Modern Pharmaceutical Science

History, regulatory aspects, and current landscape

ISAT 635 ♦ April 2012
Not-so-modern pharmaceutical science

- 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
- Ignaz Semmelweis: microbial theory of disease (1961)

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!

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.


1920-1930s

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

**Antibiotic revolution!**

- Domagk (I.G. Farben): Prontosil $\rightarrow$ 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.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: attenuated 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\(^1\)

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2. M. Pollan “In Defense of Food” (2007)
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

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

Zidovudine: AZT.
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
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

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’
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

**Impetus**: William S. Merrell Co. and Kevadon
- FDA’s Francis Kelsey scrutinizes NDA: pregnancy data?

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

The FDA today
Drug product development and approval: overview.

Drug discovery

New Therapeutic molecule

Preclinical Testing

IND Application

Clinical Trials (I,II,III)

R&D

NDA

FDA Approval and Post-Marketing Surveillance

Natural products
organic synthesis
Animals
Genetic Engineering
Gene Therapy

Physicochemical properties
Safety and bioactivity (in vivo/ in vitro)
preformulation

Product formulation
Long term animal toxicity
Scale-up and manufacturing
Package / label design

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

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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

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<th>Sales</th>
<th>Earnings</th>
<th>profit margin (%)</th>
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<tr>
<td>Abbott Laboratories</td>
<td>25914</td>
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<td>Bristol-Myers Squibb</td>
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<td>Eli Lilly</td>
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<td>Merck and Co.</td>
<td>24197</td>
<td>7020</td>
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<tr>
<td>Pfizer</td>
<td>48613</td>
<td>15300</td>
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<td>Sanofi-Aventis</td>
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Figures are in USD millions. 1) Adapted from Chemical and Engineering News 25 February 2008 p29.
**Phases – and duration- of drug development.**

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<tr>
<th>Preclinical testing</th>
<th>Clinical Trials</th>
<th>FDA</th>
<th>Postmarketing Surveillance</th>
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<td>Phase I</td>
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<td>Phase IV</td>
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<td>Characterization</td>
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<td></td>
<td>postmarketing testing</td>
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<tr>
<td>Toxicity</td>
<td>Phase II</td>
<td>Review and approval</td>
<td>report adverse side effects</td>
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<tr>
<td>Bioactivity</td>
<td></td>
<td></td>
<td>report product defects</td>
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<tr>
<td>(in vitro - cell culture)</td>
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<td>(in vivo - ADME / Tox)</td>
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<td>Phase II</td>
<td>Patients (1000-3000)</td>
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<td>expanded / uncontrolled trials</td>
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<td>confirm effectiveness</td>
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<td>Labelling decision</td>
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3-5 years  1.5+2+4 = 7.5 years  6-10 months

~5000 compounds <1% enter clinic  1 approved

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

- Pharmacology
- Pharmacognosy
- 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


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
• Timeframe: 10-15 years
• Me, Too! 75% of approved drugs in 2005 are Derivatives of proven medicines
• “R&D Spending by US Pharma and Biotech Firms Reaches Record High”
  – $58.8 billion in research and development (R&D) in 2007 (Pharmaceutical Research and Manufacturers of America (PhRMA) and Burrill & Company)
  – 18% of sales on R&D

• Marketing
  – 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

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

Lyrica (Pregabalin)
Pfizer
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 system²

- Competition from developing country pharmaceutical firms

- Sourcing concerns: Deaths in Haiti, Panama, India. DEG ≠ Glycerine!

- 2700 drugs in development in the US³

Credits

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