5th Year Anniversary
Rapid Pharma Development

May 4th, 2012

Drug Discovery Strategies Today –
What We Have Learned From The Past?

Helmut Buschmann
Four Possible Strategies in Research

- No hypotheses, no experiments
- Hypotheses but no experiments
- No hypotheses, only experiments
- Hypotheses and experiments

Rolf Zinkernagel (Nobel prize in Medicine 1996)

R & D Performance: Drug Discovery Technologies
The original approach to Drug Discovery.

- Drug Discovery had its origins in the late 1800’s with the identification and manufacture of natural products, and their derivatives.
  - Dye makers
  - Pharmacists

- The original approach to Drug Discovery focused on the screening of natural products for biological activity in defined assay systems.
  - “Pharmacology-to-Protein” concept
  - Serendipitous Drug Discovery
  - Extremely laborious/time consuming
  - Limited areas of success (why?)
    - Antimicrobials*
    - Aspirin
  - …but, still practiced today.

Paradigm Shifts in Drug Discovery
- Product of the Genomics Revolution -
The Key Lock Principle

"Um ein Bild zu gebrauchen, will ich sagen, daß Enzym und Glucosid wie Schloß und Schlüssel zueinander passen müssen, um eine chemische Wirkung aufeinander ausüben zu können"

„To use a model I would like to say, that an enzyme and an glycoside have to fit to each other like a lock and a key to be able to have a chemical reaction on each other.“

Emil H. Fischer (1852-1919) Nobel Price 1902

E. Fischer, 1894
The specific interaction between receptors on the cell surface and ligands

Receptor Theory at 1900

Paul Ehrlich (1854-1915)
The Changing Climate in Pharmaceutical Research

- **Scientific Advances**
  - The Human Genome
  - Advances in Screening Technologies
  - Advances in Synthesis Technologies

- **Raising bar on drug-like characteristics**
  - Attrition rates too high
  - Increasing multi-parameter property optimization

- **Increasing Scale**
  - Data volumes and complexity soar
  - Global, multi-site, multi-cultural organizations
  - Rising costs of drug discovery and development

The human body is complex

- 100 organs,
- 1500 different cell types,
- 10,000 diseases
The Human Genome Project - Timelines -

1985
- Conference on HGP Feasibility

1986
- Congress Recommends 15 year HGP Project

1987
- HGP Officially Begins

1988
- Low Resolution Linkage Map of HG Published

1989
- High Resolution Maps of Specific Chromosomes Announced

1990
- E.coli Genome Completed

1991
- S. cerevisiae Genome Completed

1992
- C. elegans Genome Completed

1993
- President announces genome working draft completed

1994
- Celera Genomics Formed

1995
- 1st Human Chromosome Sequenced

1996
- Human Genome Published

1997
- President announces genome working draft completed

1998
- Fly Genome Completed

1999
- Human Genome Published

2000
- Human Genome Published

2001
- Science (Feb. 16, 2001) – Celera; Nature (Feb. 15, 2001) - HGP
April 2003: 99% of the Human Genome Sequenced

3.12 billion nucleotides

(cf. 200 telephone books worth of information)
Development of target identification

(Number of targets)

Pharmaceutical Industry – The R & D Process

A series of measurements ranging from genetic/genomic through to clinical are made and a comparison between normal versus perturbed (eg diseased/drug treated/toxin administration) populations is performed. Complex datasets are integrated and a variety of informatic, biostatistical and knowledge assembly tools are used to produce new knowledge and understanding about the perturbed system compared to the normal system. The output can range from molecular and cellular biomarkers to pathways and networks of the system under investigation.
The Chemical Universe

$10^{40} - 10^{120}$ compounds with C, H, O, N, P, S, F, Cl, Br, I, and MW < 500 ??
Chemogenomics

Chemical Universe

Target Universe

Pharmaceutical Industry – The R & D Process
Pharmaceutical Industry – The R & D Process

Drug Discovery in the 21st Century

Human Genome (30-40K genes)

Chemical Space

10,000/30,000 Proteins?

10^{40} - 10^{120} Compounds?

New Drugs

Proteomics

Chemical Genetics

Functional Genomics

Structure-based Design

In silico prediction

CombiChem

Chemical diversity

Organic Synthesis

The Playground

The Game

The Players
Drug Discovery in the 21st Century

Pharmaceutical Industry – The R & D Process

- Automated Synthesis & Combinatorial Chemistry
- High Throughput Screening
- in silico Screening

- Functional genomics
- Proteonomics
- Pharmacogenomics

- Genomics
- Knowledge Management

- Cheminformatics
- Data Mining
- Bioinformatics

- Competitive Intelligence
- Patent Strategy
Pharmaceutical Industry – The R & D Process

Science and technology advances present significant opportunities

Understanding human physiology

‘omic Imaging

IT

Public investment

Pre-competitive collaborative research

Industry investment

Better understanding of disease/drug mechanisms

More efficient drug discovery and development

Better medicines, faster

Health benefits for EU citizens
Pharmaceutical Industry – The R & D Process

From Gene to Drug
Potential outcome of new technologies

- Proteomics
- Genomics
- Genetics
- Imaging
- Tissue banks
- Disease definition
- Nanosciences
- Knowledge management

- Molecular definition of disease
- New Drug targets
- Prediction of Efficacy
- Prediction of Toxicity
- Better clinical trials design
- Reduced side-effects
- Diagnostic tools
- Personalised Treatments
Drug Discovery Strategies Today –
What We Have Learned From The Past?

Nothing
Drug Research was and is...

...the Search for a Needle in a Haystack
Creating New Medicines is a High Risk Journey

- Synthesis of compounds
- Screening
- Formulations developed
- Extensive safety studies
- Candidate
- Early safety studies
- Studies in healthy volunteers (Phase I)
- Studies in 100-300 patients (Phase II)
- Risk assessment analysis
- Gaining approval
Pharmaceutical R&D investment is substantial

R&D Spending as a percentage of sales

- Pharmaceutical Industry: 17.7%
- Computer Software & Services: 10.2%
- Electrical & Electronics: 8.1%
- Automotive: 3.8%
- Aerospace & Defense: 3.8%
- Telecommunications: 3.8%
- Other Industries: 0%
R&D is getting more and more expensive

**Average R&D costs per NCE medicine launched**

- **1976**: $54M
- **1987**: $231M
- **2000**: $802M
- **2003**: $1700M

*Post-launch costs*

- Bain & Co Dec 03
- R&D Heads @ IBC mtg 2003

*Pharmaceutical Industry – The R & D Process*
## Estimates of the component costs of drug development

<table>
<thead>
<tr>
<th>Component</th>
<th>Pre-approval costs: US $ million (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Boston Consult Group (2001)</td>
</tr>
<tr>
<td>Biology</td>
<td>370 (42%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td>160 (18%)</td>
</tr>
<tr>
<td>Preclinical safety</td>
<td>90 (10%)</td>
</tr>
<tr>
<td>Overall preclinical</td>
<td>620 (70%)</td>
</tr>
<tr>
<td>Clinical</td>
<td>260 (30%)</td>
</tr>
<tr>
<td></td>
<td>DiMasi et al. (2003)</td>
</tr>
<tr>
<td>Biology</td>
<td>-</td>
</tr>
<tr>
<td>Chemistry</td>
<td>-</td>
</tr>
<tr>
<td>Preclinical safety</td>
<td>-</td>
</tr>
<tr>
<td>Overall preclinical</td>
<td>335 (42%)</td>
</tr>
<tr>
<td>Clinical</td>
<td>467 (58%)</td>
</tr>
<tr>
<td>Total</td>
<td>880 (100%)</td>
</tr>
<tr>
<td></td>
<td>802 (100%)</td>
</tr>
</tbody>
</table>
Forty-Year Coupling of Investments and Return in the Pharmaceutical Industry

- Product Discovered 1986
- Product Discovered 2006
- Investment
- Income
- 1986
- 2006
- 2026
- Today
- 40 Years

Pharmaceutical Industry – The R & D Process
Challenges of drug discovery
Finding one molecule that meets multiple criteria

Valid Biomedical Hypothesis?

10,000 Drug Candidates

1 Drug Molecule

potent
selective
reversible
targeted
soluble
permeable
long lasting
non-toxic
non-mutagenic
non-teratogenic
physically stable
manufacturable
patentable

The role of the medicinal chemist in the drug discovery process: current status and future prospects; Stevan W. Djuric; DDW, Winter 2005/6
An compound with an interesting structure has not necessarily a biological activity.

A compound with biological activity is not a hit.

A hit is not a lead.

An optimized lead is no candidate.

A candidate is not a drug.

A drug is not a success.

A successful drug is luck!

10^{100} Chemical Space of Organic Molecules
The Discovery Phases

Exploratory Research

Drug Discovery

Drug Profiling

Pre-Development

Research Phases

Target-identification

Target-validation

Leadstructure search

Leadstructure optimization

Candidate selection

GLP-Phase

Phase I

Phase Ila
Drug Discovery: A Historical Perspective

Drug Discovery – The Early Times

Natural Products and their Analogues

- **pro:** High percentage of active compounds
  - Large chemical diversity

- **con:** Availability may pose problems
  - Most often difficult chemistry

Animal Experiments

- **pro:** ADMET included
  - Disease models

- **con:** Slow, expensive
  - Ethical issues
  - Species differences
Drug Discovery: A Historical Perspective

Drug Discovery – The Golden Age

Endogenous Transmitters & Hormones

- pro: Active lead structures with defined biological function
  - Involved in many different diseases

- con: Limited number of lead structures

Isolated Organs as Test Models

- pro: Include membrane permeability

- con: Slow, expensive
  - No ADME(T)
  - Ethical issues
Drug Discovery – „Rational“ Approaches

Structure-based & Computer Aided Design

- **pro:** Straightforward approach

- **con:** Only targets with 3D structures
  - Only ligand design
  - No ADMET
  - High risk of failure

In vitro Test Models

- **pro:** Very fast: 100.000`s a day
  - Target focussed

- **con:** No ADMET
  - Single target approach

**HIV - VIRACEPT**

**Different Types of Microtiterplates**
Drug Discovery: A Historical Perspective

Drug Discovery – Nowadays

Combinatorial Chemistry Compound Libraries

- **pro:** Generate a multitude of compounds
- **con:** Limited chemical diversity
- Chemistry driven libraries (most often outside the biological space)

Chemical Biology

- **pro:** Fast screening in biological systems
  - Membrane permeability included
- **con:** No ADMET in cellular systems
  - Target(s) remain(s) unknown
Compounds in each sublibrary are located in different regions of the diversity space.

Compounds in each sublibrary allocated are homogeneously distributed throughout the diversity space.
Drug Discovery – Nowadays

Virtual Screening & Fragment-Based Design ➔ Chemogenomics

- **pro:**
  - Straight forward approach
  - Saves time and resources

- **con:**
  - Only ligand design
  - Risk of failure is remaining

- **pro:**
  - Fast information on multitarget.orientated selectivity

- **con:**
  - No ADMET
Drug Discovery: A Historical Perspective

Technology Changes in Drug Research

**Up to the 70s**
- Chemistry & Hypotheses guide the synthesis

**Up to the 90s**
- Molecular Modelling
- *In vitro* models
  - enzyme inhibition
  - receptor binding
- Gene technology
  - Production of proteins
- Combinatorial chemistry
  - Mixtures, chemistry driven
- Structure-based design of ligands
- High-throughput test models (HTS)

**Up to the year 2000**
- Animal experiments
- Isolated organs
- Dedicated synthesis of compounds
- ADMET Properties
## Technology Changes in Drug Research

### Today

<table>
<thead>
<tr>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genomics</td>
</tr>
<tr>
<td>- Proteonomics &amp; bioinformatic</td>
</tr>
<tr>
<td>Transgenic animals for proof of concept</td>
</tr>
<tr>
<td>Combinatorial chemistry</td>
</tr>
<tr>
<td>- Single compounds</td>
</tr>
<tr>
<td>- Design driven</td>
</tr>
<tr>
<td>Structure-based and computer-aided design of ligands</td>
</tr>
<tr>
<td>Ultra-high-throughput test models (uHTS)</td>
</tr>
<tr>
<td>Data mining</td>
</tr>
<tr>
<td>Virtual screening</td>
</tr>
<tr>
<td>ADMET properties</td>
</tr>
<tr>
<td>- HTS &amp; in silico</td>
</tr>
</tbody>
</table>

### Bottlenecks

<table>
<thead>
<tr>
<th>Bottlenecks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target validation</td>
</tr>
<tr>
<td>- „Drugable“ targets</td>
</tr>
</tbody>
</table>
## Development of Drug Research

<table>
<thead>
<tr>
<th>Time</th>
<th>Materials</th>
<th>Test systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>ancient time</td>
<td>plants, venoms minerals ...</td>
<td>Humans</td>
</tr>
<tr>
<td>1806</td>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td>1850</td>
<td>Chemicals</td>
<td></td>
</tr>
<tr>
<td>1890</td>
<td>synthetics, dyes</td>
<td>animals</td>
</tr>
<tr>
<td>1920</td>
<td></td>
<td>animals, isolated organs</td>
</tr>
<tr>
<td>1970</td>
<td></td>
<td>enzymes, membranes</td>
</tr>
<tr>
<td>1990</td>
<td>combinatorial libraries</td>
<td>human proteins, HTS</td>
</tr>
<tr>
<td>2000</td>
<td>focused libraries</td>
<td>uHTS, virtual screening</td>
</tr>
</tbody>
</table>

### 40 Years of Drug Discovery
Based on recent current success rate estimates (calculated by monitoring the progress of individual new chemical entities (NCEs) between clinical development phases), it is predicted that just one in 9 NCEs tested in man will make it to the market.

Of those NCEs that enter phase III evaluation, only 44% are predicted to reach the market place.
Indexed number of active substances entering each phase of development from 2001 to 2009.

A cohort of 14 companies pushed 61 agents into Phase I, 44 into Phase II, 16 into Phase III and 14 into regulatory review in 2001. Data provided by CMR International.
Pharmaceutical Industry – Success Rates of the R & D Process

Probability of success to market from key milestones.

Data, from a cohort of 14 companies, provided by CMR International.
Reasons for NME Attrition in Major Pharma

1996-2000

- Clinical Efficacy: 27%
- Miscellaneous: 20%
- Toxicity: 20%
- Clinical Safety: 13%
- Pharmacokinetics: 9%
- Commercial: 7%
- Formulations: 4%
- Pharmaceutical Industry – Success Rates of the R & D Process
Pharmaceutical Industry – Success Rates of the R & D Process

Top Flops 2011

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Indication*</th>
<th>Status</th>
<th>Lost revenue (US$ billion)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lilly/Bristol-Myers Squibb</td>
<td>Necitumumab</td>
<td>NSCLC</td>
<td>INSPIRE trial discontinued</td>
<td>12.6</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Zibotentan</td>
<td>Castration-resistant prostate cancer (monotherapy)</td>
<td>Discontinued</td>
<td>11.8</td>
</tr>
<tr>
<td>Merck &amp; Co./Sanofi</td>
<td>Vorapaxar</td>
<td>Acute coronary syndrome</td>
<td>TRACER study discontinued</td>
<td>9.1</td>
</tr>
<tr>
<td>Abbott</td>
<td>Briakinumab</td>
<td>Psoriasis</td>
<td>NDA &amp; MAA filings withdrawn</td>
<td>5.6</td>
</tr>
<tr>
<td>Sanofi</td>
<td>Iniparib</td>
<td>Metastatic triple-negative breast cancer</td>
<td>Discontinued</td>
<td>4.6</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Cediranib</td>
<td>NSCLC</td>
<td>Discontinued</td>
<td>4.4</td>
</tr>
<tr>
<td>Merck &amp; Co.</td>
<td>Telcagepant</td>
<td>Migraine</td>
<td>Discontinued</td>
<td>3.9</td>
</tr>
<tr>
<td>Targacept/AstraZeneca</td>
<td>TC-5214</td>
<td>Major depressive disorder</td>
<td>RENAISSANCE 3 trial failed; awaiting more trial data</td>
<td>3.7</td>
</tr>
<tr>
<td>Novartis</td>
<td>Omadacycline</td>
<td>Skin infections</td>
<td>Discontinued</td>
<td>2.7</td>
</tr>
<tr>
<td>Actelion/GlaxoSmithKline</td>
<td>Almorexant</td>
<td>Insomnia</td>
<td>Discontinued</td>
<td>2.6</td>
</tr>
</tbody>
</table>

*Drugs may also be in development for other indications. ‡Lost revenue is risk adjusted 20 year revenue. Data from Thomson Reuters. MAA, marketing authorization application; NDA, new drug application; NSCLC, non-small-cell lung cancer.
Expensive pivotal trial failures and regulatory setbacks continued to plague industry in 2011.

Thirty-one drugs, for either an initial indication or a major new indication, faltered during the filing process or in Phase III trials.

Lack of efficacy accounted for 51% of these failures, and safety concerns accounted for 16% of the failures.

Cancer (32%), nervous system (19%) and cardiovascular (19%) drugs were the highest ranking failures by therapeutic area. Despite the poor outlook, some of these agents could still make it to market.
Drug development is a lengthy process, taking over 11 years from the identification of a suitable drug target to the introduction of a new medicine. Furthermore, the vast majority of drug candidates do not make it to the market; only 1 compound in every 9 tested in the clinic are likely to reach the market.
Pharmaceutical Industry – The R & D Process

Attrition Rate

Research

Development

Research Attrition Rate

R&D Attrition Rate

$$$

$$$
In 2001, global pharmaceutical R&D expenditure on ethical pharmaceuticals reached US $ 45 billion.

Over the last 10 years, global R&D spend has grown by 75% - a matter of concern for the industry given that the size of the crop of new medicines launched annually has fallen.
Global Pharmaceutical Sales 1992-2003p

The number of new molecular entities (NMEs) launched per year reached an all time low in 2000 and again in 2001 - at a time when more investment than ever is being made into pharmaceutical R&D.
Pharmaceutical Industry – The R & D Process

Global pharmaceutical R&D expenditure, development time, NME output and sales 1992-2002p

Indexed values (1992 = 100)

- Global sales
- Global R&D expenditure
- Development time (3 year moving average)
- Global NME output

Year

[Graph showing trends in pharmaceutical R&D expenditure, development time, NME output, and sales from 1992 to 2002p]
FDA drug approvals since 1993.

New molecular entities and biologics license applications approved by the US Food and Drug Administration’s (FDA’s) Center for Drug Evaluation and Research, by year.
### Pharmaceutical Industry – The R & D Process

<table>
<thead>
<tr>
<th>Generic name (Trade name)</th>
<th>Sponsor</th>
<th>Indication</th>
<th>Properties</th>
<th>Date (review features)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iloprost (Dostinex)</td>
<td>Banyu</td>
<td>Pulmonary hypertension and severe airway disease</td>
<td>Causes neural excitation in insects</td>
<td>4 Jan (P)</td>
</tr>
<tr>
<td>Spironolactone (Aldactone)</td>
<td>Pfizer</td>
<td>Hypertension</td>
<td>Causes neural excitation in insects</td>
<td>4 Jan (P)</td>
</tr>
<tr>
<td>Valsartan (Exforge)</td>
<td>Novartis</td>
<td>Major depressive disorder</td>
<td>Selective serotonin reuptake inhibitor</td>
<td>4 Jan (P)</td>
</tr>
<tr>
<td>Azilsartan (Edarbi)</td>
<td>Teva</td>
<td>Hypertension</td>
<td>Antagonist</td>
<td>4 Jan (P)</td>
</tr>
<tr>
<td>Fluvastatin (Zocor)</td>
<td>Pfizer</td>
<td>Hypercholesterolemia</td>
<td>HMG-CoA reductase inhibitor</td>
<td>4 Jan (P)</td>
</tr>
<tr>
<td>Rosuvastatin (Crestor)</td>
<td>AstraZeneca</td>
<td>Hypercholesterolemia</td>
<td>HMG-CoA reductase inhibitor</td>
<td>4 Jan (P)</td>
</tr>
</tbody>
</table>

*The data table contains a list of drugs, their sponsors, indications, properties, and dates of review features.*
Classification of New Medicines

**Major Innovation**
- **Breakthrough**

A breakthrough could be defined
- as a first agent with a particular clinical action or pharmacological action
- or the first with the same clinical effect as existing agents but a different mechanism of pharmacological action

**Incremental Innovation**
- **me-too**

A me-too could be defined
- as a follow-on modification in molecular structure
- or dosage formulation

having similar but not identical pharmacological action or a different absorption, metabolism or excretion profile
Pharmaceutical Industry - Innovation
"Even a drug that reaches the marketplace does not always return its investment"

Peter Corr (Senior Vice President, Science & Technology, Pfizer)

Drug Discovery Today 10, 1017 (2005)

“People have to understand that in order to survive, the returns must be commensurate with the risks”

Peter Corr (Senior Vice President, Science & Technology, Pfizer)

Drug Discovery Today 10, 1017 (2005)
### Ranking System for New Drug Approvals Using FDA Characterizations as Criteria

<table>
<thead>
<tr>
<th>New Drug Approval (NDA) Type</th>
<th>Level of Innovation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority NMEs</td>
<td>Most Innovative</td>
</tr>
<tr>
<td>Standard NMEs</td>
<td></td>
</tr>
<tr>
<td>Priority IMDs</td>
<td></td>
</tr>
<tr>
<td>Standard IMDs</td>
<td></td>
</tr>
<tr>
<td>Other Drugs</td>
<td>Least Innovative</td>
</tr>
</tbody>
</table>

Two-thirds of new drugs approved in 1989-2000 used active ingredients already on the market

Source: FDA 2001

### New Drug Approvals by the FDA in 1989-2000*)

<table>
<thead>
<tr>
<th>Most Innovative</th>
<th>Least Innovative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority NMEs</td>
<td>Standard IMDs</td>
</tr>
<tr>
<td>15 %</td>
<td>46 %</td>
</tr>
<tr>
<td>Standard NMEs</td>
<td>Other Drugs</td>
</tr>
<tr>
<td>20 %</td>
<td>11 %</td>
</tr>
<tr>
<td>Priority IMDs</td>
<td>New Active Ingredients</td>
</tr>
<tr>
<td>8 %</td>
<td>Old Active Ingredients</td>
</tr>
<tr>
<td>Standard IMDs</td>
<td></td>
</tr>
<tr>
<td>46 %</td>
<td></td>
</tr>
</tbody>
</table>

**Distribution of NDAs, 1989-2000: Total 1.035 New Drugs**

Only 15 % of new drugs approved in 1989-2010 were highly innovative priority NMEs  
Source: FDA 2001

*) [www.nihcm.org](http://www.nihcm.org); Changing Patterns of Pharmaceutical Innovation
Eroom’s Law in pharmaceutical R&D.

The number of new drugs approved by the US Food and Drug Administration (FDA) per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years.

R & D Performance

Moore’s Law

INTEL CPUs

<table>
<thead>
<tr>
<th>Microprocessor</th>
<th>Year of Introduction</th>
<th>Transistors</th>
</tr>
</thead>
<tbody>
<tr>
<td>4004</td>
<td>1971</td>
<td>2,300</td>
</tr>
<tr>
<td>8008</td>
<td>1972</td>
<td>2,500</td>
</tr>
<tr>
<td>8080</td>
<td>1974</td>
<td>4,500</td>
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<tr>
<td>8086</td>
<td>1978</td>
<td>29,000</td>
</tr>
<tr>
<td>Intel286</td>
<td>1982</td>
<td>134,000</td>
</tr>
<tr>
<td>Intel386™ processor</td>
<td>1985</td>
<td>275,000</td>
</tr>
<tr>
<td>Intel486™ processor</td>
<td>1989</td>
<td>1,200,000</td>
</tr>
<tr>
<td>Intel® Pentium® processor</td>
<td>1993</td>
<td>3,100,000</td>
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<td>Intel® Pentium® II processor</td>
<td>1997</td>
<td>7,500,000</td>
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<tr>
<td>Intel® Pentium® III processor</td>
<td>1999</td>
<td>9,500,000</td>
</tr>
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<td>Intel® Pentium® 4 processor</td>
<td>2000</td>
<td>42,000,000</td>
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<tr>
<td>Intel® Itanium® processor</td>
<td>2001</td>
<td>25,000,000</td>
</tr>
<tr>
<td>Intel® Itanium® 2 processor</td>
<td>2003</td>
<td>220,000,000</td>
</tr>
<tr>
<td>Intel® Itanium® 2 processor (9MB cache)</td>
<td>2004</td>
<td>592,000,000</td>
</tr>
</tbody>
</table>
R&D Performance and Productivity

R&D productivity = R&D efficiency \cdot R&D effectiveness

For the industry

Volume of innovation

Cost

\( \text{Value} = \frac{WIP \cdot p \cdot (TS) \cdot \frac{1}{CT}}{\frac{1}{C}} \cdot V \)

For economists

R&D productivity = R&D efficiency \cdot Value

Goal: maximize
Eroom’s Law in pharmaceutical R&D.

How can some parts of the R&D process improve, yet the overall efficiency decline?

- Dramatic improvements in brute force screening methods and basic science should have tended to increase the efficiency of the research process (more leads tested against more targets, at a lower cost; shown in gold) and raised its quality (better targets as disease pathways and mechanisms are understood, better leads that avoid old mistakes surrounding ADMET (absorption, distribution, metabolism, excretion and toxicity) characteristics, and so on).
- This, in turn, should have increased the probability that molecules would succeed in the clinic (shown in red), which in turn should have increased overall efficiency, as research and development (R&D) costs are dominated by the cost of failure.
- However, the probability that a small molecule successfully completes clinical trials has remained more or less constant for 50 years, whereas overall R&D efficiency has declined.

Technological Inputs into Drug Research & Development

Number of drug like molecules that could be synthesized per chemist per year

1970s
- 100 compounds per chemist per year

1980s
- 100 compounds per chemist per year

1990s
- 10,000 – 100,000 compounds per chemist per year

2000s

2010s

x 1,000
R & D Performance: Drug Discovery Technologies

Technological Inputs into Drug Research & Development

DNA Sequencing

1970s  1980s  1990s  2000s  2010s

1st Genome Sequence  Genomics

x 1,000,000,000 faster
R & D Performance: Drug Discovery Technologies

Technological Inputs into Drug Research & Development

X-ray Crystallography

1970s
1980s
1990s
2000s
2010s

1st Protein X-ray Structures
Structure-Based Design

x 1.000 faster calculation
Technological Inputs into Drug Research & Development

Three Dimensional Protein Structures

1970s
1980s
1990s
2000s
2010s

Some 100s Structures

> 50,000 Structures

x 300 more entities in the last 25 years

R & D Performance: Drug Discovery Technologies

Technological Inputs into Drug Research & Development
The chart shows the trend in storage capacity needed to store biological data at EMBL-EBI (a terabyte is a million million bytes).
R & D Performance: The „Beatle-Effect“ (Statins)

Numbers of People with Diabetes (in millions) for 2000 (top) and 2010 (middle) and the Percentage Increase (bottom)

2000: 151 million
2010: 221 million
Increase: 46%

Zimmet et al. Nature 2001; 414:782-787

Discovery of compactin, the first potent inhibitor of cholesterol synthesis.

Discovery of lovastatin.

Clinical trials with lovastatin resume.

Lovastatin becomes available for prescription, first of the class.

Lovastatin shown to be effective in healthy volunteers in early clinical trials; compactin withdrawn from clinical trials, causing suspension of further trials with lovastatin.

Unequivocal reduction of mortality with simvastatin in 4S trial resolves the cholesterol controversy.

The cholesterol controversy, Phase 1, which lasted until 1984.

The cholesterol controversy, Phase 2.

Four five-year clinical outcome trials with pravastatin and lovastatin all show reduction of coronary events with very few adverse effects.

Heart Protection Study confirms safety of simvastatin in five-year trial in 20,000 patients and demonstrates clinical benefit in a broad array of patient types, including those with low cholesterol levels.

Withdrawal of cerivastatin due to excessive risk of rhabdomyolysis.

Cholesterol biosynthesis is a complex process involving more than 30 enzymes.

A simplified version is shown here, which highlights the step inhibited by statins, and shows the chemical structures of the starting material (HMG-CoA) and product (mevalonate) of this step.

Lovastatin and beyond: the history of the HMG-CoA reductase inhibitors; J A. Tobert; Nat Rev Drug Discovery, Vol 2 July 2003, 517
R & D Performance: Drug Discovery Technologies

Mevastatin (Compactin)  
Natural Product

Lovastatin  
US 4,231,938 (1979, Merck)  
Launched: 1987 (MSD)

Simvastatin  
US 4,444,784 (1979, Merck)  
Launched: 1988 (MSD)

Pravastatin  
DE 3,122,499 (1980, Sankyo)  
Launched: 1989 (Sankyo)

Fluvastatin  
EP 114,027 (1982, Sandoz)  
Launched: 1994 (Novartis)

Atorvastatin  
Launched: 1997 (Pfizer)

Cerivastatin  
EP 00491,226 (1987, Bayer)  
Launched: 1997 Bayer  
Withdrawn: 2001

Pitavastatin  
US 5,102,888 (1987, Nissan)  
Launched: 2003 (Nissan)  
Withdrawn: 2001

Rosuvastatin  
Launched: 2003 (AstraZeneca)
Drug Discovery – The Ancient Times

Folk Medicine (mainly plants)

- **pro:** Thousands years of human experience
- **con:** Lack of reproducibility (varying doses)

Experiments in Humans

- **pro:** The „right“ object
- **con:** Toxicity

*Public theriak preparation at a market.*

*J. Lind, 1747, „Treatmant of Scurvy“*
Drug Discovery: „Clinical Studies“ in Ancient Times

Feel sick

Eat plant

Feel worse

Feel better

Eat another plant

New Drug
In late 18th century Gustav III, King of Sweden, performed a "clinical study" to confirm the negative effects of coffee drinking on health.

One convicted murder had to drink only coffee, another one tea, instead.

Two physicians supervised the study.

First, one physician died.

Then the other physician died.

Then the king was murdered.

The tea drinker died in the age of 83.

The coffee drinker survived all others.

Nevertheless, in 1794 coffee drinking was forbidden in Sweden and later again, in 1822.
The big clinical trial problem

First randomized controlled trial:
- 109 patients were recruited
- 107 were randomized

Number of patients per pivotal trial for an antihypertensive agent:
- 109 patients were recruited
- 107 were randomized

Number of patients per pivotal trial for a new oral antidiabetic drug:
- Simvastatin (Merck): 4,400
- Anacetrapib (Merck): >30,000

Number of patients for post marketing study:
- Long-lasting bronchodilator: >53,000

R & D Performance: Clinical Trials
The big clinical trial problem

1999

3 pivotal Phase III trials

2011

12 pivotal Phase III trials

R & D Performance: Clinical Trials
The effective number of exploitable drug targets can be determined by the intersection of the number of genes linked to disease and the ‘druggable’ subset of the human genome.

Eroom’s Law in pharmaceutical R&D.

Venn diagram illustrating hypothetical headwinds to R&D efficiency

- Research and development (R&D) efficiency could decline if scientific, technical and managerial improvements are offset by other factors.
- For example, R&D efficiency could be limited by the supply of validated targets that could be drugged without failing the 'cautious regulator' test and/or the 'better than the Beatles' test.
- In this hypothetical illustration, the increase in the number of validated targets between 1970 and 2010 is outweighed by increasing regulatory caution and an improving catalogue of approved drugs.

The Evolution of Drug Discovery Strategies

1900
- *in vivo* screening of any available chemical compound: industrial chemicals, dyestuffs, natural compounds, copies of existing drugs, mimics of endogenous molecules
- Pharmacological tests on whole animals or isolated organs
- Objective: detection of the therapeutic effect
- Knowledge of mechanism of action was not considered as mandatory

1960
- Progress in biochemistry and Structural biology

1985
- Development of miniturized and automated bioassays
- Progress in molecular biology
- Receptor identification
- Cloning techniques
- Automatized combinatorial chemistry

1995
- High throughput screening programs
- Screening of > 100,000 compounds/day
- Timeconsuming and expensive process
- Many hits and too few leads
- Low diversity of many libraries: large series of similar in house cpds, chemical catalog series,...
- Low drug likeness

R & D Performance: Target Selectivity
Over the past decades, one of the key goals of drug design has been the discovery of maximally selective ligands for specific binding sites on individual molecular targets.

The assumption being that if a ligand’s potency and selectivity for the desired target is increased, there should be a corresponding decrease in undesirable side effects that may arise from binding in secondary targets.
Many Targets for one Disease
Multiple Mode of Actions for Analgesics

Ascending Pathways of Pain Perception

Descending Pathways of Pain Modulation

One Disease

Indication Orientated Drug Research

Scaffold - Target - Indication

Scaffold 1
Scaffold 2
Scaffold 3
Scaffold 4
Scaffold 5
Scaffold 6

Target A
Target B
Target C

Focussed Indication

Highly Diverse Chemistry
Diverse in vitro Screening
Focussed in vivo Screening

R & D Performance: Target Selectivity
### Affinities of Some Antipsychotics for Various Neuronal Receptors

<table>
<thead>
<tr>
<th>Compound</th>
<th>$D_1$</th>
<th>$D_2$</th>
<th>$D_3$</th>
<th>$D_{4.2}$</th>
<th>$5-HT_2A$</th>
<th>$5-HT_2C$</th>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
<th>Muscarinic receptors</th>
<th>$H_1$</th>
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<tbody>
<tr>
<td>Haloperidol</td>
<td>270</td>
<td>1.4</td>
<td>21.0</td>
<td>11</td>
<td>25.0</td>
<td>&gt;5000.0</td>
<td>19.0</td>
<td>&gt;5000.0</td>
<td>4670</td>
<td>730.0</td>
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<tr>
<td>Clozapine</td>
<td>540</td>
<td>150.0</td>
<td>360.0</td>
<td>40</td>
<td>3.30</td>
<td>13.0</td>
<td>23.0</td>
<td>160.0</td>
<td>34</td>
<td>2.1</td>
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<td>Risperidone</td>
<td>620</td>
<td>3.3</td>
<td>13.0</td>
<td>16</td>
<td>0.16</td>
<td>63.0</td>
<td>2.3</td>
<td>7.5</td>
<td>&gt;5000</td>
<td>2.6</td>
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<tr>
<td>Olanzapine</td>
<td>250</td>
<td>17.0</td>
<td>54.0</td>
<td>28</td>
<td>1.90</td>
<td>7.1</td>
<td>60.0</td>
<td>230.0</td>
<td>26</td>
<td>3.5</td>
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<tr>
<td>Sertindole</td>
<td>210</td>
<td>7.4</td>
<td>8.2</td>
<td>21</td>
<td>0.85</td>
<td>1.3</td>
<td>1.8</td>
<td>1680.0</td>
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<td>570.0</td>
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<tr>
<td>Quetiapine</td>
<td>4240</td>
<td>310.0</td>
<td>650.0</td>
<td>1600</td>
<td>120.00</td>
<td>3820.0</td>
<td>58.0</td>
<td>87.0</td>
<td>1020</td>
<td>19.0</td>
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<td>Ziprasidone</td>
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<td>7.5</td>
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<td>0.30</td>
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<td>Zotepine</td>
<td>84</td>
<td>13.0</td>
<td>16.0</td>
<td>39</td>
<td>0.91</td>
<td>2.9</td>
<td>3.4</td>
<td>960.0</td>
<td>550</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Receptorsome reveals multiple targets implicated in antipsychotic drug actions

Neuronal Circuits implicated in Schizophrenia Aetiology and Treatment

Target Orientated Drug Research

**Scaffold - Target - Indication**

R & D Performance: Target Selectivity
### R & D Performance: Target Selectivity

Duloxetine, a potent dual reuptake inhibitor of serotonin and noradrenalin

![Duloxetine Structure](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Noradrenalin (NA) Uptake $K_i$/nmol/l</th>
<th>Serotonin (5-HT) Uptake $K_i$/nmol/l</th>
<th>Ratio NA : 5-HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>2480.00</td>
<td>82.00</td>
<td>30</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>7.50</td>
<td>0.80</td>
<td>9</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>38.00</td>
<td>0.28</td>
<td>136</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>240.00</td>
<td>0.81</td>
<td>296</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>40.00</td>
<td>0.13</td>
<td>308</td>
</tr>
<tr>
<td>Fluvoxamin</td>
<td>1300.00</td>
<td>2.20</td>
<td>591</td>
</tr>
<tr>
<td>Sertralin</td>
<td>420.00</td>
<td>0.29</td>
<td>1448</td>
</tr>
<tr>
<td>Citalopram</td>
<td>4070.00</td>
<td>1.20</td>
<td>3392</td>
</tr>
</tbody>
</table>

Diagram showing the mechanism of action and selectivity of SSRIs and duloxetine, with key targets and transporters labeled.
R & D Performance: Target Selectivity

Indications for Duloxetine

- major depressive disorder (MDD)
- Generalized anxiety disorder (GAD)
- moderate to severe stress incontinence (SUI)
- Painful diabetic peripheral neuropathy (DN)
- Fibromyalgia Syndrome

Duloxetine

Xeristar® Cymbalta®

Ariclaim®, Yentreve®
Three Main Clinical Scenarios for Multitarget Therapy

<table>
<thead>
<tr>
<th>Scenario A</th>
<th>Scenario B</th>
<th>Scenario C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Cocktail</td>
<td>Multicomponent Drug</td>
<td>Multiple Ligand</td>
</tr>
<tr>
<td>2 Tablets 2 Drugs</td>
<td>1 Tablet 2 Drugs</td>
<td>1 Tablets 1 Drugs</td>
</tr>
</tbody>
</table>

R & D Performance: Target Selectivity

**Designed Multiple Ligand Continuum**

- **Cleavable Conjugate**
- **Fixed Conjugate**
- **Fused Structure**
- **Slightly Overlapped**
- **Highly Integrated**

* Decreasing molecular size and structural complexity
* Increasing degree of overlap of two pharmacophores

The Discovery of Tapentadol
A New Option for Pain Treatment
Case Study: Tapentadol
**Case Study: Tapentadol**

**Tapentadol – The Path To The Market**

- **Start of the pre-clinical GLP-program**
- **First synthesis of BN-200 (February 8, 1994)**
- **Start of the pre-clinical GLP-program INN for BN 200 (CG5503) base**
- **Start of the pharmaceutical development**
- **Start of co-operation with J&J**
- **Start of co-operation with J&J**
- **Start of clinical trials with oral IR formulation**
- **First in man trial with PR formulation**
- **US submission acute pain**
- **EU submission acute pain**
- **EU and US submission chronic pain**
- **EU submission acute pain**
- **EU and US submission chronic pain**
- **US submission acute pain**
- **US submission acute pain**
- **EU and US submission chronic pain**
- **Completion EU registration procedure acute and chronic pain**
- **Extension of co-operation with J&J**
- **First national EU registration**

Timeline:
- 1994
- 1996
- 1998
- 2000
- 2002
- 2004
- 2006
- 2008
- 2010
- 2012
- 2014
- 2016
Case Study: Tapentadol

Tapentadol – A New Analgesic with a Dual Mode of Action
Tapentadol – A New Analgesic with a Dual Mode of Action

Morphine

Tramadol

Tapentadol

Metabolic Activation
Tapentadol – A New Analgesic with a Dual Mode of Action

μ-Rezeptor-Agonism (MOR) and Noradrenalin Reuptake Inhibition (NRI)

50-fold weaker μ-receptor binding in comparison to Morphine
Effect on Noradrenalin- und Serotonin

Tapentadol – A New Analgesic with a Dual Mode of Action

extracellular noradrenaline (NA) levels

extracellular serotonin (5-HT) levels

% binding

% binding

extracellular noradrenaline (NA) levels

extracellular serotonin (5-HT) levels

5HT-Transporter human

NA-Transporter human

t-zschentke, JPET 2007
Tapentadol – A New Analgesic with a Dual Mode of Action

Neue Substanzklasse MOR-NRI

Enkephalin

Noradrenalin

Tapentadol
Tapentadol – A New Analgesic with a Dual Mode of Action

Binding Affinity of $\mu$-Opioids

Hydromorphone  Buprenorphine  Fentanyl  Morphine  Methadon  Pentacocin  Dextropropoxyphene  Oxycodone  Pethidin  Propiram  Codein  Tildin  Tramadol
Spinal Mechanism of Action: MOR-NRI

Tapentadol – A New Analgesic with a Dual Mode of Action

Ascending Pathway

Descending Pathway

NA

Tapentadol

MOR

α₂-R

SP

Glut

Pain signal
Data are for the seven major markets (the United States, Japan, France, Germany, Italy, Spain and the United Kingdom).

The neuropathic pain market is expected to grow from US$2.4 billion in 2010 to reach $3.6 billion by 2020. Nucynta ER is forecast to be the market leader by 2020, achieving neuropathic pain-specific sales of $1.2 billion in 2020.

Marketed drugs will continue to lose market share to generics, and the current pipeline is set to account for 59.1% of market share by 2020. *'Other' corresponds to other marketed drugs and drugs that are prescribed off-label in this market.

Launched Chiral Switches: Successful Examples

**Omeprazole to Esomeprazole**

- In commercial terms, probably the most important chiral switch so far has been the switch from the blockbuster gastric anti-secretory proton pump (H+/K+-ATPase) inhibitor (PPI) omeprazole (Losec®, Prilosec®) to esomeprazole magnesium (Nexium®).
- Omeprazole is a very potent inhibitor of gastric acid secretion, with a long-lasting duration of action.
- In clinical studies, it proved superior to previous treatments for gastroesophageal reflux disease and peptic ulcers.
- Omeprazole is a gastric anti-secretory proton pump inhibitor marketed under the tradenames Losec® and Prilosec® by AstraZeneca.
- Launched in 1988 by Astra AB, Omeprazole was a blockbuster commercial success and became the world’s best-selling drug with sales of **US $6.2 billion in 2000**.
Case Study: Omeprazol

Mechanism of Action of Proton Pump Inhibitors – Drug Activation in Acidic-Producing Cells

Sulfenic Acid - H₂O → Sulfene amide

H⁺/K⁺-ATPase – SH

H⁺/K⁺-ATPase – SH
Case Study: Omeprazol

Discovery of Omeprazol

*Preclinical Tox-Study*

Picoprazol, 1876
Preclinical Candidate

Breeding Dog
Fabian

Vaskulitis

Picoprazol Group

Placebo Group
Irreversible Proton Pump Inhibitors
The „Prazole Family“ on the Market

Case Study: Omeprazol
Irreversible Proton Pump Inhibitors
The „Prazole Family“ in the Pipeline

Case Study: Omeprazol

Ilaprazole

Tenatoprazole

Leminoprazole

TY-11345
Launched Chiral Switches: Successful Examples

**Omeprazole to Esomeprazole**

- Omeprazole is a racemate. Its chirality stems from the presence of a chiral centre at the sulphur atom of the methylsulphinyl bridge between the 1H-benzimidazole and the pyridine moieties.
- Omeprazole is in fact a prodrug, acting as a PPI by means of the ‘omeprazole cycle’, which involves achiral intermediates.
- Omeprazole undergoes polymorphic metabolism. Approximately 3% of Caucasian individuals and 15–20% of Oriental individuals are slow metabolizers of omeprazole.
- Based partly on the fact that omeprazole exhibits polymorphic metabolism, AstraZeneca developed the chiral switch drug esomeprazole (which is the (S)-(−)-enantiomer of omeprazole) based on the premise that therapeutic benefit would be achieved by less inter-individual variation, (slow versus rapid metabolizers), and that average higher plasma levels would provide higher dose efficiency in patients.
Launched Chiral Switches: Successful Examples

Omeprazole to Esomeprazole

- Esomeprazole was introduced as the magnesium trihydrate salt first in Europe (in 2000) and later in the US (in 2001) under the now famous trade name Nexium®. (Market in 2003: 3.6 Billions U.S. $)

- Esomeprazole is completely metabolized by the cytochrome P450 system, mainly by the polymorphic isoform CYP2C19, which is responsible for the formation of the 5-hydroxymethyl and desmethyl metabolites.

- Healing of reflux oesophagitis with a 40 mg per day dose of esomeprazole magnesium occurred in ~78% of patients after four weeks of treatment and in 93% of patients after eight weeks, compared with 65% and 87% of patients, respectively, treated with 20 mg per day of omeprazole.

- lower first pass metabolism, slower plasma clearance and increased systemic availability compared to the (R)-enantiomer.

- Clinical evidence that the single enantiomer maintains intragastric pH above 4 in patients with gastro-oesophageal reflux disease significantly longer, with a 24 median intragastric pH greater than an equal dose of the racemate.

- Reduction in interpatient variability in response.
Discovery of Aspirin

by Felix Hoffmann (October 10th, 1897)

Felix Hoffmann (1900)

First Aspirin-bottle
Die Geschichte der Salicylsäure

Antike:
Seit der Antike ist die Verwendung von Weidenrinde (Salicis cortex) als pflanzliches Heilmittel belegt (antipyretische und analgetische Wirkung)

300 v. Chr.
Erwähnung im Corpus Hippocraticum

Rembert Dodoens (belgischer Kräuterspezialist) beschreibt die schmerzstillende Wirkung der Weidenrinde; Verwendung des Mädesüßkrauts (Spiaea ulmaria) bei Erkältungen, Muskel- und Gelenkrheumatismus

1763
Edward Stone (Vikar in Chipping Norton); Verwendung der Weidenrinde als Ersatz für die Chinarinde

1792
Samuel James (englischer Arzt) empfiehlt die Palmweidenrinde (Salix caprea) zur Fiebersenkung

1828
Johann Buchner (Münchener Pharmazieprofessor) isolierte das Salicin

1839
Salicylsäure als Bestandteil des Salicins konnte durch Raffaele Piria nachgewiesen werden

1859
Aufklärung der Struktur als Hydroxybenzosäure durch Hermann Kolbe und erste Synthese

1870
Beweis der ortho-Substitution durch V. Meyer

1874
Verbesserte Synthese der Salicylsäure (Kolbe-Schmitt-Synthese) und Gründung einer Fabrik zur Synthese von Salicylsäure durch Kolbes Freund und Schüler Friedrich von Heyden (Arzneimittelwerke Dresden)

ab 1876
Anwendung von Natriumsalicylat an der Berliner Charité als Antipyretikum und Antirheumatikum

1991
Aufnahme der Weidenrinde in das Deutsche Arzneibuch (DAB)
Case Study: Aspirin

Der Verpackungen von Aspirin
im Laufe der Geschichte

Aspirin Verpackung
1899

Aspirin Verpackung
1919

Aspirin Verpackung
1934

Aspirin Verpackung
heute
Case Study: Aspirin

Aspirin
The Neverending Story

Historical Aspirin Advertisings
Rolle der COX-1 und der COX-2 im Arachidonsäurestoffwechsel

Membranlipide

Phospholipase A2

Arachidon-säure

COX-1

konstitutive Expression

TXA₂, PGI₂, PGE₂

Anthithrombotische Effekte
Thrombozytenaggregation
Schleimhautprotektion
Gefäßdurchblutung

COX-2

induzierte Expression

TXA₂, PGI₂, PGE₂

Antiinflammatorische Wirkung
Schmerz
Entzündung
Fieber

Prostanoide

→ anthithrombotische Effekte
→ Thrombozytenaggregation
→ Schleimhautprotektion
→ Gefäßdurchblutung
Case Study: Aspirin

The multiple pharmacological actions of aspirin

Inhibition of COX activity

Arachidonic acid

Prostaglandins
Thromboxane A₂

Suppression of gene transcription

Salicylate ≥1 mM

Salicylate ≤1 mM

C/EBPβ

NF-κB

mRNA

COX-2

mRNA and others

Posttranscriptional modifications (Ferritin, eNOS, and others)
Case Study: Aspirin

From 1899 to 2005 (projected) turnover of Bayer aspirin in millions of DM (Deutsche Mark).

1 DMn (Deutsche Mark) is equivalent to 0.51 D or 0.67 USD (January 2007).
The Future of R & D

Key R&D bottlenecks to overcome

- Discovery research
- Preclinical develop.
- Translational medicine
- Clinical develop.
- Pharmacovigilance

Predictive pharmacology
Predictive toxicology
Identification of biomarkers
Patient recruitment
Validation of biomarkers
Risk assessment with regulatory authorities

Efficacy → Safety

Data → Knowledge → Prediction
Preclinical models that are more predictive of clinical efficacy and safety
Towards Personalised medicine!
*Treatment tailored to specific patient groups*

New effective medicines create more value for:

- Patients
- Healthcare providers
- Science - Society

*today, one-size-fits-all*

*New medicines*

*New diagnostics*

*tomorrow, treatment will be tailored to patient groups defined by their disease pattern*
Innovation in the Pharmaceutical Industry

What is the future?

Overall Treatment Benefit

Personalised medicine

Pharmacology

Time

1900  2000  2100
Potential drug development futures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Today</th>
<th>Current trend</th>
<th>Bright future</th>
<th>Sustained future</th>
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<tbody>
<tr>
<td>Patent life*</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
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<tr>
<td>Development time*</td>
<td>10</td>
<td>14</td>
<td>5</td>
<td>10</td>
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<td>Sales life</td>
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<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Average yearly sales</td>
<td>$0.5</td>
<td>$2</td>
<td>$0.2</td>
<td>$0.33</td>
</tr>
<tr>
<td>Gross margin</td>
<td>80%</td>
<td>50%</td>
<td>80%</td>
<td>65%</td>
</tr>
<tr>
<td>Lifetime gross profit</td>
<td>$4</td>
<td>$6</td>
<td>$2.4</td>
<td>$2.15</td>
</tr>
<tr>
<td>Payback ratio±</td>
<td>4</td>
<td>3</td>
<td>9.6</td>
<td>4.3</td>
</tr>
</tbody>
</table>

* In years; ± Gross margin divided by development costs.

Innovation in the Pharmaceutical Industry

What is the future?

There will be winners and losers among companies and countries:
- Hugue need and opportunities remain
- Industry is under pressure and is changing
- Europe is losing competitiveness

Success will depend on:
- Innovation
- Productivity
- Managing benefit/risk
- Reward for innovation
- Market responsiveness

Where will the pharmaceutical industry invest in the future?
- Where it is cost effective
- Where researchers can be recruited
- Where medicines can be prescribed and used
- BRIC countries – Brazil, Russia, India and China are rapidly growing