Chapter 3

INTRODUCTION TO

MEDICINAL CHEMISTRY

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SUMMARY

- Introduction: Definitions.
- History of pharmacology.
- Drug development.
  - Origin of new drugs
  - The drug development process
- The pharmaceutical market
**DEFINITIONS**

**DRUG:** Natural or synthetic substance which (when taken into a living body) affects its functioning or structure, and is used in the diagnosis, mitigation, treatment, or prevention of a disease or relief of discomfort.

(DO NOT MIX WITH: Habit-forming stimulant or narcotic substance which produces a state of arousal, contentment, or euphoria)

**Sistematic name (IUPAC):** 1-[2-Hydroxy-4-(2-hydroxy-indan-1-yl-carbamoyl)-5-phenyl-pentyl]-4-pyridin-3-ylmethyl-piperazine-2-carboxylic acid tert-butylamide

**International nonproprietary name (INN):** Indinavir

**MEDICINE:** one or more drugs, integrated in a pharmaceutical form, submitted for sale and intended for use in humans or animals.

**Commercial name:** Crixivan® (Merck, Sharp & Domme) (anti- HIV)
**Prehistory:**

Man has found, by trial and error, which berries, roots, leaves and barks could be used for “medicinal purposes” to alleviate symptoms of illness

- All ancient civilisations made discoveries in this field
- Chinese herbal remedies are probably the most well known

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**Mesopotamia**

Code of Hamurabi

Nippur tablet

**China**

The Pen Tsao, or Great Big Book of Herbs, contains 40 volumes with thousands of prescriptions.

**Egypt**

Ebbers papyrus (1500BC)

**India**

Atharva–Veda (1000-1500BC)
Sanskrit text with several prescriptions
HISTORY OF PHARMACOLOGY

Greeks and Romans:

Hippocrates:

- Greek physician of the Classical Athens, who is considered the father of Western medicine
- Hippocrates is the first person to believe that diseases were caused naturally and not as a result of superstition and gods.
- Medicine at the time of Hippocrates knew almost nothing of human anatomy and physiology because of the Greek taboo forbidding the dissection of humans.
- Theory of Humorism: An excess or deficiency of any of four distinct bodily fluids (black bile, yellow bile, phlegm, and blood) in a person directly influences their temperament and health
- Hippocratic medicine was passive. The therapeutic approach was based on "the healing power of nature" The body contains within itself the power to re-balance the four humors and heal itself

Galen (Aelius Galenus):

- Roman (of Greek ethnicity) physician, surgeon and philosopher
- Galen contributed a substantial amount to the Hippocratic understanding of pathology
- His principal interest was in human anatomy, but Roman law had prohibited the dissection of human cadavers. Because of this restriction, Galen performed anatomical dissections on living and dead animals, mostly focusing on pigs and primates.
- His anatomical reports remained uncontested until 1543.
Middle age:

- Galenic system is dominating
- The first pharmacies, were established in 754 in Baghdad under the Abbasid Caliphate during the Islamic Golden Age. By the 9th century, these pharmacies were state-regulated
  - Muhammad ibn Zakariya Razi (Rhazes) (865-915), Acted to promote the medical uses of chemical compounds.
  - Al-Biruni (973-1050) the works pharmacology entitled *Kitab al-Saydalalah (The Book of Drugs)*, where he gave detailed knowledge of the properties of drugs and outlined the role of pharmacy and the functions and duties of the pharmacist.
  - Ibn-Sina (Avicenna), described no less than 700 preparations, their properties, mode of action and their indications. He devoted a whole volume to simple drugs in *The Canon of Medicine*.
- The first pharmacy in Europe (still working) was opened in 1241 in Trier, Germany.

One example: Extracts form the Strychnine tree (also known as Nux vomica or Poison Nut).

- A tree native to India and southeast Asia. It is a major source of the highly poisonous alkaloids strychnine (in the seeds) and brucine (in the bark)
- Brucine is an antiinflammatory and analgesic compound which was used to treat intense feeling of itchiness and also as a local pain killer
- Strichnine is a well-known poison
Modern ages: From myths to the birth of a scientific discipline

Theophrastus von Hohenheim (1493–1541 A.D.), called Paracelsus, began to question doctrines handed down from antiquity, demanding knowledge of the active ingredient(s) in prescribed remedies, while rejecting the irrational concoctions and mixtures of medieval medicine. He prescribed chemically defined substances with such success that professional enemies had him prosecuted as a poisoner. Against such accusations, he defended himself with the thesis that has become an axiom of pharmacology:

"If you want to explain any poison properly, what then isn't a poison? All things are poison, nothing is without poison: the dose alone causes a thing not to be poison."

Johann Jakob Wepfer (1620–1695) was the first to verify by animal experimentation assertions about pharmacological or toxicological actions, "I pondered at length. Finally I resolved to clarify the matter by experiments."
**HISTORY OF PHARMACOLOGY**

**XIX Century:**
- Discovery of many different bioactive compounds
- Extraordinary development of synthetic organic chemistry
- Several established drugs obtained either by isolation (natural products) or synthesis.
- Some examples

- There was an opium-based elixir used by Byzantine alchemists (formula lost during the Ottoman conquest
- In 1522 Paracelsus made reference to an opium-based elixir (*laudanum*) described as a potent painkiller.
- Morphine was discovered from extracts of the opium poppy plant in 1804 by Friedrich Sertürner who also marketed the drug to the general public as an analgesic.
- Commercial production began in Darmstadt, Germany in 1827 by the pharmacy that became the pharmaceutical company Merck.
- Extensively used as painkiller during World War II

- Quinine was used by the Quechua Indians to halt shivering due to low temperatures. The Peruvians mixed the ground bark of cinchona trees with sweetened water to offset the bark’s bitter taste (tonic water).
- Used in unextracted form by Europeans by the early 17th century. The Jesuit brother Agostino Salumbrino an apothecary who lived in Lima introduced it as a malaria treatment.
- Quinine was isolated and named in 1820 by P.J. Pelletier and J. Bienalme.
- A formal chemical synthesis was accomplished in 1944 by R.B. Woodward and W. E. Doering (needs for supply during WWII)
- Quinine is a potent painkiller and used as a sedative for kids prior to TAC, NMR or related diagnostic procedures.

- Salicilic acid
- Hippocrates described a bitter powder extracted from willow bark that could ease aches and reduce fevers.
- Native Americans used an infusion for fever.
- The Reverend Edward Stone, a vicar from England, noted in 1763 that the bark of the willow was effective in reducing a fever.
- The active extract (salicin), isolated and named by J. A. Buchner.
Paul Ehrlich (1854-1915): a German scientist and Nobel laureate. He is noted for discovering the syphilis treatment salvarsan, the first drug targeted against a specific pathogen. He coined the term chemotherapy and popularized the concept of a magic bullet. (Observed that some tissues were selectively stained (e.g. bacteria with methylene blue). Ehrlich reasoned that if a compound could be made that selectively targeted a disease-causing organism, then a selective toxin for that organism could be delivered along with the agent of selectivity. (the "magic bullet")
Origin of new drugs: Sources

FDA: (Food and Drug Administration) is an agency of the United States Department of Health and Human Services, one of the United States federal executive departments. The FDA is responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and marketing of pharmaceutical drugs, vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), veterinary products, and cosmetics.

EMA (European Medicines Agency) is a decentralised agency of the European Union, located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union.

490 NCE’s 1990-2003 (FDA)

22 NCE’s 2011 (FDA)
DRUG DEVELOPMENT

Origin of new drugs: Sources

New drugs approved (FDA + EMA)
1990-2005

Origin of new drugs 1990-2009

NUMBER OF NEW CHEMICAL OR BIOLOGICAL ENTITIES (1990-2009)

Source: SCRIP – EFPIA calculations (according to nationality of mother company)

Sources: CIR International Institute for Regulatory Science, EFPIA
Drug development process

Three stages:

1. Discovery
   1. Programme selection (choosing a disease to work on)
   2. Identification and validation a drug target
   3. Identification of a “lead compound”
   4. Lead optimization

2. Preclinical development
   1. Toxicity
   2. Pharmacokinetics
   3. Pharmacodynamics

3. Clinical development
   1. Phase I
   2. Phase II
   3. Phase III

4. Register, approve and market

“**In vitro**”

“**In vivo**” (animals)

“**In vivo**” (people)
DRUG DEVELOPMENT

THE DISCOVERY STAGE

Pathology
Where is the origin/cause of the disease

Development of models
in vitro enzymatic assays

Hit to lead
“Hit” → “Lead”

Optimization
in vitro enzymatic assays

Drug design
Select possible drug candidates

Drug synthesis
diversity (automatization)

Decision
- Market
- Public policy
- Private sponsorship
- …..

2 – 20 Years

Year 0 (patent)
DRUG DEVELOPMENT

THE DISCOVERY STAGE

- Automated synthesis (synthesis robots)
- Diversity oriented synthesis (DOS)
- Combinatorial synthesis
Drug Development

The Preclinical Stage

2 – 3
Years

Toxicity
Side effects
Comparison with other drugs

Pharmacokinetics
Absorption
Distribution
Metabolism
Excretion

Pharmacodynamics
Effect on other organs

IMP *
(Investigational Medicinal Product)

GLP: Good laboratory practice
GMP: Good manufacturing practice

- Chemical synthesis development (production)
- Analysis development (quality control)
- Pharmacological development

Year 3.5

* IND in USA (Investigational new drug)
DRUG DEVELOPMENT

THE PRECLINICAL STAGE

- High scale production
- Development of analytical protocols
- Automated biological activity screening
DRUG DEVELOPMENT

THE CLINICAL STAGE

6 Years

Phase I
20 – 100 healthy volunteers

Phase II
100 – 500 Patients (volunteers)*

Phase III
1000 – 3000 Patients (volunteers)*

NDA (New drug application) or Registry

GCP: Good clinical practice
GMP: Good manufacturing practice

Year 4.5

Year 6.5

- Chemical synthesis development (production)
- Analysis development (quality control)
- Pharmacological development

Year 9.5

* Compassionate drug use programs
MARKETING AND LAST CLINICAL STAGE

Revision by Government agencies (FDA or EMA)

Phase IV
Long term revision

Year 12
DRUG DEVELOPMENT

Discovery

Preclinical

Clinical Phase I

Clinical Phase II

Clinical Phase III

Registry

10,000 - 20,000 products

250

5

1
DRUG DEVELOPMENT

LIFE CYCLE OF A DRUG

Development

Launching

Recovery

End of patent

Competitor
LIFE CYCLE OF A DRUG

The case of Viagra

Sildenafil (Viagra®) Pfizer
Patented: 1992
Launched 1998
End of patent: 2012
Sales
$ 2.02 Billion in 2008
$ 1.84 Billion in 2009
$ 0.57 Billion in 2010

Tadalafil (Cialis®) Lilly
Patented: 1997
Launched 2001
End of patent: 2017
Sales
$ 1.56 Billion in 2009

Valdenafil (Levitra®) Bayer
Patented: 1999
Launched 2003
End of patent: 2019
Sales
$ 0.49 Billion in 2010
DRUG DEVELOPMENT

LIFE CYCLE OF A DRUG

GENERIC DRUGS

ORIGINAL DRUG

Improved analogues

End of Patent for A

D

C

B

A

Ag1

Ag2

Ag3

Ag4

Generic drug
DRUG DEVELOPMENT

COSTS

- Discovery: 50%
- Phase III: 13%
- Phase II: 20%
- Phase I: 7%
- Preclinical: 10%
DRUG DEVELOPMENT

COSTS

1 Airbus 380 = $300 million
1 New drug = 4-5 Airbus 380

Total Cost $1.3 Billion

1 Luxury yacht ≈ $3 Billion
1 New drug = 0.5 luxury yacht
## THE PHARMACEUTICAL MARKET

### THE BIG PHARMA COMPANIES

**WW Prescription Drug Sales (2009/16): Top 20 Companies & Total Market**

<table>
<thead>
<tr>
<th>Company</th>
<th>WW Prescription Sales ($bn)</th>
<th>WW Market Share</th>
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<tbody>
<tr>
<td></td>
<td>2009</td>
<td>2016</td>
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<tr>
<td><strong>Total Top 20</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Other</strong></td>
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<td></td>
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<tr>
<td><strong>Total</strong></td>
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<table>
<thead>
<tr>
<th>Company</th>
<th>WW Prescription Sales ($bn)</th>
<th>WW Market Share</th>
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</thead>
<tbody>
<tr>
<td>1 Pfizer (Wyeth)*</td>
<td>55.3</td>
<td>47.1</td>
</tr>
<tr>
<td>2 Merck &amp; Co (SGP)*</td>
<td>41.6</td>
<td>46.3</td>
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<tr>
<td>3 Novartis</td>
<td>37.3</td>
<td>46.0</td>
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<tr>
<td>4 Roche</td>
<td>38.0</td>
<td>43.9</td>
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<tr>
<td>5 Sanofi-Aventis</td>
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<td>38.9</td>
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<tr>
<td>6 GlaxoSmithKline</td>
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<td>7 Abbott Laboratories</td>
<td>16.5</td>
<td>26.1</td>
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<tr>
<td>8 Johnson &amp; Johnson</td>
<td>21.3</td>
<td>24.8</td>
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<tr>
<td>9 AstraZeneca</td>
<td>31.6</td>
<td>22.1</td>
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<td>10 Teva Pharmaceutical</td>
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<td>11 Amgen</td>
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<td>12 Bayer</td>
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<td>14 Bristol-Myers Squibb</td>
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<td>15 Novo Nordisk</td>
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<td>16 Boehringer Ingelheim</td>
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<td>18 Baxter International</td>
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<td>19 Takeda</td>
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<tr>
<td>20 Daichi Sankyo</td>
<td>9.3</td>
<td>11.3</td>
</tr>
</tbody>
</table>

Source: EvaluatePharma® (30 APR 2010)
THE PHARMACEUTICAL MARKET

THE BIG PHARMA COMPANIES

Where do they come from?

- Pfizer
- Abbott
- Bristol Myers Squibb
- Merck
- Johnson & Johnson
- Novartis
- AstraZeneca
- Roche
- Teva (generics)
- Boehringer Ingelheim
- Gilead
- Baxter
- Sanofi Aventis
- GlaxoSmithKline
- Bayer
- Takeda
- Daiichi-Sankyo
- Lilly
THE PHARMACEUTICAL MARKET

THE BIG PHARMA COMPANIES

Where do they come from?

PHARMACIA

UPJOHN (1995)

PHARMACIA-UPJOHN

MONSANTO (1999)

PHARMACIA CORP.

PFIZER INC.

WARNER-LAMBERT (2000)

PFIZER INC. (2003)

PFIZER

PFIZER
THE BIG PHARMA COMPANIES

HISTORY

Where do they come from?

Pfizer is named after German-American cousins Charles Pfizer and Charles Erhardt (originally from Ludwigsburg, Germany) who launched a fine chemicals business, Charles Pfizer and Company, from a building Booklyn in 1849. There, they produced an antiparasithec called santonin. This was an immediate success, although it was the production of citric acid that really kick-started Pfizer’s growth in the 1880s. Pfizer continued to expand its lab and by 1906, sales totaled nearly $3 million.

World War I caused a shortage of calcium citrate that Pfizer imported from Italy for the manufacture of citric acid, and the company began a search for an alternative supply. Pfizer chemists learned of a fungus that ferments sugar to citric acid and were able to commercialize citric acid from this source in 1919. As a result Pfizer developed expertise in fermentation technology. These skills were applied to the production of penicillin during World War II.

Following the success of penicillin in the 1940s, penicillin became very inexpensive and Pfizer made very little profit for its efforts. As a result, in the late 1940s Pfizer decided to search for new antibiotics with greater profit potential. The discovery and commercialization of terramycin (oxytetracyclin) by Pfizer in 1950 moved the company from a manufacturer of fine chemicals to a research-based pharmaceutical company. Pfizer began a program to discover drugs through chemical synthesis. In 1980 Pfizer launched Feldene (pyroxicam) an anti-inflammatory that became Pfizer's first product to reach a total of a $1.000 million in sales.

During the 1980s and 1990s Pfizer underwent a period of growth sustained by the discovery and marketing of Zoloft, Lipitor, Norvasc, Zithromax, Aricept, Diflucan, and Viagra. Pfizer has recently grown by mergers, including those with Warner–Lambert (2000), with Pharmacia (2003), and with Wyeth (2009).
THE PHARMACEUTICAL MARKET

THE BIG PHARMA COMPANIES
Where do they come from?

SANOFI

STERLING W (1992)

SANOFI-WINTHROP

SYNTHELABO (1999)

FISON

SANOFI-SYNTHELABO

RHONE-POULENC R (1995)

AVENTIS (2004)

SANOFI-AVENTIS

Warp Drive (2012)

SANOFI (2012)
THE PHARMACEUTICAL MARKET

THE BIG PHARMA COMPANIES

Other interesting stories

Merck & Co. traces its origins to Friedrich Jacob Merck who purchased a drug store in Darmstadt, Germany in 1668 and also to Emanuel Merck, who took over the store several generations later, in 1816. Emanuel and his successors gradually built up a chemical-pharmaceutical factory that produced—in addition to raw materials for pharmaceutical preparations—a multitude of other chemicals.

In 1891, George Merck established his roots in the United States and set up Merck & Co. in NY as the US arm of the family partnership, E. Merck (named for Emanuel Merck), which is now Merck KGaA. Merck & Co. was confiscated in 1917 during World War I and set up as an independent company in the United States. Today, the US company is larger than its German ancestor.

In 1965 Merck acquired Charles E. Frosst Ltd. of Montreal (founded 1899) and created Merck-Frosst Canada Inc. In November 2009, Merck announced that it would merge with competitor Schering-Plough in a US$41 billion deal.

Bayer AG was founded in Barmen (today a part of Wuppertal), Germany in 1863 by Friedrich Bayer and his partner, Johann Friedrich Weskott. Bayer's first major product was acetylsalicylic acid. By 1899, Bayer's trademark Aspirin was registered worldwide for Bayer's brand of acetylsalicylic acid, but because of the confiscation of Bayer's US assets and trademarks during World War I by the United States - and the subsequent widespread usage of the word to describe all brands of the compound, "Aspirin" lost its trademark status.

In 1904, the Bayer company introduced the Bayer cross as its corporate logo. Because Bayer's aspirin was sold through pharmacists and doctors only, and the company could not put its own packaging on the drug, the Bayer cross was imprinted on the actual tablets, so that customers would associate Bayer with its aspirin. As part of the reparations after World War I, Bayer's assets and trademarks were acquired by Sterling Drug. The Bayer company then became part of IG Farben, a German chemical company conglomerate. During World War II, the IG Farben used slave labor in factories, notably the Mauthausen concentration camp. (IG Farben manufactured Zyklon B). After World War II, the Allies broke up IG Farben and Bayer reappeared as an individual business. In 1978, Bayer purchased Miles Laboratories. In 1994, Bayer AG purchased Sterling Drug from SmithKline Beecham and merged it with Miles Laboratories, thereby reacquiring the U.S. and Canadian trademark rights to "Bayer" and the Bayer cross, as well as the ownership of the Aspirin trademark in Canada.
### THE PHARMACEUTICAL MARKET

#### THE BIG PHARMA COMPANIES

#### The Spanish market

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<th>No.</th>
<th>Empresa</th>
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<th>Ventas-04</th>
<th>% 04/03</th>
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<td>1</td>
<td>NOVARTIS (GRUPO)</td>
<td>869,00</td>
<td>957,51</td>
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<td>PFIZER, S.A.</td>
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<td>933,61</td>
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<td>SANOFI-AVENTIS, S.A.</td>
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<td>900,00</td>
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<td>5</td>
<td>GLAXOSMITHKLINE, S.A.</td>
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<td>850,00</td>
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<td>KERN PHARMA, S.A.</td>
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<td>71,70</td>
<td>53,2</td>
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</table>
THE BIG PHARMA COMPANIES

The influence of the market: Case 1

August 2001: The Lipobay case.

Cerivastatin is synthetic member of the class of statins used to lower cholesterol. It was in the late 1990s, competing with Pfizer's highly successful atorvastatin (Lipitor®).

Gemfibrozil is synthetic member of the class of fibrates used to lower triglyceride levels.

During Phase-IV (market), 52 deaths were reported in patients using cerivastatin, mainly from rhabdomyolysis and its resultant renal failure. Risks were higher in patients using gemfibrozil (Lopid®). Bayer A.G. added contraindication about the concomitant use of cerivastatin and gemfibrozil to the package 18 months after the drug interaction was found. Cerivastatin was voluntarily withdrawn from the market worldwide in 2001.

October 2001: The anthrax crisis.

Gemfibrozil is synthetic antibiotic of the fluoroquinolone drug class. It kills bacteria by interfering with the enzymes that cause DNA to rewind after being copied, which stops synthesis of DNA and of protein.

What Bayer lost with Lipobay was soon afterwards recovered with the anthrax crisis.
THE BIG PHARMA COMPANIES

The influence of the market: Case 2

September 2004: The Vioxx case.

Rofecoxib is a nonsteroidal anti-inflammatory drug that was marketed by Merck & Co. to treat osteoarthritis and acute pain. Rofecoxib was approved by the FDA on May 1999.

Rofecoxib gained widespread acceptance among physicians treating patients with arthritis. Worldwide, over 80 million people were prescribed rofecoxib at some time. On September 2004, Merck voluntarily withdrew rofecoxib from the market because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use. Merck withdrew the drug after information about rofecoxib’s risks from doctors and patients for over five years, resulting in between 88,000 and 140,000 cases of serious heart disease. Rofecoxib was one of the most widely used drugs ever to be withdrawn from the market. In the year before withdrawal, Merck had sales revenue of US$2.5 billion from Vioxx.

December 2004: The consequences.

Revision of related drugs affected Valdecoxib (Bextra®) marketed by Pfizer, which had been approved on 2001 and had to be withdrawn on 2005.

On September 2, 2009, the US Department of Justice fined Pfizer $2.300 million. Pfizer admitted to criminal conduct in the promotion of Bextra, and agreed to pay the largest criminal fine ever imposed in the USs for any matter, $1.195 million. A former Pfizer district sales manager was indicted and sentenced to home confinement for destroying documents regarding the illegal promotion of Bextra.
April 2009: The H5N1 case.

Oseltamivir is an antiviral drug, slows the spread of influenza (flu) virus between cells in the body. The drug is has been used to treat and prevent influenza A virus and influenza B virus infection in over 50 million people since 1999. Oseltamivir is a prodrug, a which is converted into its active form by metabolic process after it is taken into the body.

Oseltamivir was the first orally active neuraminidase inhibitor commercially developed. It was developed by Gilead Sciences and licensed to Genentech. Roche Swiss pharma purchased Genentech in 2009.

On 2009, interactions between the H5N1 swine flu virus with humans and the high mortality related to it set the WHO to declare a global pandemic. Governments purchases millions of doses for tamiflu.

Zanamivir a neuraminidase inhibitor used in the treatment and prophylaxis of influenza caused by influenza A virus and influenza B virus.
A “Blockbuster” is a drug which reaches $1,000 million per year sales.

Represent around 35% total sales/year.

Currently there are 110 registered blockbusters (2010).

35 drugs report > $2,000 million/year.

16 drugs report > $3,000 million/year.

Having a blockbuster is the ultimate target of all pharmaceutical companies.

**Atorvastatin (Lipitor®)**

Pfizer

Hypercholesterolemia

$11,810 million (2010)
THE PHARMACEUTICAL MARKET

THE 10 BEST BLOCKBUSTERS

1) Atorvastatin (Lipitor®)
   Pfizer
   Hypercholesterolemia
   $11810 million

2) Clopidogrel (Plavix®)
   Bristol-Myers Squibb
   Myocardial Infarction
   $8910 million

3) Fluticasone/salmeterol (Seretide/advair)
   GlaxoSmithKline
   COPD, Asthma
   $7947 Million

4) Infliximab (Remicade®)
   Johnson & Johnson
   Rheumatoid arthritis/autoimmune diseases
   7833 million

5) Etanercept (Enbrel®)
   Pfizer
   Rheumatoid arthritis/autoimmune diseases
   $7156 million

6) Aripiprazole (Abilify®)
   Otsuka
   Psychosis, depression, anxiety disorders
   $6629 million

7) Adalimumab (Humira®)
   Crohn’s disease, Psoriasis
   $6282 million

8) Esomeprazole (Nexium®)
   AstraZeneca
   Peptic ulcer, Gastroesophageal reflux
   $6331 million

9) Bevacizumab (Avastin®)
   Roche
   Cancer
   $6212 million

10) Valsartan (Diovan®)
    Novartis
    Hypertension
    $6053 million
THE PHARMACEUTICAL MARKET

GENERIC DRUGS

Gemfibrozil (LOPID®)
Warner-Lambert (1978)
hyperlipidemia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Costs per year</th>
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<tbody>
<tr>
<td>LOPID</td>
<td>$1038</td>
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<tr>
<td>Generic gemfibrozil</td>
<td>$157</td>
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Generic drugs are not associated to discovery/development costs
## THE PHARMACEUTICAL MARKET

### GENERIC DRUGS: COMPANIES (2010)

<table>
<thead>
<tr>
<th>#</th>
<th>Company</th>
<th>$ Billions (2010)</th>
<th>Growth %</th>
<th>Market Share</th>
</tr>
</thead>
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<tr>
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<td><strong>US GENERIC PHARMACEUTICALS MARKET</strong></td>
<td></td>
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<td></td>
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<tr>
<td>1</td>
<td>TEVA</td>
<td>14.65</td>
<td>14%</td>
<td>33%</td>
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<tr>
<td>2</td>
<td>MYLAN</td>
<td>4.65</td>
<td>15%</td>
<td>10%</td>
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<tr>
<td>3</td>
<td>SANDOZ</td>
<td>3.49</td>
<td>52%</td>
<td>8%</td>
</tr>
<tr>
<td>4</td>
<td>WATSON</td>
<td>3.49</td>
<td>6%</td>
<td>8%</td>
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<tr>
<td>5</td>
<td>APOTEX</td>
<td>1.75</td>
<td>-32%</td>
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<td>6</td>
<td>HOSPIRA</td>
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<td>7</td>
<td>PAR PHARM</td>
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<td>8</td>
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<td>9</td>
<td>RANBAXY</td>
<td>0.90</td>
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<tr>
<td>10</td>
<td>GREENSTONE LTD</td>
<td>0.97</td>
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<table>
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<tr>
<th>#</th>
<th>Company</th>
<th>$ Billion (2010)</th>
<th>Growth %</th>
<th>Market Share %</th>
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<tr>
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<td><strong>EU GENERIC PHARMACEUTICALS MARKET</strong></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>TEVA</td>
<td>4.52</td>
<td>2%</td>
<td>18%</td>
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<tr>
<td>2</td>
<td>SANDOZ</td>
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<td>9%</td>
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<tr>
<td>5</td>
<td>STADA</td>
<td>1.71</td>
<td>3%</td>
<td>7%</td>
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<tr>
<td>6</td>
<td>ACTAVIS</td>
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<td>3%</td>
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<td>IBRAHIM</td>
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<td>8</td>
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<td>ESTEVE</td>
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<td>5%</td>
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GENERIC DRUGS: FUTURE AND PERSPECTIVES

### Patent Expiring in 2011

- **Atorvastatin (Lipitor®)**
  - Condition: cholesterol
  - Company: Pfizer
- **Olanzapin (Zyprexa®)**
  - Condition: antipsychotic
  - Company: Eli Lilly
- **Levofloxacin (Levaquin®)**
  - Condition: antibiotics
  - Company: Johnson & Johnson
- **Methylfenidate (Concerta®/Ritalin®)**
  - Condition: ADHD/ADD
  - Company: Johnson & Johnson
- **Pantoprazole (Protonix®)**
  - Condition: antacid
  - Company: Pfizer

### Patent Expiring in 2012

- **Plavix®**
  - Condition: anti-platelet
  - Company: Bristol-Myers Squibb / Sanofi-Aventis
- **Seroquel®**
  - Condition: antipsychotic
  - Company: AstraZeneca
- **Singulair®**
  - Condition: asthma
  - Company: Merck
- **Actos®**
  - Condition: type 2 diabetes
  - Company: Takeda

---

**Table Notes:**

- **Plavix®** is also known as **Clopidogrel (Plavix®)**
- **Seroquel®** is also known as **Quetiapine (Seroquel®)**
- **Singulair®** is also known as **Montelukast (Singulair®)**
- **Actos®** is also known as **Pioglitazone (Actos®)**
## THE PHARMACEUTICAL MARKET

### PIPELINES

<table>
<thead>
<tr>
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<td><strong>U.S. DRUG COS.</strong></td>
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<tr>
<td>Bristol-Myers/BBMY</td>
<td>Plavix (stroke)</td>
<td>$5.8</td>
<td>2012</td>
<td>Ipilimumab</td>
<td>Melanoma ($1.0)</td>
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<tr>
<td>Eli Lilly/LLY</td>
<td>Zyprexa (schizo.)</td>
<td>4.8</td>
<td>2011</td>
<td>Semagacestat</td>
<td>Alzheimer’s ($0.3)</td>
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<td>Merck/MSK</td>
<td>Singulair (asthma)</td>
<td>5.0</td>
<td>2012</td>
<td>Vorapaxar</td>
<td>Stroke ($1.5)</td>
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<tr>
<td>Pfizer/PFE</td>
<td>Lipitor (cholesterol)</td>
<td>11.1</td>
<td>2011</td>
<td>Tasocitinib</td>
<td>Rheum. arthritis ($1.3)</td>
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</table>

| **EUROPEAN DRUG COS.** | | | | | |
| Astra-Zeneca/AZN | Seroquel (bipolar) | $5.5 | 2012 | Brilinta | Blood thinner ($1.5) |
| Novartis/NVS | Diovan (hypertension) | 6.2 | 2012 | FTY 720 | Multiple sclerosis ($1.0) |
| Sanofi-Aventis/SNY | Lovenox (blood thinner) 3.8 | | 2012 | BSI-201 | Breast cancer ($0.4) |
| Roche/RHBY | Xeloda (cancer) | 1.3 | 2013 | PLX-4032 | Melanoma ($0.25) |
| GlaxoSmithKline/GSK | Advair (asthma) | 7.5 | 2013 | Relovair | Asthma ($2.0) |

*Top drug with looming competition.

---

### PROMISING PIPELINE

Numerous small-molecule drugs are in late-stage development to treat MS:

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<th>ORGANIZATION</th>
<th>PHASE</th>
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<td>Fampirine</td>
<td>Acorda</td>
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<tr>
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<td>Biogen Idec</td>
<td>III</td>
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<td>Cladribine</td>
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<td>Sanofi-Aventis</td>
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<td>Biogen Idec/LCB</td>
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<td>MN-166</td>
<td>MediCNova</td>
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<tr>
<td>Nerivipidine</td>
<td>Sanofi-Aventis</td>
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<tr>
<td>SB-683699</td>
<td>GlaxoSmithKline</td>
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</table>

NDA = New Drug Application

**SOURCES:** National Multiple Sclerosis Society, companies.
THE PHARMACEUTICAL MARKET

CONCLUSIONS

The Pharma market is organized in the following way:

1. Big corporations (and increasingly larger) develop and market innovative trade drugs.

2. Smaller corporations market generic drugs (emerging markets)

3. Developing a new drug is very expensive, a long process and a highly risky business.

4. Rare diseases are ignored

Investing in the development of a new drug is expensive but:

“For every dollar spent on developing a drug, Society saves six dollars on hospital and sanitary costs”