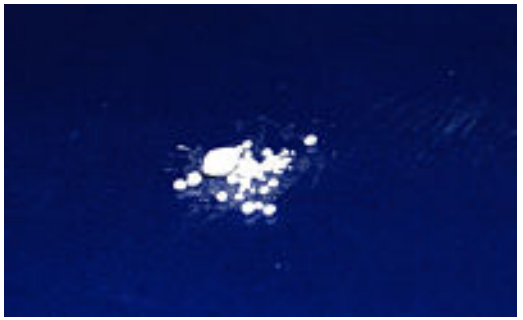
Modern Pharmaceutical Science

History, regulatory aspects, and current landscape

ISAT 635 ♦ April 2012

Not-so-modern pharmaceutical science[1]

- Prior to the mid 1800's, the 'cure' could kill you (calomel treatment, bloodletting)
- Homeopathy and patent medicines: First do no harm
- The first pharmacologically useful substances appreciated in the West were natural products
  - Quinine
  - Digitalis
  - Antipyrine
  - Aspirin
  - Quinine



Calomel : $HgCl^2$

- Ignaz Semmelweis: microbial theory of disease (1961)

1. M.S. Lesney "Patents and Potions" in *The Pharma Century* American Chemical Society Pubs (2000) p 20 2. Images from Wikipedia.org "patent medicines" and "calomel"

Science drives medicine into the 20th century

- The development of “immunologicals”
  - Attenuated Rabies vaccine: Pasteur
  - Tetanus, diptheria: Von Behring and Kitasato
  - Tuberculin antitoxin: Hoechst Pharma (1892)

- An appreciation arose for product standardization and control
- The roots of Medicinal chemistry
  - Perkins (1856)
  - Antifebrin (1886)
  - Phenacetin (Bayer 1887)
  - Acetylsalicylic acid (Hoffman, 1899)

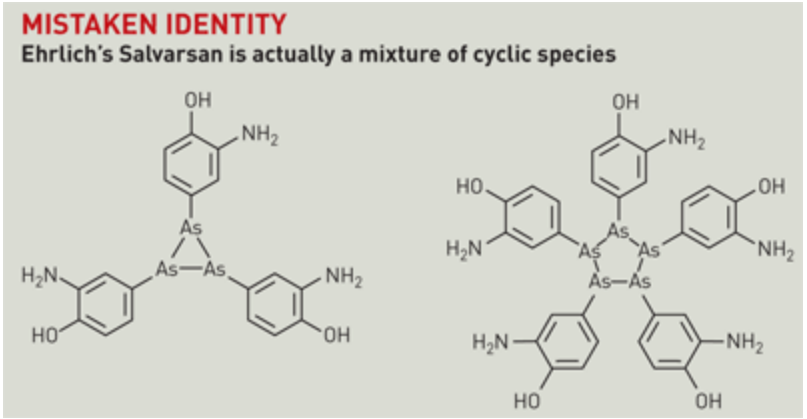
- The pharmaceutical industry is born!

Louis Pasteur: fearless

1. M.S. Lesney “Patents and Potions” in *The Pharma Century* American Chemical Society Pubs (2000) p 22 2. Image from Wikipedia “Louis Pasteur”

Biochemistry and Metabolic Medicine:1880-1910

- Biochemical breakthroughs
  - Myedema (Sheep thyroid injections)
  - Addison's disease (animal adrenal glands)
- Metabolic understanding grows
  - Landsteiner: human blood types (1900)
  - Eugene Opie: diabetes
  - Mikhail Tswett: column chromatography (1906)
  - Arrhenius: pH measurement (1909)
  - Takamine: discovery of adrenaline
  - Ehrlich: Salvarsan
- Logical Chemotherapy blossoms… and stumbles: influenza.



From Chemical and Engineering News, "The Top Pharmaceuticals That Changed The World" Vol. 83, Issue 25 (6/20/05)

1. M.S. Lesney "Patents and Potions" in *The Pharma Century* American Chemical Society Pubs (2000) p 28-31

1920-1930s

- Further study of physiological disorder: Diabetes mellitus (F. Banting)
- Early process chemistry: estrogen, testosterone, corticosteroid

Antibiotic revolution!

- Domagk (I.G. Farben): Prontosil → sulfonamides
- A. Fleming: Penicillin

Virology

- Stanley: The tobacco mosaic virus
- The scourge of Polio

“Vital Amines” and metabolic deficiency

- Ascorbic acid, 2-methylnaphthoquinone

1940-1950s

- Chain, Florey: isolation and scaleup of Penicillin (Merck, Pfizer, Squibb)
- Malaria treatment: Quinine, Atabrine (Abbott, Lilly, Merck)
- Streptomycin and Tuberculosis
- Tetracycline antibiotics: broad spectrum antibiotics

Developmental genetics / virology

- Avery, Macleod, McCarty: the genetic role of DNA in cells
- Weller, Robbins: growing the poliovirus

Analytical advances:

Early NMR spectroscopy

A.J.P Martin: liquid-liquid chromatography

A.T. James: GLC

1940-1950s

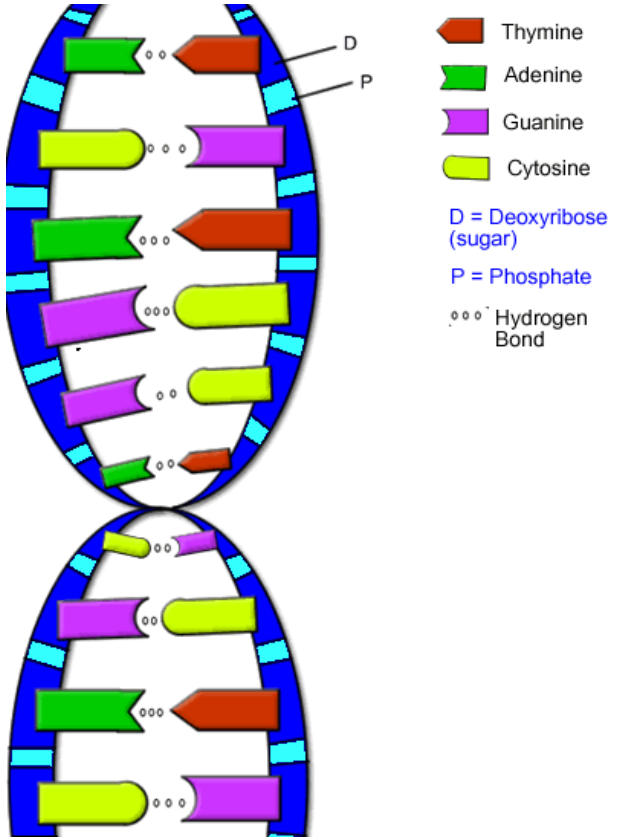
DNA era / protein science

- Watson and Crick elucidate the structure of DNA (1953)
- Ochoa: RNA polymerase
- Vigneaud: hormone oxytocin synthesized (1954)
- J. Kendrew: solved first 3-D protein structure (1957)

The war on Polio

- Jonas Salk: the killed virus approach
- Sabin: attentuated oral polio vaccine (1957)

- 1958: Jack Kilby and integrated circuitry (TI)
- Pincus, Djerassi: oral contraceptives



From http://www.biologycorner.com/bio1/DNA.html

1960-1970s

Commercial pharmacy

- Sedatives (librium, valium , Miltown)
- Oral contraceptives
- Tragedy: thalidomide

Commercial instrumentation available

- GE X-Ray diffraction
- LKC Model 9000 GC/MS
- DuPont Liquid Chromatograph
- JOEL nucleic acid analyzer

Fortified Food:

Cyclamate (Diet Rite)

Processed foods[2] (Tang, Wonder bread)

Child with congenital abnormalities associated with Kevadon[1]

1. Thalidomide Victim's Association of Canada Website (http://www.thalidomide.ca/en/index.html) 2. M. Pollan "In Defense of Food" (2007 3. Ettlinger, S. "Twinkie, Deconstructed" (2006)

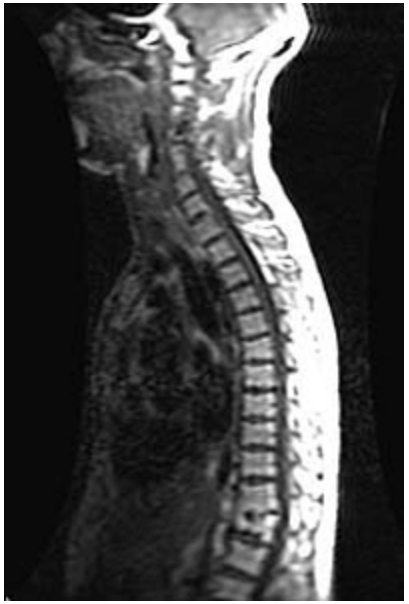
1960-1970s

NCI: The fight against cancer

- Program between NIH, industry, and universities
- 15000 new compounds tested
- Infectious model of Cancer?
- RNA transcriptase viruses: Retroviruses

A measure of success

- Allogenic bone marrow transplants
- Autologous marrow transplantation: lymphoma (1977)
- Damadian: “Tumor detection by Nuclear Magnetic Resonance”(Science, 1971)
- Tomography / MRI

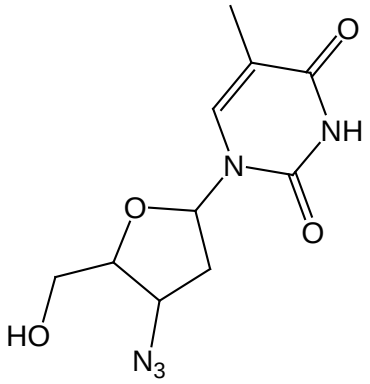


MRI imagery from http://www.howstuffworks.com/mri8.htm

1980-1990s

HIV / AIDS

- Gallo / Montagnier determine viral origin
- Immunology advances (B cells / T cells)
  - Arthritis
  - Lupus
- AZT: orphan drug



Zidovudine: AZT.

Biotechnology

- PCR: DNA replication
- Genetically engineered drugs
- The human genome project (Watson,1989)

1980-1990s rational therapeutic engineering

Combinatorial technology /computational advances

- High throughput Screening (HTS)
- Bioinformatics: proteomics

Human Biotechnology

- Stem cell technology (traumatic spinal injury, Parkinson's disease)
- Tissue engineering (Carticel)

Ethical concerns

- Cloning
- Transgenic food / GMOs (Monsanto)
- Bacterial resistance
- Pharmaceutical marketing

Regulation: a historical overview[2]

The early 1800's: The wild west of medicine

- Drug adulteration
- Lax labelling policy
- General chicanery

- **US Congress** establishes a 'vaccine agent' in 1813 in response to distribution of spurious vaccines
- **The United State Pharmacopeia (USP):** Lyman Spalding (1820)
- **Lewis Caleb Beck (1846)** "Adulteration of various substances used in Medicine and the Arts, with the means of Detectig them: Intended as a Manual for the Physician, Apothecary, and the Artisan"
- **The Mexican American War** (1846-1848): "A sense of outrage"
- **Drug Import Act of 1848:** Establishes the USP as the source of standards for drug appraisal at ports

Adapted from J. Swann, in "The Pharmaceutical Regulatory Process" (2005) p3

Regulation: a historical overview[2]

The early 1900's

- Tragedy: St. Louis tetanus cases
- **Biologics Control Act (1902):** Annual licensing based on inspections, and mandatory record keeping.

- **AMA / APA joint compendium combats patent medicine:** *New and Unofficial Remedies (*1905*)*
  - Fact-based submission to support drug claims
  - Nonlegal (but effective) Penalties

- **The Marketplace**
  - Eli Lilly: Succus Alterans (based on Creek Indian formula for syphilis, rheumatism!)
  - Parke-Davis: 20 chemically assayed botanical extracts
  - "Benjamin Bye's Soothing Balmy Oils" (Cancer)
  - "William Radam's Microbe Killer"

Adapted from J. Swann, in "The Pharmaceutical Regulatory Process" (2005) p10-12

The Federal Food and Drugs Act of 1906

Muckraking

- "The Great American Fraud" of medicine (Collier's Magazine 1905)
  - False testimonials
  - "red clauses"
- "The Jungle" (Upton Sinclair)

H.W. Wiley and the Food and Drugs Act of 1906

- Regulated interstate commerce of adulterated / misbranded materials
- Drug definition: "any substance intended for the cure, mitigation or prevention of disease in humans"
- Drug strength based on USP / NF
- Labelling requirements for dangerous ingredients: cocaine, heroin, alcohol
- Penalties: misdemeanor, $500 fine, up to 1 year imprisonment
- Establishes FDA under a National 'Chief Chemist'

Image from wikipedia.org "patent medicine"

Weaknesses of the 1906 act

- **Enforcement difficult**, and weighted toward food regulation
- **Supreme Court Decision (1911):** “Dr. Johnson’s Mild Combination Treatment for Cancer”
- “**BanBar**” and expert testimony: Horsetail weed extract for Diabetes? (1923)
- Pharmacist compliance poor (DC)
- **Overly collaborative relationship** between regulators and industry
- Weak penalties

1938 Food, Drug, and Cosmetic Act

"**Elixir Sulfanilamide":** 107 killed. DEG ≠ glycerin.

1938 FDCA provided for

- Identity standards
- Required labeling and instructions for self medication / use
- Instituted court injunctions for violative products
- Mandated that manufacturers document product safety before marketing
- Premarketing provision was the birth of the New Drug Application (NDA)

From toxipedia.org

Post-war regulation

- **1951 Durham-Humphrey Act**: provisions for prescriptive drugs / OTCs
- **Amphetamines / barbiturate abuse**: The 1965 Drug Abuse Control Amendments → DEA
- **Insulin Amendment** (1941): test every batch
- **Penicillin amendment** (1945)

Persisting problems:

- Hepasyn: treating cancer with Arginase
  - Lack of efficacy can confer safety problems
  - Eaton Laboratories: Altafur (furaltadone)

Adapted from J. Swann, in “The Pharmaceutical Regulatory Process” (2005) p 26-28

Kefauver Act (1962)

- **Estes Kefauver** (TN senator) investigates drug pricing
  - Development expenses
  - FDA relationship with regulated interests
  - Patent / monopoly status
- **Kefauver Act provisions**
  - Extend FDA's authority over drug production and advertising (FTC authority→FDA)
  - Repeal drug clearance provision of 1938 FDCA (60 day review period)
  - Advertising must include explicit and prominent warning
  - Sponsors must show that **drugs are effective**, in addition to being safe.
  - Compliance with GMPs

Francis Kelsey[2]

- **Impetus**: William S. Merrell Co. and Kevadon
  - FDA's Francis Kelsey scrutinizes NDA: pregnancy data?
  - Congenital birth defects in DE: drug withdrawn before US marketing.

Adapted from J. Swann, in "The Pharmaceutical Regulatory Process" (2005) p 30-31 2. Image from Wikipedia.org "Francis Oldham Kelsey"

Post-Kefauver Act regulation

- **1962 Grandfather clause**: some drugs exempted from efficacy requirements (but not safety)
- **DESI review:** Drug Efficacy review required for pre-1962 drug substances
- **The Orphan Drug Act of 1983**
  - Federal incentives for drug development of medicines for ‘unprofitable’ indications
  - Tax incentives
  - 7 year exclusivity period for nonpatentable drugs

Post-Kefauver Act regulation

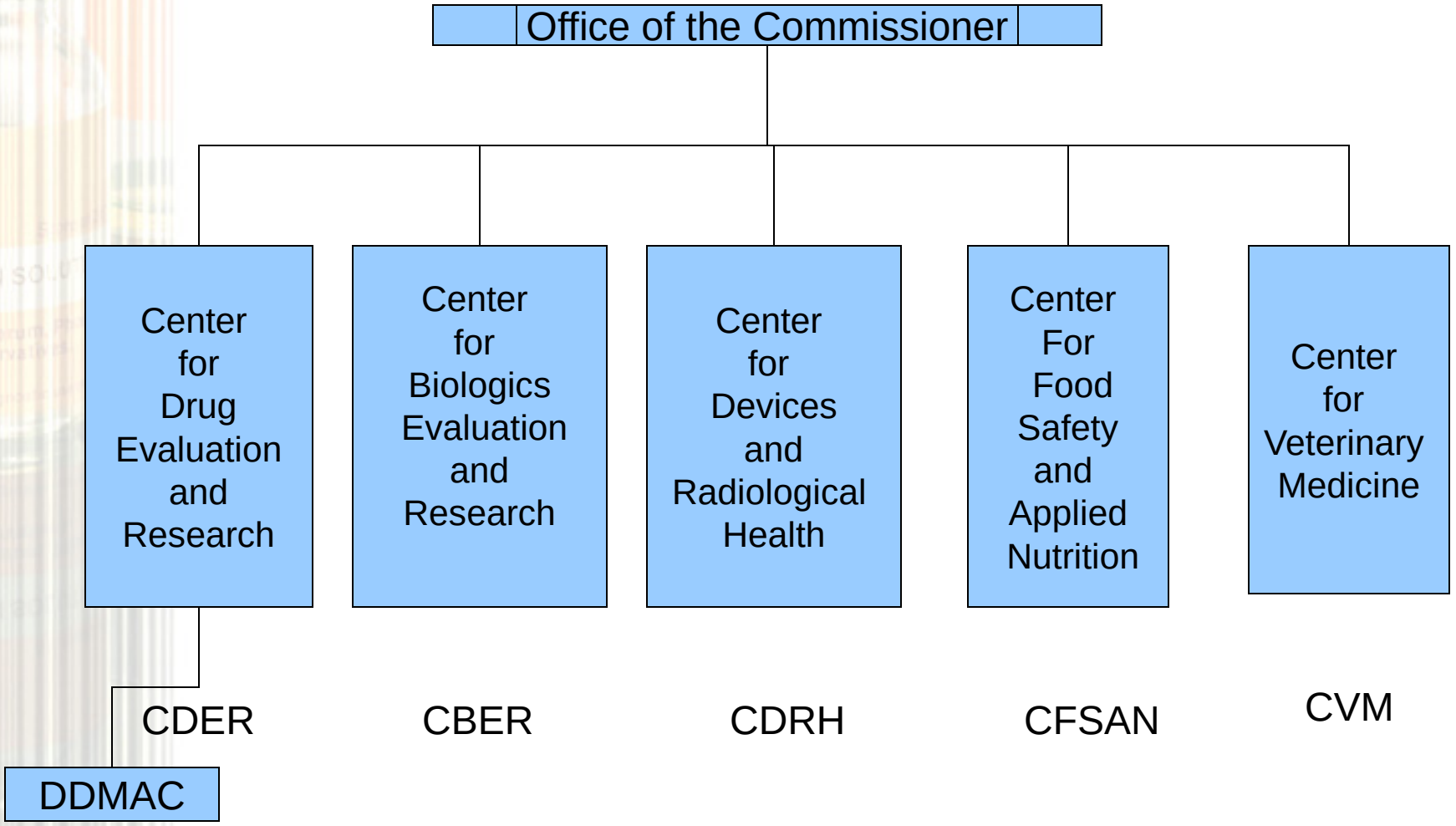
- **1984 Waxman-Hatch reform:** balance the needs of innovator company, consumers, and generic drug manufacturers
    - Expedited approval process: ANDAs
    - From 1984-2004, generics have increased from 19-47% of prescribed medications
    - Originator patents listed in ‘Orange Book’

- **The Prescription Drug User Fee Act of 1992**
    - Set limits on NDA / BLA + supplement fees
    - Action on 90% of ‘standard’ applications in 12 months

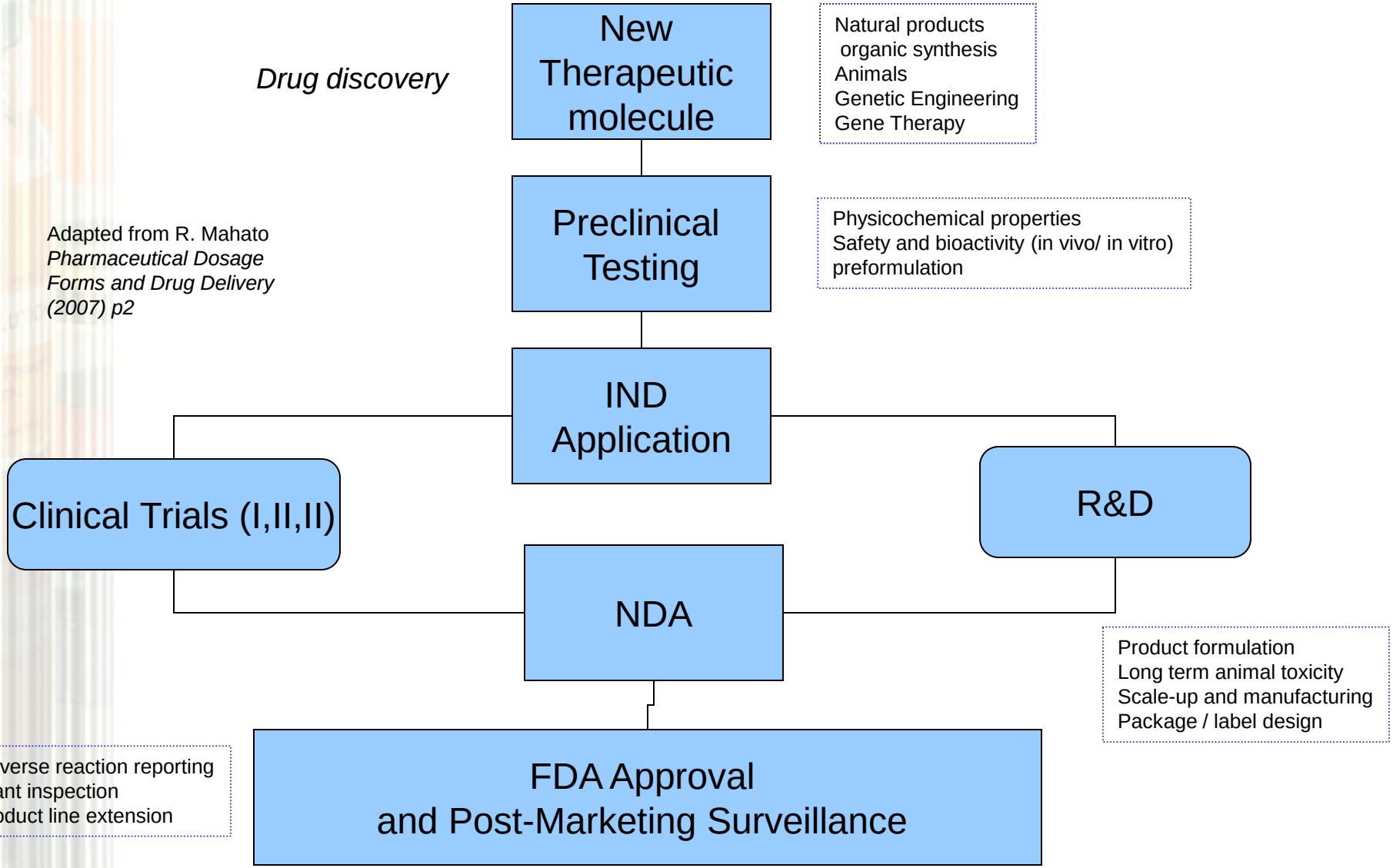
- **Food and Drug Administration Modernization Act of 1997**
    - Pediatric studies
    - Expanded access to investigational therapies and Diagnostics
    - Increased reporting requirements of post-marketing approval studies
    - ‘Fast Track’ NDA for unmet medical needs

Adapted from Gross, et al., in “The Pharmaceutical Regulatory Process” (2005) p 108

The FDA today



Drug product development and approval: overview.



New Drug Application (NDA)[1]

After phase III clinical trials are finished, a company submits the results of all studies to FDA to obtain approval for sale and marketing in the US.

- Average NDA length: 100,000 pages (!)
- FDA formally allowed 6 months to review
- Average review time in 2001: 16.4 months

FDA reviewers must determine from NDA data that:

- Drug is safe and effective for proposed uses
- The drug's benefits outweigh its risks
- The drug proposed labelling is appropriate
- Manufacturing CMC is appropriate

1. R. Mahato *Pharmaceutical Dosage Forms and Drug Delivery (2007) p7*

The pharma industry today

- ‘Big Pharma’ profitability increasingly driven by the sales performance of ‘blockbuster’ drugs.
- Generic competition: the role of IP protection
  - Statins (Zocor)
- 2007 saw only 16 NMEs approved[1]
- Life cycle extension strategies (Zetia + Zocor = Vytorin)

2008 Earnings overview

US	Sales	Earnings	profit margin (%)
Abbott Laboratories	25914	4429	17.1
Bristol-Myers Squibb	19348	2700	14
Eli Lilly	18633	3863	20.7
Merck and Co.	24197	7020	29
Pfizer	48613	15300	31.5
Schering-Plough	12690	2259	17.8
Wyeth	22399	4810	21.5
EU			
AstraZeneca	29599	5627	19
GlaxoSmithKline	45370	15840	34
Novartis	39800	11968	30.1
Roche	40983	10160	24.8
Sanofi-Aventis	41316	10252	24.8

Figures are in USD millions. 1) Adapted from Chemical and Engineering News 25 February 2008 p29.

Phases – and duration- of drug development.

Preclinical testing	Clinical Trials	FDA	Postmarketing Surveillance
synthesis Characterization Toxicity Bioactivity (in vitro - cell culture) (in vivo - ADME / Tox)	Phase I 20-80 healthy volunteer safety profiles drug tolerance Phase II Patients (100-300) Controlled, randomized trials Double blinded Decision on final dosage form Phase II Patients (1000-3000) expanded / uncontrolled trials confirm effectiveness Labelling decision	Review and approval	Phase IV postmarketing testing report adverse side effects report product defects
3-5 years	1.5+2+4 = **7.5 years**	**6-10 months**	
~5000 compounds	<1% enter clinic	1 approved	

IND submission NDA filing NDA approval

Adapted from R. Mahato *Pharmaceutical Dosage Forms and Drug Delivery (2007) p2*

Peripheral disciplines

- Pharmacology
- Pharcognosy
- Pharmacy
- Drug discovery (HTS, computational modeling, proteomics)
- Formulation
  - Dosage forms (vaccines, semisolids, transdermals, oral)
  - Excipients
  - Stability
  - Preformulation
- Process science
- Biostatistics
- Drug delivery
- Contract manufacturing / packaging

Discovery and development

- Molecular Modeling
- Organic Synthesis (chemical, biological, biotechnological)
- Animal origin (insulin)
- Formulation development (preformulation goals, formulation studies)
- Process chemistry & engineering
- Genetic engineering
    - monoclonal antibodies: specific protein bonding
    - Recombinant DNA: protein synthesis

Active Pharmaceutical Ingredients (APIs) and excipients

Manufactured to Good Manufacturing Practices (GMPs)

- Based on ICH (International Conference on Harmonization) Q7A guidelines
- Preapproval inspections (PAI)
- 483 warning

Compendial standards (USP, JP, EP): API official monographs

Drug Master Files (Type I, II): DMF

- US: reviewed by FDA when referenced by applicant
- Contains confidential Chemistry, Manufacturing and Controls (CMC) information
    - Impurity profile
    - Facility layout
    - Raw materials, solvents, catalyst disclosure
    - Sample batch record
    - Raw materials specification data

Drug Development: Costs

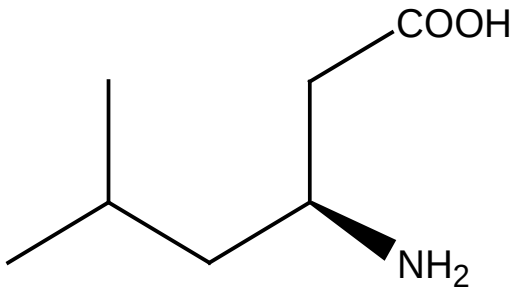
- Typical development cost: $802 million[2]
- Timeframe: 10-15 years
- Me, Too! 75% of approved drugs in 2005 are Derivatives of proven medicines[1]
- "R&D Spending by US Pharma and Biotech Firms Reaches Record High"
  - $**58.8 billion** in research and development (R&D) in 2007[3] (Pharmaceutical Research and Manufacturers of America (PhRMA) and Burrill & Company)
  - 18% of sales on R&D
- Marketing[1]
  - Industry spends $29 billion / year in promotional expenses
  - Detailing: $18.9 billion in samples of brand-name drug substances
  - Off Label promotion: Eli Lilly and Zyprexa

1. Consumer Reports, November 2007 2. R. Mahato *Pharmaceutical Dosage Forms and Drug Delivery (2007) p2 3.* Van Arnum, P. ePT--the Electronic Newsletter of Pharmaceutical Technology 3 April 2008

Licensing

Increasingly, “Big Pharma” is looking to “little Pharma” for good ideas.

- Lyrica (Pregabalin): Northwestern University’s $700 million royalty
- Taxol (Florida State): Money doesn’t always make you happy[1]



Lyrica (Pregabilin)
Pfizer

1. Chemical and Engineering News, 10 March 2008 p 56 - 61

The pipeline future challenges

The pharmaceutical industry is facing a number of relatively new challenges:

- Aggressive competition from sophisticated generics producers
- (over)reliance on blockbuster products
  - "Merck, Schering-Plough Skid as Analysts Expect Trial results to hurt Cholesterol Drug Sales"[1]
- Public Perception: 76% of those polled believe that the Pharmaceutical industry is to blame for broken Healthcare system[2]
- Competition from developing country pharmaceutical firms
- Sourcing concerns: Deaths in Haiti, Panama, India. DEG $\neq$ Glycerine!
- 2700 drugs in development in the US[3]

1. D. Troise, Associated Press 31 March 2008 2. Consumer Reports Magazine 2007 3. C. Moreton " Big Pharma & Suppliers Collaborate on Excipient Quality" *Drug Delivery Technology (March 2008) p 30. 3. 3.* Van Arnum, P. ePT--the Electronic Newsletter of Pharmaceutical Technology 3 April 2008

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