2008	19.4	16.6
2007	19.8	17.5
2006	19.4	17.1
2005	18.6	16.9
2004	18.4	16.1**
2003	18.3	16.5**
2002	18.4	16.1
2001	18.0	16.7
2000	18.4	16.2
1999	18.2	15.5
1998	21.1	16.8
1997	21.6	17.1
1996	21.0	16.6
1995	20.8	16.7
1994	21.9	17.3
1993	21.6	17.0
1992	19.4	15.5
1991	17.9	14.6
1990	17.7	14.4
1989	18.4	14.8
1988	18.3	14.1
1987	17.4	13.4
1986	16.4	12.9
1985	16.3	12.9
1984	15.7	12.1
1983	15.9	11.8
1982	15.4	10.9
1981	14.8	10.0
1980	13.1	8.9
1979	12.5	8.6
1978	12.2	8.5
1977	12.4	9.0
1976	12.4	8.9
1975	12.7	9.0

*Estimated.

**Revised in 2007 to reflect updated data.

SOURCE: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2012.

Table 1

Ranking of Countries Based on 2002 Pharmaceutical Sales

Rank	Country	Percent of World Market	PCT National Stage Cost (USD)	Translation Costs[21] (percentage)
1	USA	45.83	3,287	0
2	EPO (+ Extension States)	25.05	13,623	0
3	Japan	12.35	17,382	66
4	Canada	1.87	2,440	0
5	Mexico	1.76	7,351	57
6	China	1.44	8,032	64
7	Brazil	1.18	4,842	48
8	South Korea	1.11	12,386	65
9	India	0.92	1,963	0
10	Australia	0.87	3,006	0
11	Taiwan (non-PCT)	0.61	6,932	66
12	Saudi Arabia (non-PCT)	0.36	10,974	51
13	Venezuela (non-PCT)	0.35	2,650	*
14	Russia	0.34	7,895	55
15	Indonesia	0.33	5,942	46
16	Argentina (non-PCT)	0.32	3,160	*
17	Colombia	0.29	5,417	*
18	Philippines	0.27	2,252	0
19	Norway	0.26	19,088	55
20	Pakistan (non-PCT)	0.23	2,350	0
21	Thailand (non-PCT)	0.21	7,735	68
22	Egypt	0.20	6,185	47
23	South Africa	0.19	2,014	0
24	Israel	0.17	2,208	0
25	Chile (non-PCT)	0.15	2,962	*
26	Ecuador	0.12	4,427	*
27	Morocco	0.11	9,976	72
28	New Zealand	0.10	1,972	0
29	Hong Kong (non-PCT)	0.10	2,687	*
30	Bangladesh (non-PCT)	0.10	1,596	0
31	Peru (non-PCT)	0.09	5,548	*
32	Malaysia (non-PCT)	0.08	2,362	0
33	Dominican Rep. (non-PCT)	0.07	2,912	*
34	UAE	0.07	5,227	*
35	Lebanon (non-PCT)	0.06	2,336	*
36	Ukraine	0.06	7,023	*
37	Singapore	0.06	1,684	0
38	Tunisia	0.05	3,505	*
39	Uruguay (non-PCT)	0.05	3,496	*
40	Belarus	0.04	5,932	*
41	Kuwait (non-PCT)	0.03	2,066	*
42	Jordan (non-PCT)	0.02	18,229	*
43	Paraguay (non-PCT)	0.01	3,276	*
44	Bolivia (non-PCT)	0.01	3,419	*

Some Statistics

- In 2003 there were 6,199 Clinical trials in the US involving 1.1 million participants
- 17.5% of GDP goes to national health expenditures
- In 2014, $9,523 was spent on health care expenses per capita
- Roughly 9.8% of the medical expenses in the USA go to purchase prescription drugs (CDC in 2014)
  - This expense offsets considerably higher costs for hospitalization

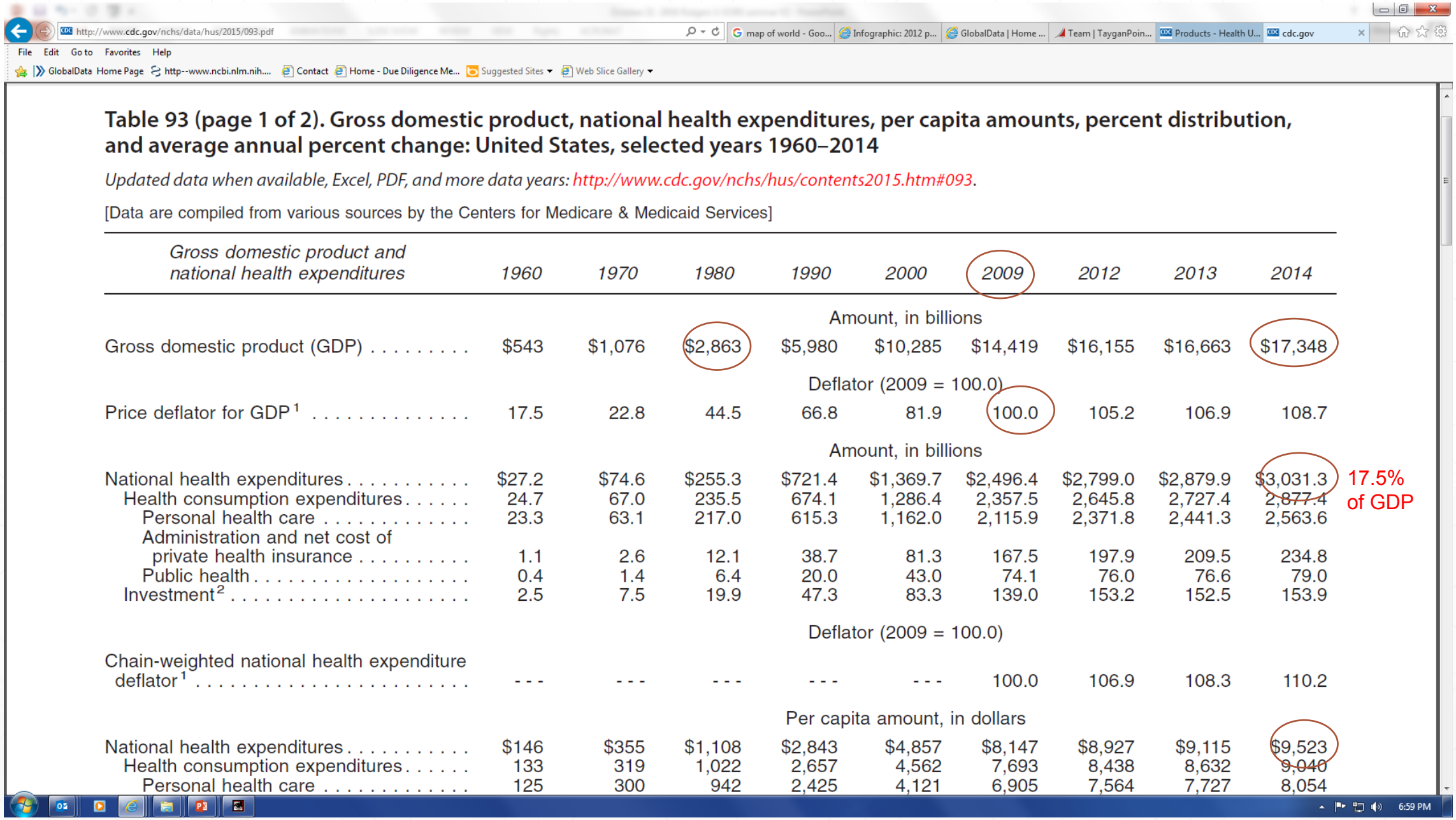


Table 93 (page 1 of 2). Gross domestic product, national health expenditures, per capita amounts, percent distribution, and average annual percent change: United States, selected years 1960–2014

Updated data when available, Excel, PDF, and more data years: http://www.cdc.gov/nchs/hus/contents2015.htm#093.

[Data are compiled from various sources by the Centers for Medicare & Medicaid Services]

Gross domestic product and national health expenditures	*1960*	*1970*	*1980*	*1990*	*2000*	*2009*	*2012*	*2013*	*2014*
					Amount, in billions				
Gross domestic product (GDP)	$543	$1,076	$2,863	$5,980	$10,285	$14,419	$16,155	$16,663	$17,348
					Deflator (2009 = 100.0)				
Price deflator for GDP [1]	17.5	22.8	44.5	66.8	81.9	100.0	105.2	106.9	108.7
					Amount, in billions				
National health expenditures	$27.2	$74.6	$255.3	$721.4	$1,369.7	$2,496.4	$2,799.0	$2,879.9	$3,031.3
Health consumption expenditures	24.7	67.0	235.5	674.1	1,286.4	2,357.5	2,645.8	2,727.4	2,877.4
Personal health care	23.3	63.1	217.0	615.3	1,162.0	2,115.9	2,371.8	2,441.3	2,563.6
Administration and net cost of private health insurance	1.1	2.6	12.1	38.7	81.3	167.5	197.9	209.5	234.8
Public health	0.4	1.4	6.4	20.0	43.0	74.1	76.0	76.6	79.0
Investment [2]	2.5	7.5	19.9	47.3	83.3	139.0	153.2	152.5	153.9
					Deflator (2009 = 100.0)				
Chain-weighted national health expenditure deflator [1]	- - -	- - -	- - -	- - -	- - -	100.0	106.9	108.3	110.2
					Per capita amount, in dollars				
National health expenditures	$146	$355	$1,108	$2,843	$4,857	$8,147	$8,927	$9,115	$9,523
Health consumption expenditures	133	319	1,022	2,657	4,562	7,693	8,438	8,632	9,040
Personal health care	125	300	942	2,425	4,121	6,905	7,564	7,727	8,054

17.5% of GDP

Health, United States, 2015: At a Glance

National Center for Health Statistics' (NCHS) Office of Analysis and Epidemiology

	Value (year)			*Health, United States, 2015* Table No.
Life Expectancy and Mortality				
Life expectancy, in years				Table 15
At birth	76.8 (2000)	78.8 (2013)	78.8 (2014)	
Infant deaths per 1,000 live births				Table 11
All infants	6.91 (2000)	5.96 (2013)	5.82 (2014)	
Deaths per 100,000 population, age-adjusted				Table 17
All causes	869.0 (2000)	731.9 (2013)	724.6 (2014)	
Heart disease	257.6 (2000)	169.8 (2013)	167.0 (2014)	
Cancer	199.6 (2000)	163.2 (2013)	161.2 (2014)	
Chronic lower respiratory diseases	44.2 (2000)	42.1 (2013)	40.5 (2014)	
Unintentional injuries	34.9 (2000)	39.4 (2013)	40.5 (2014)	
Stroke	60.9 (2000)	36.2 (2013)	36.5 (2014)	
Alzheimer's disease	18.1 (2000)	23.5 (2013)	25.4 (2014)	
Diabetes	25.0 (2000)	21.2 (2013)	20.9 (2014)	
Influenza and pneumonia	23.7 (2000)	15.9 (2013)	15.1 (2014)	
Nephritis, nephrotic syndrome and nephrosis	13.5 (2000)	13.2 (2013)	13.2 (2014)	
Suicide	10.4 (2000)	12.6 (2013)	13.0 (2014)	
Morbidity and Risk Factors				
Fair or poor health, percent				Table 45
All ages	8.9 (2000)	10.2 (2013)	9.8 (2014)	
65 years and over	26.9 (2000)	23.1 (2013)	21.7 (2014)	
Heart disease (ever told), percent				Table 38
18 years and over	11.3 (2000–2001)	11.4 (2011–2012)	11.5 (2013–2014)	
65 years and over	30.9 (2000–2001)	30.3 (2011–2012)	29.4 (2013–2014)	
Cancer (ever told), percent				Table 38
18 years and over	5.0 (2000–2001)	6.2 (2011–2012)	6.4 (2013–2014)	
65 years and over	15.2 (2000–2001)	18.5 (2011–2012)	18.2 (2013–2014)	
Hypertension,[1] percent				Table 54
20 years and over	30.2 (1999–2002)	32.2 (2007–2010)	33.0 (2011–2014)	

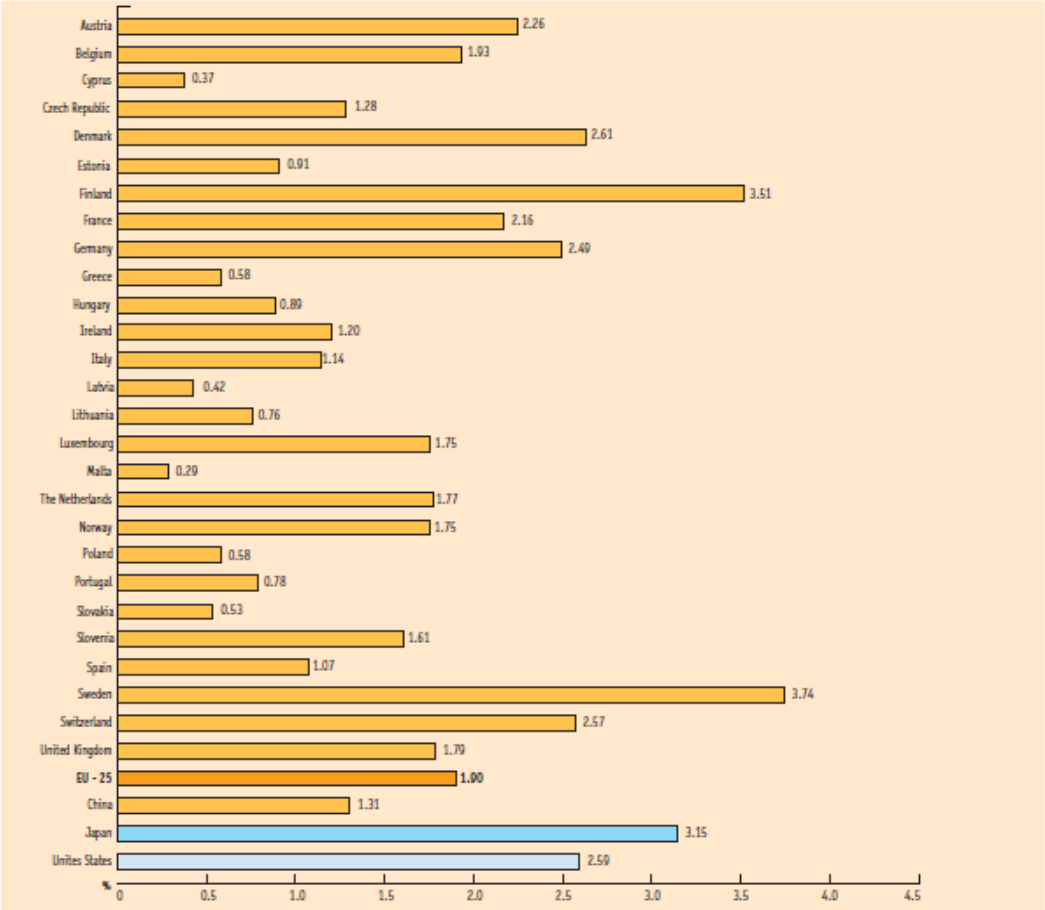
R&D Expenditures as a % of GDP
US – 2.59%

RESEARCH & DEVELOPMENT AS A PERCENTAGE OF GROSS DOMESTIC PRODUCT

According to the latest Eurostat data, Research and Development expenditure represented 1.90% of the European Union's Gross Domestic Product (GDP) in 2004 against 1.93% in 2001.

The gap with regard to R&D expenditure in the United States and Japan remains significant since these countries spent respectively 2.59% and 3.15% of their GDP on R&D. Among European countries, the lowest R&D ratios were registered in the southern countries and the new member States, whilst Sweden and Finland, with respective shares of their GDP of 3.74% and 3.51%, made the greatest research effort.

R&D EXPENDITURE AS A PERCENTAGE OF GDP (2004)



Note: Switzerland: 2001 data
China, Italy, Japan, Portugal, USA: 2003 data
Source: EUROSTAT, Statistics in Focus, Science and Technology, 6/2006, 'R&D expenditure in Europe', First preliminary data; EUROSTAT

24

Highest Selling Pharmaceuticals in 2013

- Humira - $10.7B
  - Enbrel and Remicade
- US 2013
  - Abilify - $6.53B - Antipsychotic
  - Nexium - $6B – Proton Pump Inhibitor - Ulcer
  - Humira - $5.4B – TNF alpha antibody
- Lipitor (Pfizer HMG-CoA Reductase inhibitor – Statin – Cholesterol – Park Davis Pfizer acquizition)
  - Averaged $13B annually (totaled $141B before patent expiration 2011

2015 – WebMD:

The top 10 medications by number of monthly prescriptions are:

1. Synthroid (levothyroxine), 21.5 million
2. Crestor (rosuvastatin), 21.4 million
3. Ventolin HFA (albuterol), 18.2 million
4. Nexium (esomeprazole), 15.2 million
5. Advair Diskus (fluticasone), 13.7 million
6. Lantus Solostar (insulin glargine), 10.9 million
7. Vyvanse (lisdexamfetamine), 10.4 million
8. Lyrica (pregabalin), 10.0 million
9. Spiriva Handihaler (tiotropium), 9.6 million
10. Januvia (sitagliptin), 9.1 million

The top 10 medications by sales are:

1. Humira (adalimumab), $8.2 billion
2. Abilify (aripiprazole), $7.9 billion
3. Sovaldi (sofosbuvir), $6.9 billion
4. Crestor (rosuvastatin), $5.9 billion
5. Enbrel (etanercept), $5.9 billion
6. Harvoni (ledipasvir and sofosbuvir), $5.3 billion
7. Nexium (esomeprazole), $5.3 billion
8. Advair Diskus (fluticasone), $4.7 billion
9. Lantus Solostar (insulin glargine), $4.7 billion
10. Remicade (infliximab), $4.6 billion

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab does not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro* or *in vivo*. Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T-lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which REMICADE exerts its clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

12.2 Pharmacodynamics

Elevated concentrations of TNFα have been found in involved tissues and fluids of patients with rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. In rheumatoid arthritis,

REMICADE® (infliximab)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The significance of the results of nonclinical studies for human risk is unknown. A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

14 CLINICAL STUDIES

14.1 Crohn's Disease

Active Crohn's Disease

The safety and efficacy of single and multiple doses of REMICADE were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 653 patients with moderate to severely active Crohn's disease [Crohn's Disease Activity Index (CDAI) ≥220 and ≤400] with an inadequate response to prior conventional therapies. Concomitant stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of patients continued to receive at least one of these medications

General

Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of rheumatoid arthritis (RA), polyarticular-course juvenile rheumatoid arthritis (JRA), and the resulting joint pathology.[1, 2] Elevated levels of TNF are found in the synovial fluid of RA patients and in both the synovium and psoriatic plaques of patients with psoriatic arthritis.[3, 4]

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms.[5] Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules. It inhibits the activity of TNF in vitro and has been shown to affect several animal models of inflammation, including murine collagen-induced arthritis.[6, 7] Etanercept inhibits

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List of largest selling pharmaceutical products

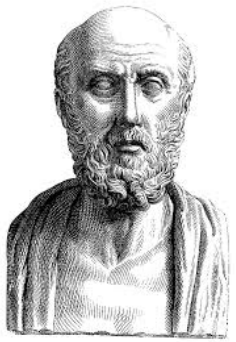
From Wikipedia, the free encyclopedia

[1]

Rank	Brand Name(s)	Generic Name	Sales Q1 2014 Sales ($000)	Change from Q4 2013	Company(ies)	Disease/Medical Use	First Approval Date	Patent Expiration Date[2][3]
1	Abilify	Aripiprazole	1,602,329	2.23%	Generic	Psychosis; depression	Nov-2002	Oct-2014
2	Humira	Adalimumab	1,561,861	3.86%	AbbVie	Crohn's disease; Rheumatoid arthritis	Dec-2002	Dec-2016
3	Nexium	Esomeprazole	1,536,435	0.74%	Generic	Gastrointestinal disorders	Mar-2000	May-2014
4	Crestor	Rosuvastatin	1,333,502	4.53%	AstraZeneca, Shionogi	Cholesterol	Nov-2002	Jul-2016
5	Enbrel	Etanercept	1,189,844	1.46%	Amgen	Rheumatoid arthritis	Nov-1998	Oct-2012
6	Advair Diskus, Seretide	Fluticasone/salmeterol	1,147,330	2.65%	GlaxoSmithKline	Asthma	Aug-2000	Mar-2012
8	Remicade	Infliximab	994,020	-2.71%	Centocor Ortho Biotech, Inc., Mitsubishi Tanabe Pharma	Crohn's disease; rheumatoid arthritis	Aug-1998	n/a
9	Lantus Solostar	Insulin glargine	939,691	9.39%	Sanofi-Aventis	Diabetes mellitus type 1 and 2	Apr-2000	Dec-2011
10	Neulasta	Filgrastim	854,508	-4.90%	Amgen	Neutropenia	Jan-2002	Mon-20XX
11	Copaxone	Glatiramer	851,351	-4.69%	Generic	Multiple sclerosis	Dec-1996	Nov-2014
12	Rituxan, MabThera	Rituximab	746,766	-0.16%	Biogen Idec, Chugai Pharmaceutical, Genentech/Roche	Non-Hodgkin's lymphoma; rheumatoid arthritis	Nov-1997	Mon-20XX
13	Spiriva	Tiotropium bromide	726,057	3.39%	Boehringer Ingelheim	Chronic obstructive pulmonary disease	Apr-2002	Jul-2018
14	Januvia	Sitagliptin	700,941	3.63%	Merck & Co., Inc.	Diabetes mellitus type 2	Dec-1996	Nov-2017
15	Lantus	Insulin glargine	685,461	5.84%	Sanofi-Aventis	Diabetes mellitus type 1 and 2	Apr-2000	Dec-2011
16	Atripla	Emtricitabine/tenofovir/efavirenz	679,418	0.36%	Gilead Sciences, Inc.	HIV infection	Dec-1996	Mar-2015
17	Cymbalta	Duloxetine	664,186	-23.06%	Generic	Depression; anxiety disorders	Aug-2004	Dec-2013
18	Avastin	Bevacizumab	650,208	-1.25%	Genentech/Roche	Cancer	Feb-2004	Mon-20XX

Evolution of Therapeutic Approaches

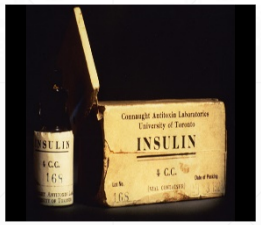
400BC — Hippocrates describes us of salicylic tea to reduce fever



1899 — Bayer begins selling "aspirin"

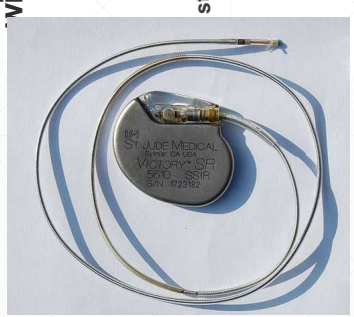
1914 — Rabies vaccine licensed in US

1922 — 1st diabetic treated with insulin

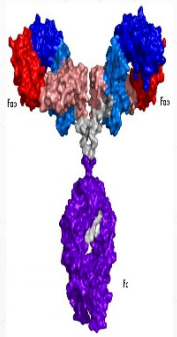


1942 — 1st success tx of septicemia with penicillin

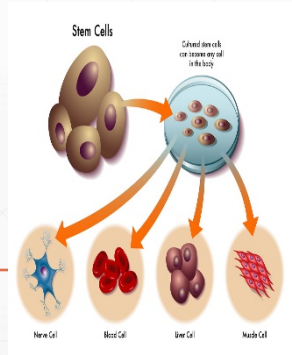
1958 — st implantable pacemaker



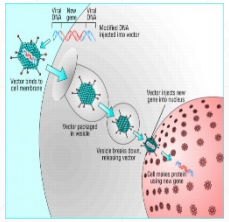
1986 — 1st antibody therapy approved for transplant rejection



2012 — 1st (only) stem cell therapy approved



2012 — 1st (only) gene therapy approved (outside of China)



2016 — 1st 3D printed pill approved

Example

Statins: Cholesterol Lowering

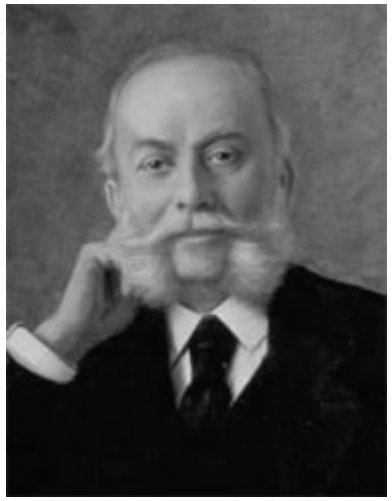
- In 1971, Akira Endo, a Japanese biochemist from Sankyo, identified mevastatin from a fungus as an inhibitor of HMG-CoA reductase, RDS for cholesterol biosynthesis
- In 1987, Roy Vagaeos (CEO of Merck) orchestrated first marketing of Mevacor
- Zocor causes 35% reduction in cholesterol and chances of dying of heart disease reduces 43%
- Sales of Zocor and Mevacor (Merck) over $1B in 1995

Historical Perspective

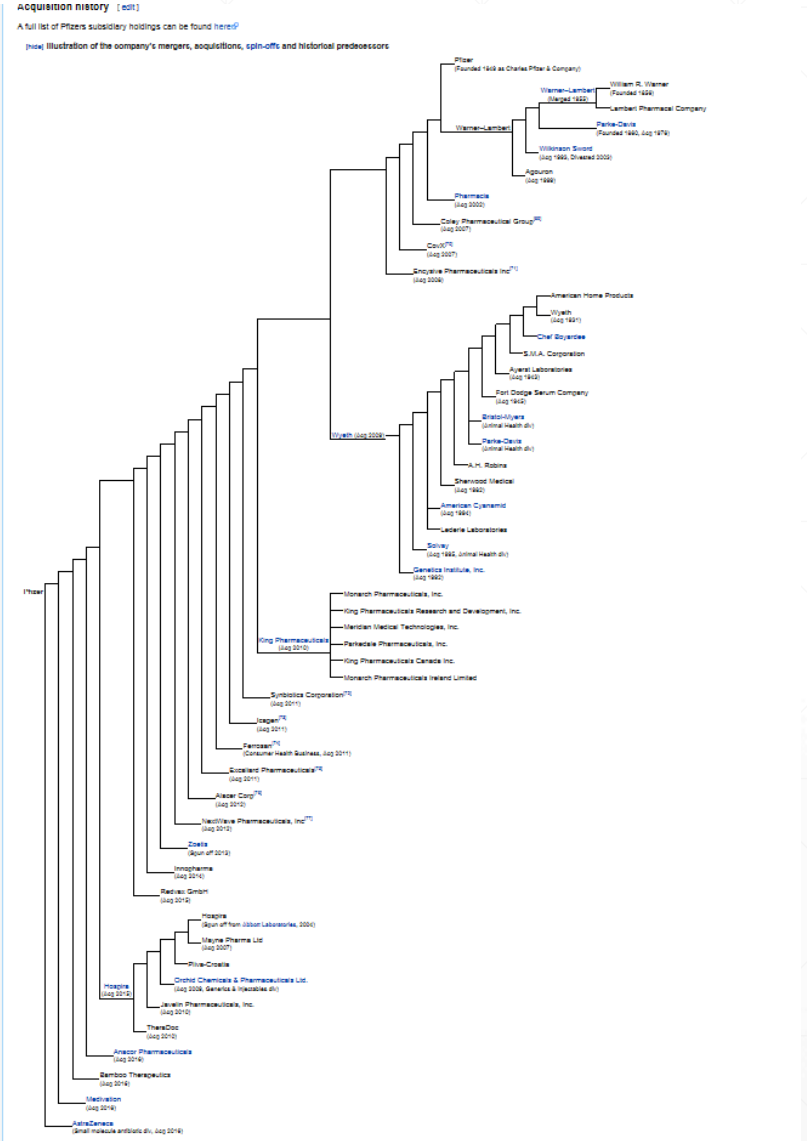
- Natural Products
- Antibiotics
- Anti-infectives
- Designer drugs such as specific kinase and receptor inhibitors
- Biologicals
- First direct-to-consumer advertisement: Merck, 1981 (Readers Digest for anti-pneumococcal vaccine)
- In 2003, $5B spent on direct-to-consumer marketing

Example

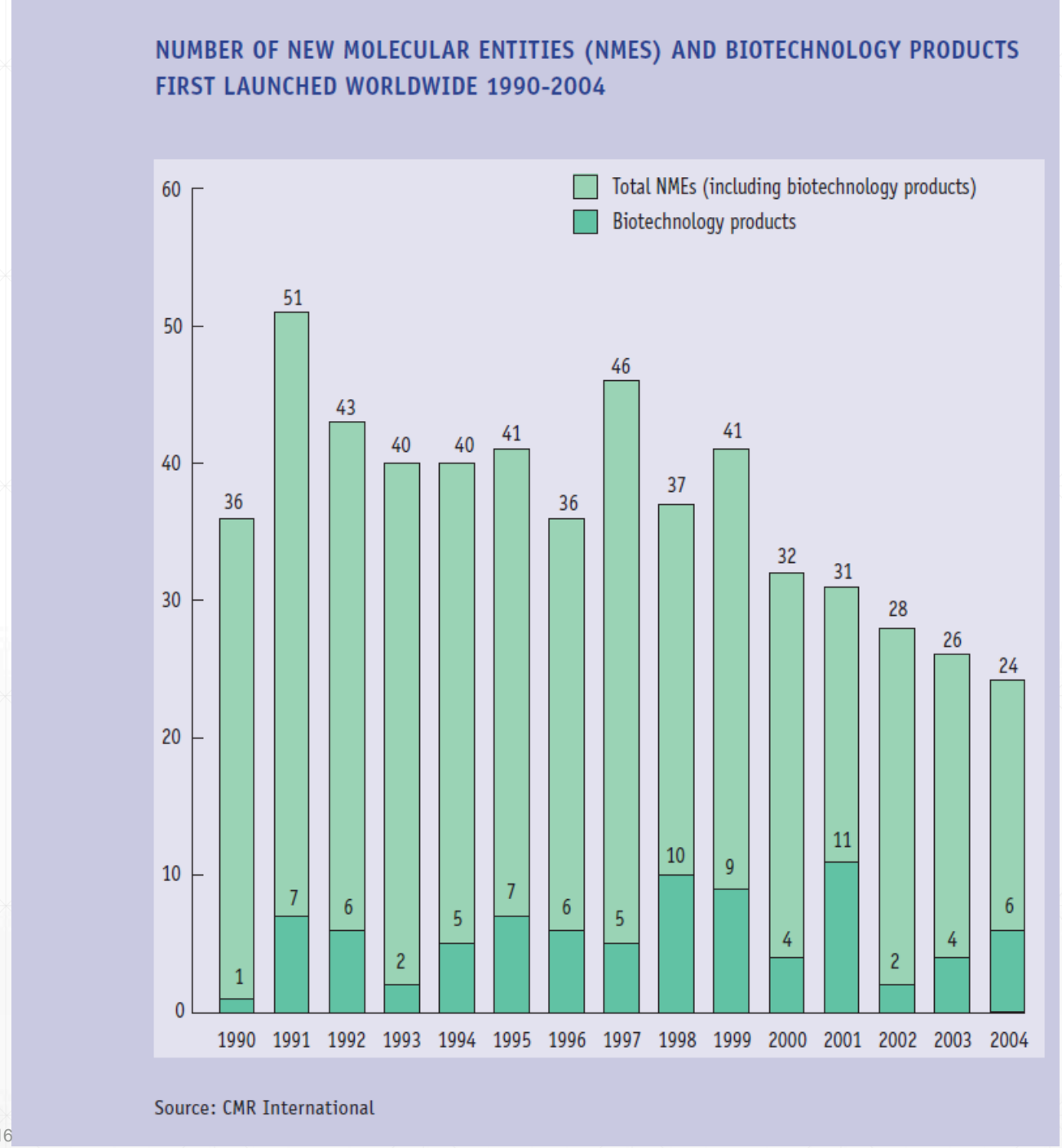
Pfizer: Legacy



- Warner-Lambert
- Agouron
- Pharmacia
- Wyeth
- American Home Products
- Parke-Davis
- American Cyanamid/Lederle Labs
- Recent failed attempts: Astra-Zeneca and Allergan

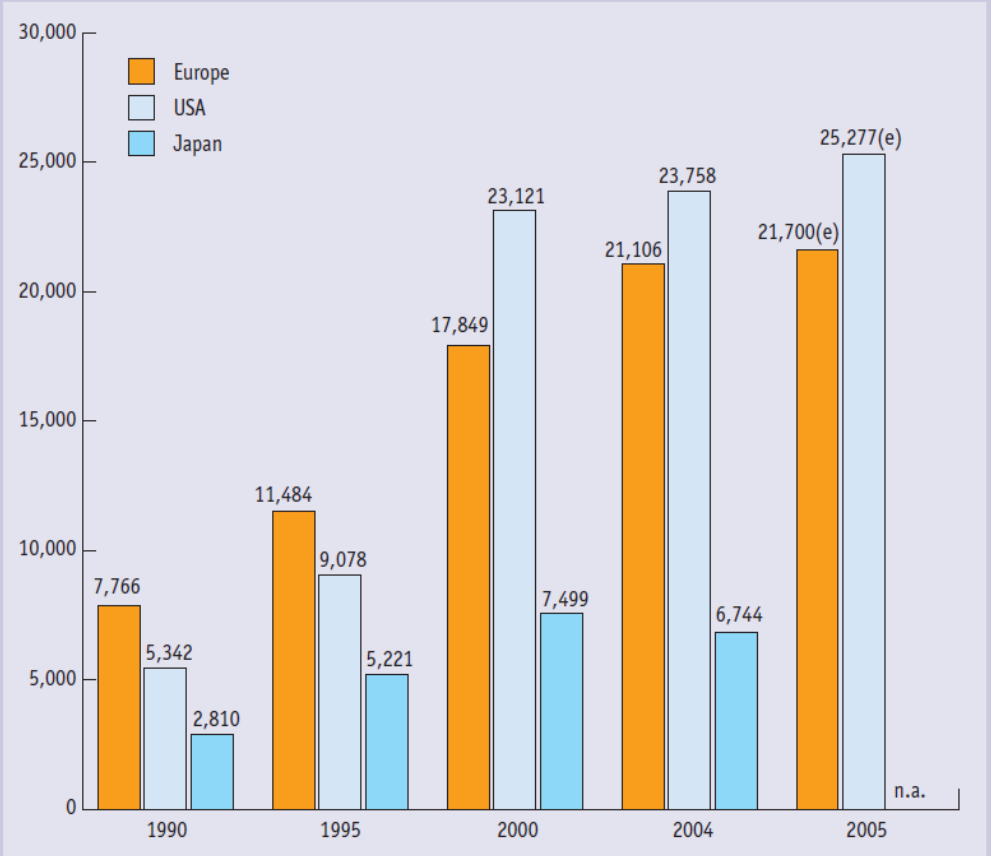


The World


NUMBER OF NEW MOLECULAR ENTITIES (NMES) AND BIOTECHNOLOGY PRODUCTS FIRST LAUNCHED WORLDWIDE 1990-2004
Total NMEs (including biotechnology products)
Biotechnology products
60
50
40
30
20
10
0
36
51
43
40
40
41
36
46
37
41
32
31
28
26
24
1
7
6
2
5
7
6
5
10
9
4
11
2
4
6
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
Source: CMR International

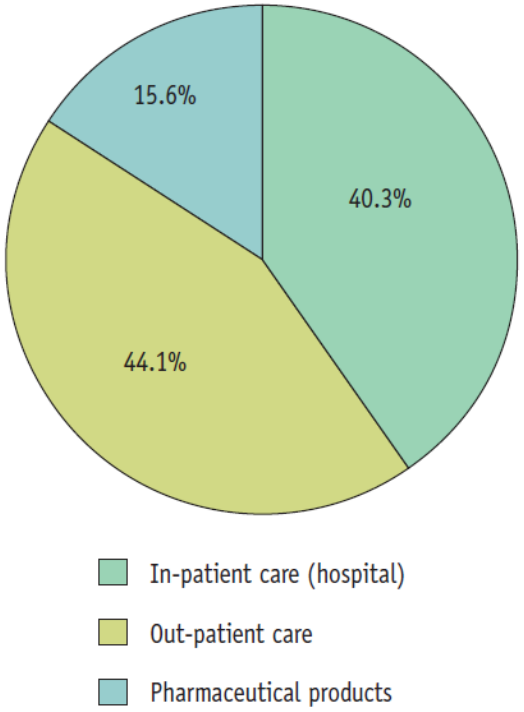
The World

PHARMACEUTICAL R&D EXPENDITURE IN EUROPE, USA AND JAPAN (€ MILLION, CURRENT EXCHANGE RATES), 1990-2005



(e): estimate
Source: EFPIA member associations, PhRMA, JPMA

BREAKDOWN OF TOTAL HEALTH EXPENDITURE IN EUROPE – 2003



Source: OECD Health Data 2005, Statistics and Indicators for 30 countries, October 2005 – EFPIA calculations (non-weighted average for 19 EU & EFTA countries)

TABLE 9: Sales by Geographic Area,* PhRMA Member Companies: 2010

(dollar figures in millions)

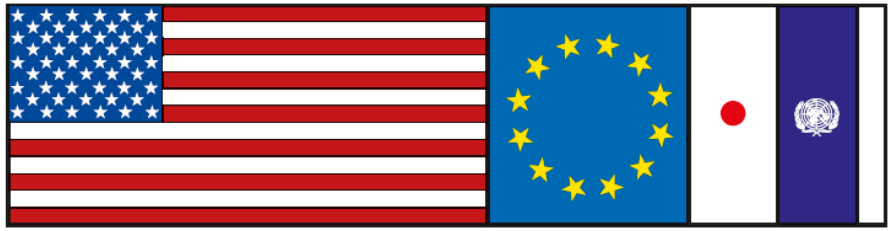
Geographic Area*	Dollars	Share
Africa		
Egypt	$368.1	0.1%
South Africa	789.0	0.3
Other Africa	730.9	0.3
Americas		
United States	$184,660.3	63.4%
Canada	6,787.0	2.3
Mexico	2,538.5	0.9
Brazil	4,101.9	1.4
Argentina	716.2	0.2
Venezuela	1,562.9	0.5
Columbia	753.8	0.3
Chile	274.7	0.1
Peru	190.2	0.1
Other Latin America (Other South America, Central America, and all Caribbean nations)	1,461.8	0.5
Asia-Pacific		
Japan	$13,429.9	4.6%
China	3,286.9	1.1
India	1,091.2	0.4
Taiwan	795.8	0.3
South Korea	1,479.2	0.5
Other Asia-Pacific	2,404.7	0.8
Australia		
Australia and New Zealand	$4,180.8	1.4%
Europe		
France	$9,547.7	3.3%
Germany	7,753.1	2.7
Italy	6,669.8	2.3
Spain	6,329.4	2.2
United Kingdom	5,650.3	1.9
Other Western European	10,956.9	3.8
Czech Republic	703.3	0.2
Hungary	484.1	0.2
Poland	878.3	0.3
Turkey	1,603.7	0.6
Russia	1,410.4	0.5
Central and Eastern Europe (Cyprus, Estonia, Slovenia, Bulgaria, Lithuania, Latvia, Romania, Slovakia, Malta, and other Eastern European countries and the Newly Independent States)	5,572.6	1.9
Middle East		
Saudi Arabia	$622.2	0.2%
Middle East (Yemen, United Arab Emirates, Iraq, Iran, Kuwait, Israel, Jordan, Syria, Afghanistan, and Qatar)	1,468.0	0.5
Uncategorized	—	0.0
TOTAL SALES	**$291,253.5**	**100.0%**

*Sales abroad include expenditures outside the United States by U.S.-owned PhRMA member companies and sales generated abroad by the U.S. divisions of foreign-owned PhRMA member companies. Sales generated abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic sales, however, include sales generated within the United States by all PhRMA member companies.

Note: Total values may be affected by rounding.

SOURCE: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2012.

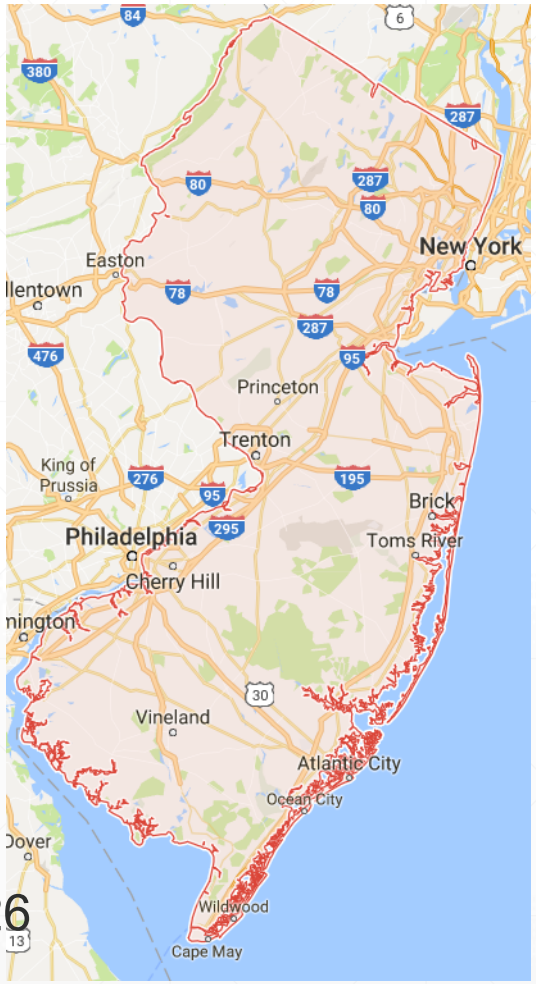
GEOGRAPHICAL BREAKDOWN (BY MAIN MARKETS) OF SALES OF NEW MEDICINES LAUNCHED DURING THE PERIOD 2009-2013



55% USA | 23% Europe | 10% Japan | 9% Rest of the World | 3% Pharmerging

State of New Jersey and Pharma

- GDP of New Jersey is 3.2% on the National GDP
- HealthCare Institute of New Jersey:
  - 78,447 employed in the Biopharmaceutical industry in NJ
- 2014: New Jersey Department of Labor and Workforce Development/Office of Research and Information estimated 115,000 workers in the Biopharmaceutical Life Sciences Cluster (Medical device manufacturing included)
  - 3.6% of the New Jersey private workforce; Nationally: 1.9%
  - $15B in wages or 8.1% of total state wages
- In 2013, there were 1,234 clinical trials ongoing in the state of New Jersey with 25,126 participants



Quick View on Patents in Pharma

- A **patent** (/ˈpætənt/ or /ˈpeɪtənt/) is a set of exclusive rights granted by a sovereign state to an inventor or assignee for a limited period of time in exchange for detailed public disclosure of an invention. An invention is a solution to a specific technological problem and is a product or a process.[1]:17 Patents are a form of intellectual property.

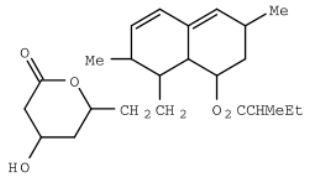
- The procedure for granting patents, requirements placed on the patentee, and the extent of the exclusive rights vary widely between countries according to national laws and international agreements. Typically, however, a granted patent application must include one or more claims that define the invention. A patent may include many claims, each of which defines a specific property right. These claims must meet relevant patentability requirements, such as novelty, usefulness, and non-obviousness. The exclusive right granted to a patentee in most countries is the right to prevent others, or at least to try to prevent others, from commercially making, using, selling, importing, or distributing a patented invention without permission.[2][3]

- Under the World Trade Organization's (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights, patents should be available in WTO member states for any invention, in all fields of technology,[4] and the term of protection available should be a minimum of twenty years.[5] Nevertheless, there are variations on what is patentable subject matter from country to country

3048. Monacolin K and pharmaceutical composition containing it

By: Endo, Akira
Assignee: Sankyo Co., Ltd., Japan

Monacolin K (I) [75330-75-5] is produced by fermn. with Monascus ruber. Thus, M. ruber FERM 4822 was inoculated into 5 L medium contg. glucose 6, peptone 2.5, corn steep liquor 0.5, and NH_4Cl 0.5% and incubated for 10 days at 28° with aeration. The broth was made pH 3 and extd. with EtOAc and the ext. was evapd. The residue was dissolved in 100 mL benzene, and the soln. was washed and extd. with 100 mL 0.2N NaOH. The aq. ext. was acidified and extd. with EtOAc. The EtOAc ext. was evapd. to leave an oil, which was dissolved in benzene and crystd. from aq. acetone to produce 87 mg I. I has anticholesteremic and hypolipemic effects in lab. animals.



I

Patent Information

Patent No.	Kind	Language	Date	Application No.	Date
DE 3006216	A1		Sep 4, 1980	DE 1980-3006216	Feb 20, 1980
DE 3006216	C2		Oct 31, 1985		
JP 55111790	A		Aug 28, 1980	JP 1979-17856	Feb 20, 1979
JP 59025599	B		Jun 19, 1984		
AU 8055673	A		Aug 28, 1980	AU 1980-55673	Feb 19, 1980
AU 532626	B2		Oct 6, 1983		
CA 1129794	A1		Aug 17, 1982	CA 1980-345983	Feb 19, 1980
BE 881825	A1		Aug 20, 1980	BE 1980-199476	Feb 20, 1980
DK 8000730	A		Aug 21, 1980	DK 1980-730	Feb 20, 1980
DK 149095	B		Jan 20, 1986		
DK 149095	C		Jun 16, 1986		
FI 8000506	A		Aug 21, 1980	FI 1980-506	Feb 20, 1980
FI 66427	B		Jun 29, 1984		
FI 66427	C		Oct 10, 1984		
NO 8000451	A		Aug 21, 1980	NO 1980-451	Feb 20, 1980
NO 153974	B		Mar 17, 1986		

QUICK LINKS
0 Tags, 0 Comments

PATENT INFORMATION
Sep 4, 1980
DE 3006216
A1

APPLICATION
Feb 20, 1980
DE 1980-3006216

PRIORITY
Feb 20, 1979
JP 1979-17856
Feb 20, 1980
DK 1980-730

SOURCE
Ger. Offen.
17 pp.
Patent
1980
CODEN:GWXXBX

ACCESSION NUMBER
1980:584283
CAN93:184283
CAPLUS

LANGUAGE
German

Typical Big Pharma Composition of Matter, Small Molecule Patent

- ~750 compounds with complicated structure relationships
- Compounds never before made
- Dozens to hundreds of claims
- Prosecuted in multiple countries
- Generally prosecuted for 5-10 years with generation of multiple continuations, divisional patent applications
  - Ex. Over 3000 patents include the structure of Lovastatin
- Major approved drugs have composition of matter, crystals, method of preparation, therapeutic applications, formulations, etc.

Summary and Conclusions

- Drug Development is risky
- Enormous investment with potential blockbuster payoffs
- Sizable fraction of personal/state/country/world economy
- Large workforce with multiple disciplines represented
- Incredible changes continue in the industry

Thank you!

My nearly 37 years in the Pharmaceuticals has been a wonderful experience.
Consider a career in Pharma!

iJOBS Workshop: Drug Development in Biotechnology - Agenda

- 9:30 – 9:45AM Introduction and Purpose of the Symposium – Janet Alder
- 9:45 – 10:15 Overview of the Pharmaceutical Industry – Larry Wennogle
- 10:15 – 10:25 Questions/Discussion
- 10:25 – 10:55 Technologies for discovery of new drug candidates – Mary Konsolaki
- 10:55 – 11:05 Break
- 11:05 – 11:35 CNS Drug Development (What is a “drug target”) – Sam Kongsamut
- 11:35 – 12:05PM Clinical Development of a Pharmaceutical Agent for Food and Drug Administration (FDA) approval – Ira Daly
- 12:05 – 12:35 The story of Entresto – Novel therapy for Heart Failure - Randy Webb
- 12:35PM Working lunch will be served
- 1:00 – 1:30 Funding the Pharmaceutical and Biotechnology Industry – Ben Bowen
- 1:30 – 2:00 Break out groups – Attendee will break out into small ~6 person groups to develop a plan to organize a biotech company designed to develop pharmaceuticals.
- 2:00 - 2:30 The long and winding road to a marketed drug – Ron Steele
- 2:30 – 3:00PM General Discussion including answers to questions submitted in advance of the symposium by participants.
- 3:00 – 4:00PM Mixer

Backup Slides

The Pharmaceutical Industry Has Had A Significant Impact on Human Health

- **Hepatitis C** – a once incurable disease that now has **cure rates above 90%**
- **HIV/AIDS** – once a death sentence, it's now a chronic **manageable** condition
- **Cancer** – **83%** of children with cancer now **survive**, compared to 58% in 1970
- **Vaccines** – **more than 730,000** children's lives have been **saved** in the last 20 years in the United States because of advances in vaccines.

https://youtu.be/-5X2kzIDroA

Developing pharmaceuticals is a costly and risky business

Figure 1 Costs per approved molecule are unsustainably high

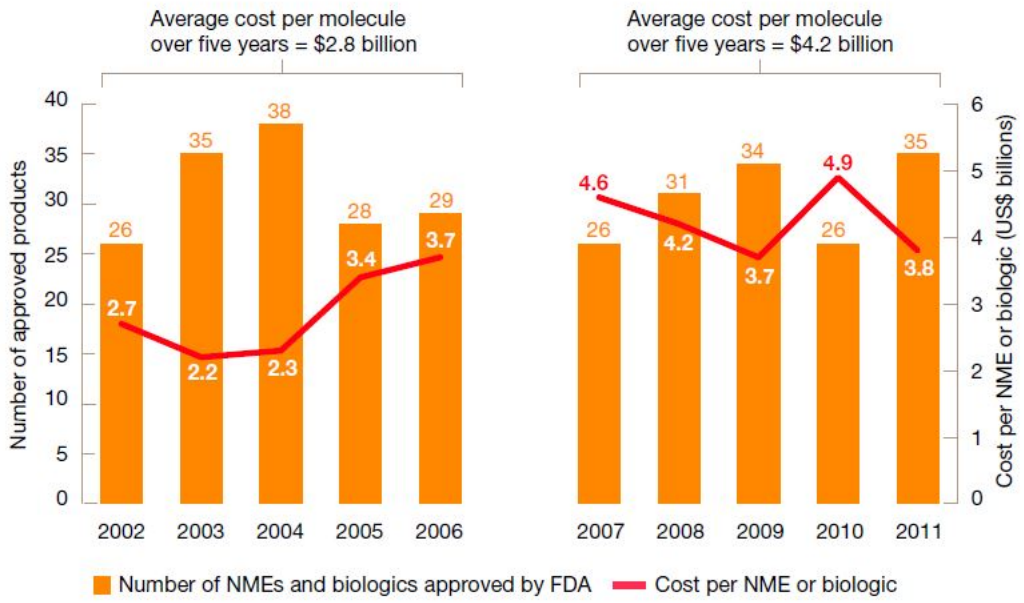


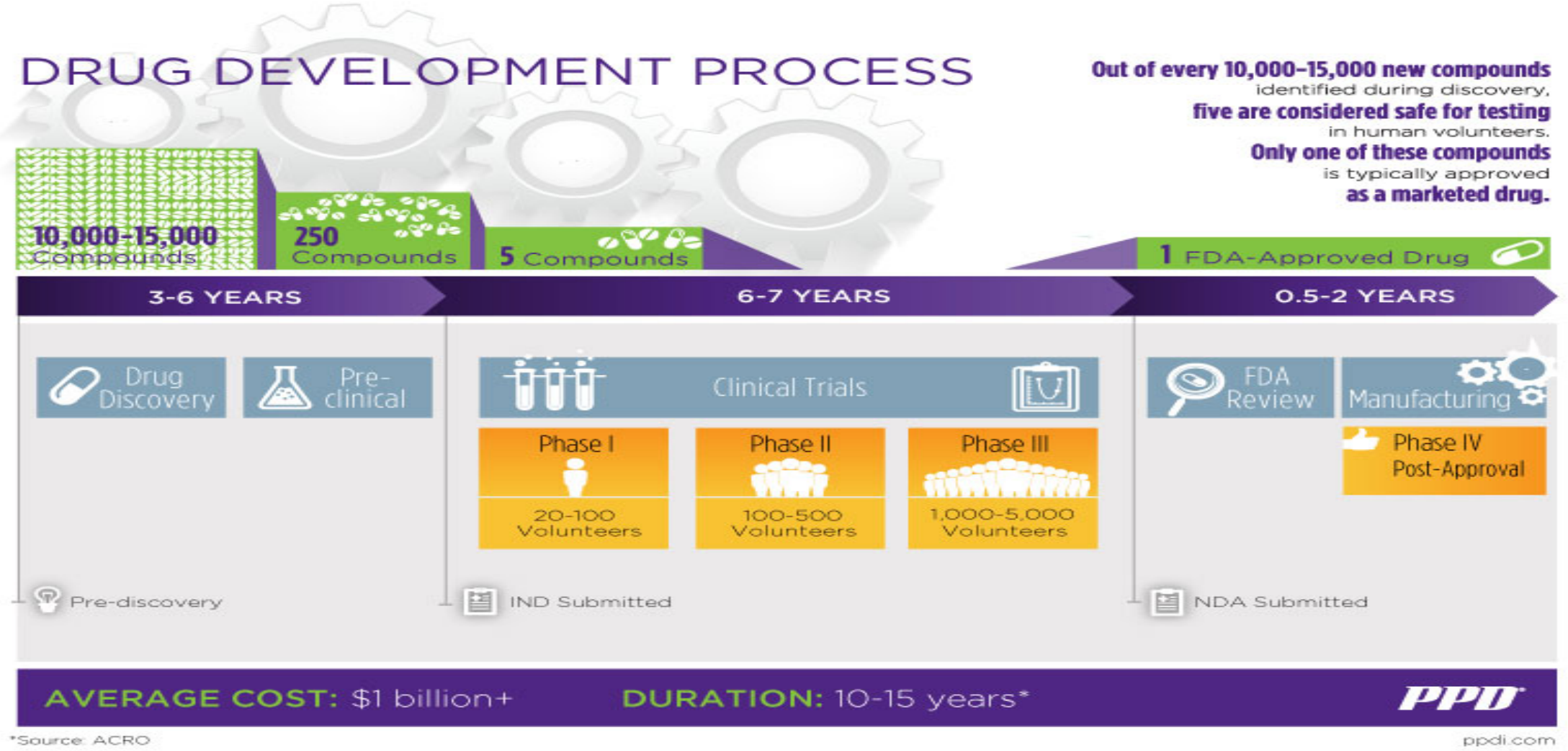
Table 2 Failure rates in clinical trials have soared in the past 20 years

	Attrition rates		Current reasons for failure
	1990	2010	
Phase I	33%	46%	
Phase II	43%	66%	Insufficient efficacy (51%)
			Safety concerns (19%)
			Strategic issues (29%)
Phase III	20%	30%	Insufficient efficacy (66%)
			Safety concerns (21%)

Sources: Fabio Pammolli et al., 'The productivity crisis in pharmaceutical R&D'; Steven M. Paul et al., 'How to improve R&D productivity; and John Arrowsmith, 'Trial watch: Phase II failures: 2008-2010'; 'Trial watch: Phase III and submission failures: 2007-2010'; and 'A decade of change'

Comparing development of different product types

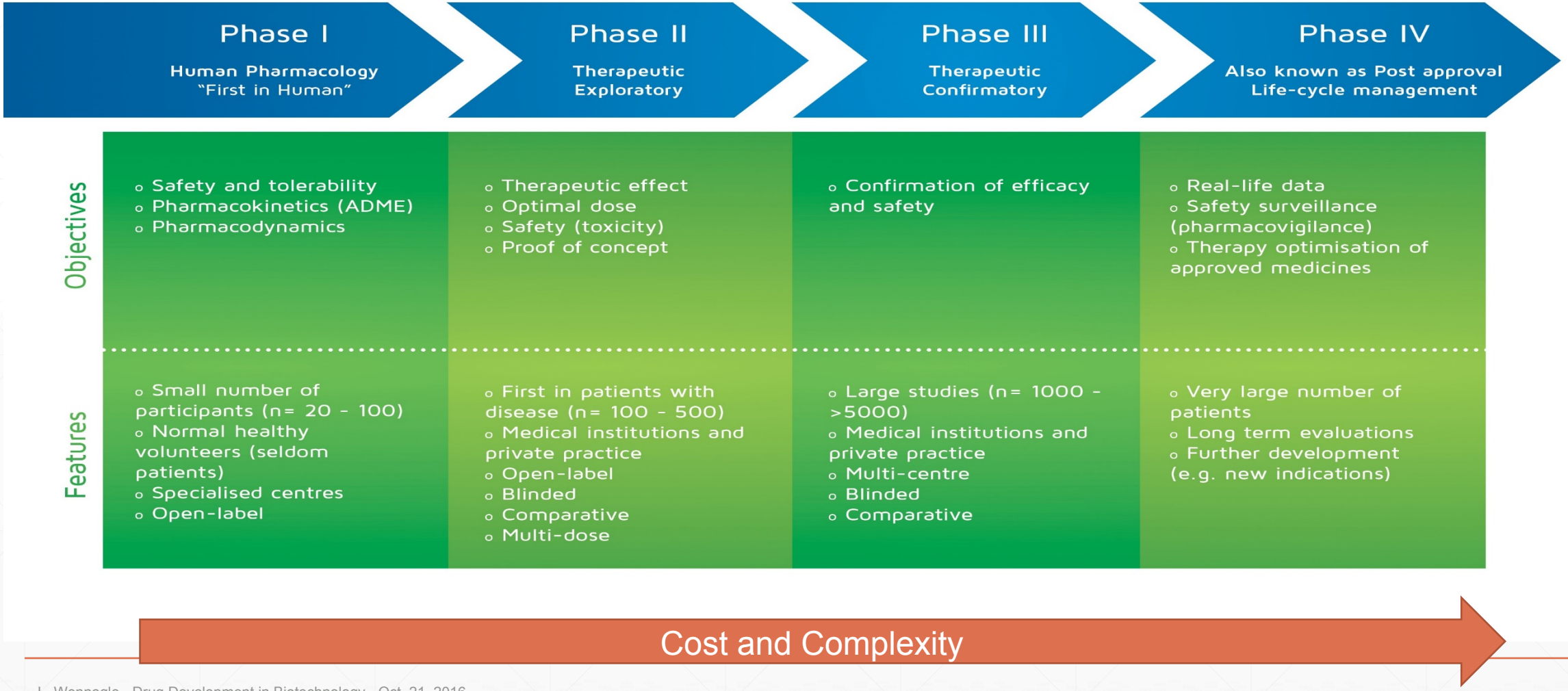
Attribute	Small molecule (pill)	Large Molecule (biologic)	Medical Device
Cycle time	10-15 yrs	10-12 yrs	3-7 yrs
Cost to develop	>$2.5B including capital and failures	>$2.5B including capital and failures	$31M
Regulatory Pathway	NDA (safe and efficacious)	BLA Safe and efficacious)	510K (clinical benefit or substantial equivalence)
Price	++	+++	+
Superiority, cost effectiveness, health economic benefit			

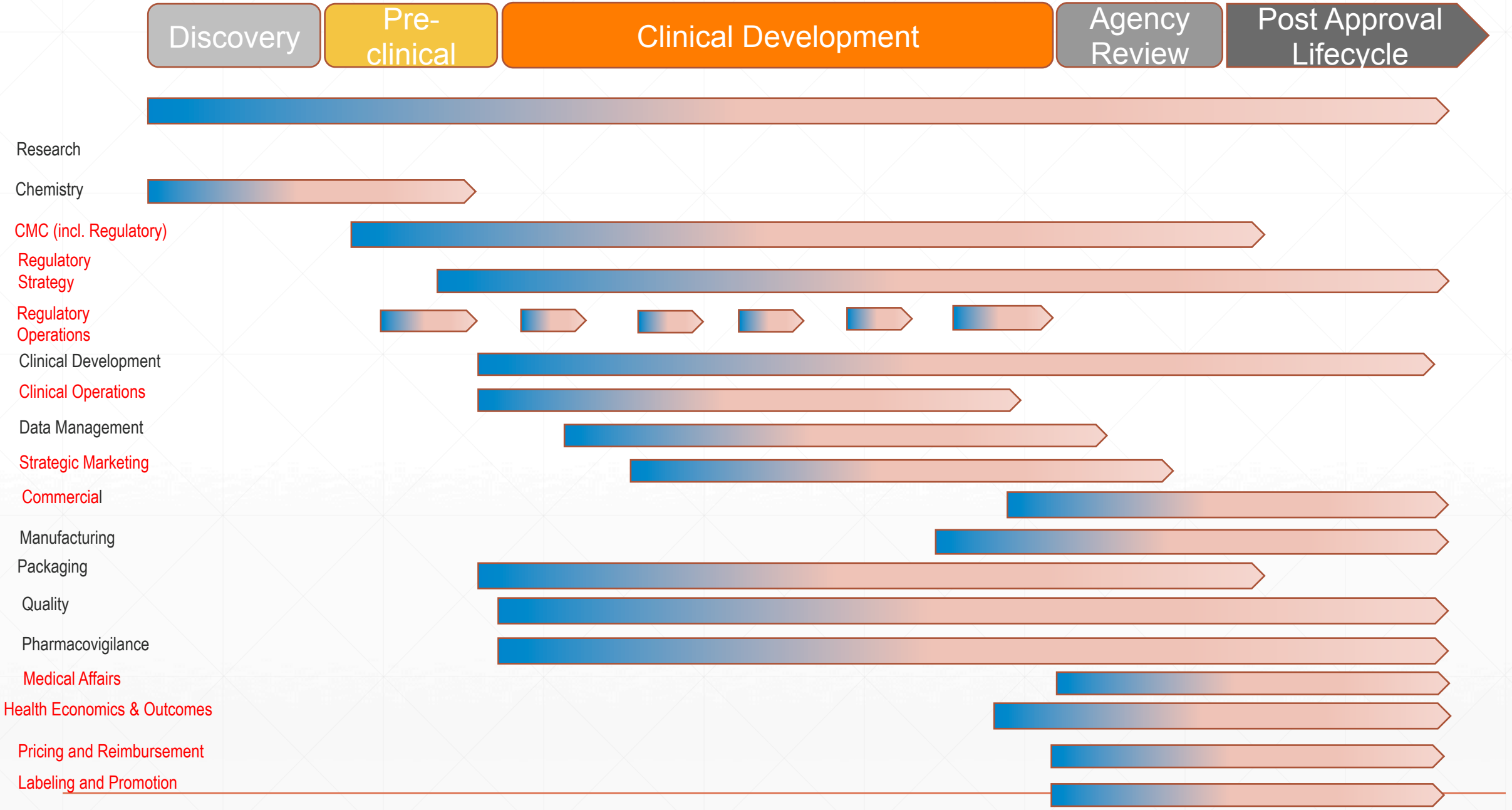

DRUG DEVELOPMENT PROCESS
Out of every 10,000–15,000 new compounds identified during discovery, five are considered safe for testing in human volunteers. Only one of these compounds is typically approved as a marketed drug.
10,000–15,000 Compounds
250 Compounds
5 Compounds
1 FDA-Approved Drug
3-6 YEARS
6-7 YEARS
0.5-2 YEARS
Drug Discovery
Pre-clinical
Clinical Trials
FDA Review
Manufacturing
Phase I
20-100 Volunteers
Phase II
100-500 Volunteers
Phase III
1,000-5,000 Volunteers
Phase IV Post-Approval
Pre-discovery
IND Submitted
NDA Submitted
AVERAGE COST: $1 billion+
DURATION: 10-15 years*
PPD
*Source: ACRO
ppdi.com

Lab to Patient Journey: Investigational New Drug (IND)

- Content of the IND
  - Cover letter (various administrative information and commitments)
  - General investigational plan
  - Previous human experience
  - Investigator Brochure
  - Drug substance and formulation
  - Summary of pharmacology and toxicology
  - Summary of biologic disposition and pharmacokinetics
  - Clinical protocol (study design, dose, etc)
  - CMC (physical, chemical , biological characteristics)
    - Quality, impurities, strength, stability, shelf life, manufacturing process, dose form
  - Labeling
  - Environmental impact
  - Drug dependence and abuse potential

Lab to Patient Journey: Clinical Trials





Those functions in red often have separate organizations outside of the headquarters country and in various regions

Regulatory Affairs Activities and Deliverables

- Strategy
  - Assist with protocol and development plan creation
  - Country and region-specific regulatory agency strategy
  - Leads preparation and conduct of agency meetings
  - Pediatric Investigation plan
  - Point of contact for all Agency correspondence
  - Draft labeling with clinical
- Operations
  - Regulatory Information Management
  - Submission planning
  - Coordination of submission preparation
  - Agency interactions
  - Submission publication
  - Document archiving

Strategic Marketing Activities and Deliverables

- Target product profile (with team)
- Global Marketing Strategy (what markets, price, etc)
- Communication plans
- Global sales and product forecasts
- Label claims needed
- Global launch plan
- Label development

Medical Affairs Activities and Deliverables

- Publication strategy (abstracts, presentations, papers)
- Investigator sponsored trials
- Medical Advisory Boards
- Medical Science Liaison (to physician; relatively new role)
- Patient, physician, payer education
- Phase IV clinical trials design, conduct, reporting and publication
- Key opinion leader and patient advocacy group education/interaction

A number of challenges have led to declining (or steadily low) productivity while costs continue to increase

- Longer cycle times
- Higher efficacy and regulatory hurdles
- Increased competition
- Comparative effectiveness and value-based pricing and stricter reimbursement
- Despite large investment limited impact of personalized medicine
- Increased complexity of targets

Figure 3 Pharma's scientific productivity has flatlined for a full decade

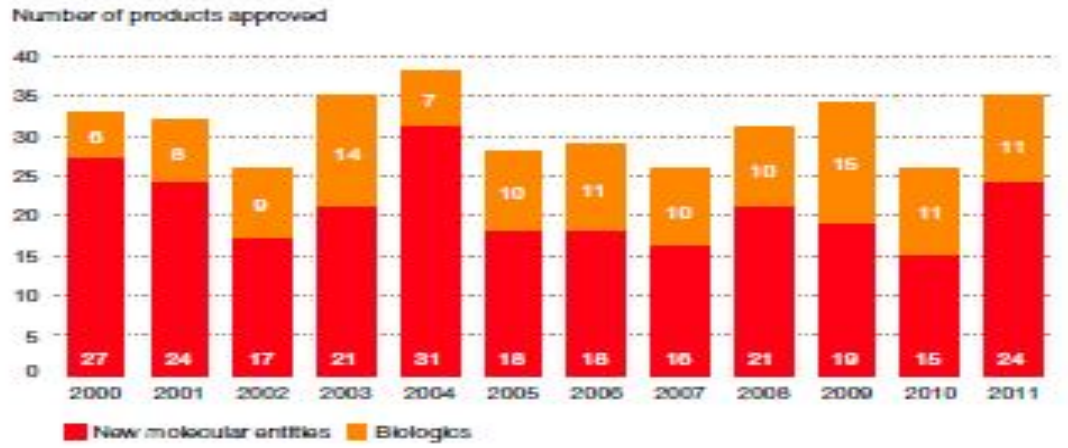


Figure 1 Costs per approved molecule are unsustainably high