Big and Small Pharma in the Development of Infectious Disease Treatment

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In the last few years big pharmaceutical companies abandoned, cut-back or spun off their antibacterial research:

Aventis, Lilly, Bristol-Myers Sqibb, Wyeth, Roche, GSK

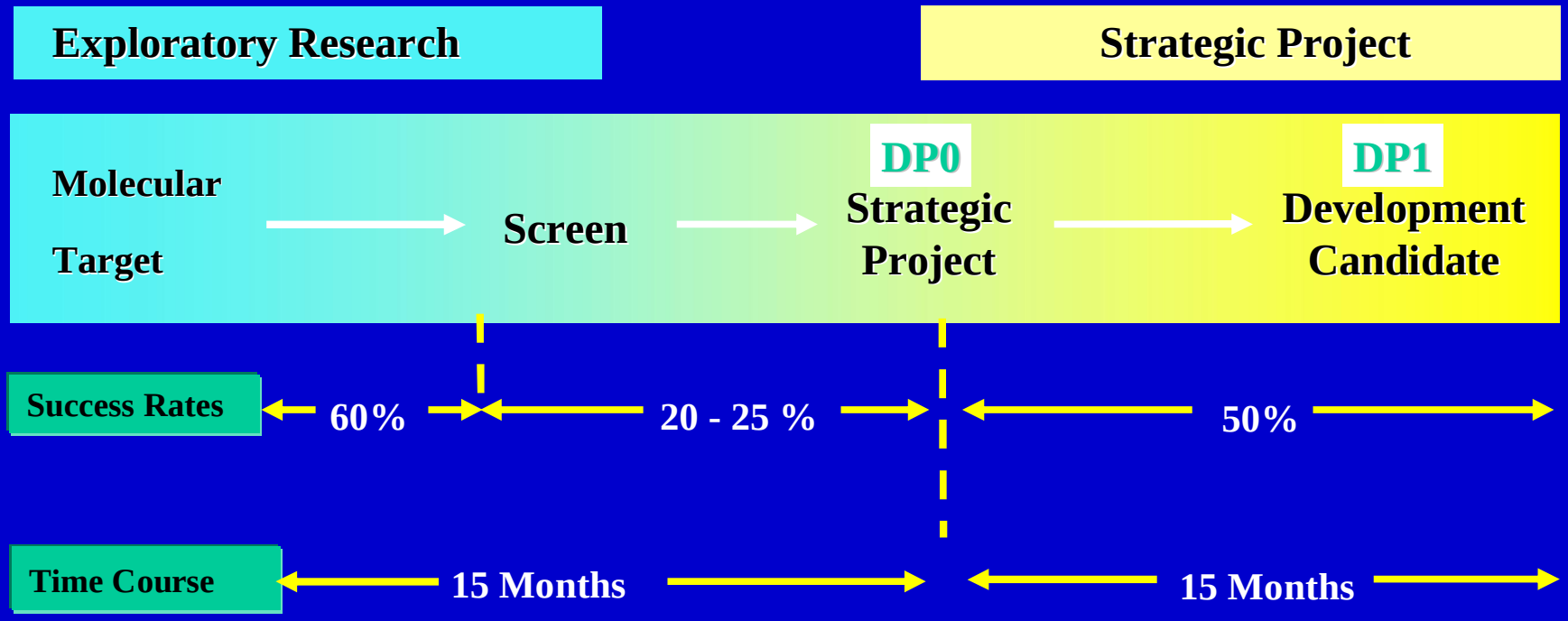
In the following presentation the

- **Impact of cut-back**
- **Reasons for abandoning or cut-back**
- **Requirements and ideas for improvement**

will be discussed

From Target to Drug

I) Research Phase



II) Development Phase

From DP1 to Market: 6 Years, 800 mio Euro

DP0 decision point 0: Decision about novel strategic project

DP1 decision point 1: Decision about start of development

Impact of Research Cut-back

New molecular entities (NMEs) publicly disclosed in the research and development programs of the world's 15 largest pharmaceutical companies

Indications or type of agent	No. of NMEs
Cancer	67
Inflammation/pain	33
Metabolic/endocrine	34
Pulmonary	32
Anti-infective	31
Neurological	24
Vaccines (passive or active)	18
Psychiatric	16
Cardiac	15
Hematologic	12
Gastrointestinal	13
Genitourinary	12
Ocular	4
Dermatological	4

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Impact of Research Cut-back

Selected new molecular entities (NMEs) publicly disclosed in the research and development programs of the world's 15 largest pharmaceutical companies

Indications or type of agent	No. of NMEs
Depression	14
Anxiety	9
Bladder hyperactivity	8
Osteoporosis	7
Antibacterials	5
Erectile Dysfunction	4
Obesity	3

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Impact of Research Cut-back

Selected new molecular entities (NMEs) publicly disclosed in the research and development programs of the world's 7 largest biotechnology companies

Indications or type of agent	No. of NMEs
Inflammation/immunodulator	24
Metabolic/endocrine	15
Cancer	13
Inherited enzyme deficiencies	9
Cardiovascular condition	6
Hematologic condition	3
Dermatologic condition	3
Renal condition	3
Neurology	2
COPD*/asthma	2
Antibacterial agent	1

* COPD, chronic obstructive pulmonary disease

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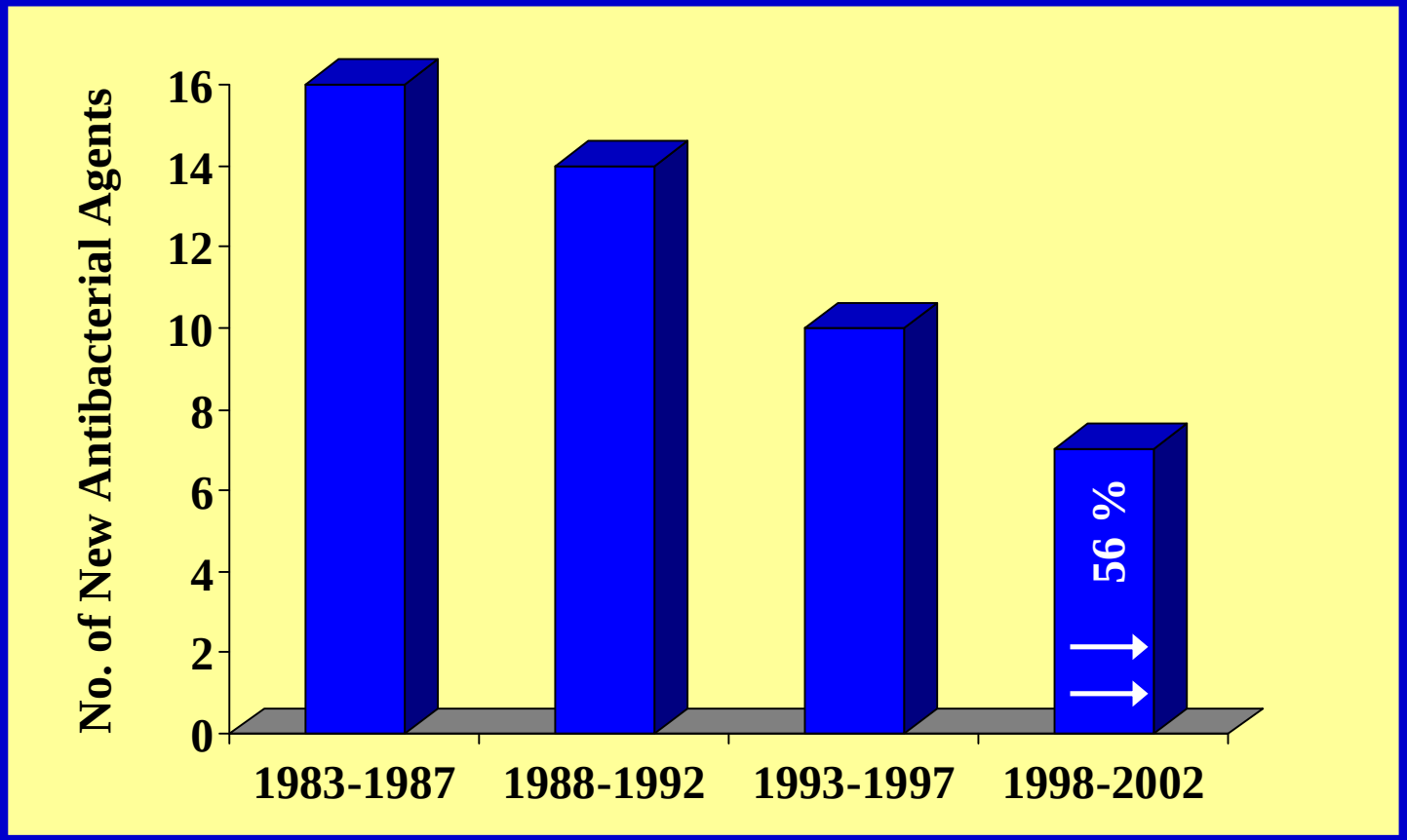
New antibacterial agents approved in the United States 1983 - 2002, per 5-year period



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Reasons for Abandoning or Cutting Back Antibiotic R & D Big Pharma Research

- **High failure rate in Research**
- **Lack of pipeline compounds**
- **Difficulty to discover new agents even for experienced people - if not shifted to different research targets**
- **Highly promising approach to genomic based new agents has failed to date**
- **Research focus in favor of chronic treatments**
  - e.g. chronic viral diseases as HIV, HCV vs. acute treatments
- **Based on cumulated experience in animal models, high safety margins have to be achieved preclinically**

Reasons for Abandoning Cutting Back Antibiotic R & D Big Pharma Development

- **High development costs**
  - multiple indications to be studied in parallel
- **High regulatory hurdles**
  - in general 2 large studies per indication plus a certain number of specific organisms (US)
  - "small delta" requirements, in particular in Europe
  - additional safety studies, e.g. QT
  - label uncertainties, e.g. label restrictions as outcome of MRP+ or centralized submission procedure
- **Main respiratory indications, e.g. AECB*, Acute Sinusitis might get lost**
- **Highly competitive field**
  - most widely used or largest selling antibiotics became generic, e.g. ciprofloxacin, co-amoxiclav, ceftriaxone

+ Mutual Recognition Procedure

*** Acute Exacerbation of Chronic Bronchitis**

Small Pharma
Biotech Companies

- **Funding not intended and sufficient to finance clinical development**
  - expected sales for a niche product could be very attractive for a small company, but development costs could be unaffordable
- **Funding usually require evidence that Big Pharma ultimately would have an interest in the product being developed**
- **Lack of finding Large Pharma partners for the clinical development leads to the risk of "going alone"**

⟹ **The outcome could decide on survival of biotech companies**

Small Pharma
Biotech Companies

- **Big Pharma gives compounds back to the originator, if the "NPV"* is not attractive enough or the research focus has changed**
- **This could lead to serious troubles because of**
  - financial resources for further development not sufficient
  - lack of experience in clinical development and bringing a drug to the market

*** Net Present Value**

Small Pharma
Biotech Companies

- **“Discovery Institution” becomes “Development Institution” which was not the initial intention**
- **Some made it: e.g. Cubist, ... changed its strategy:**
  - focus on development of compounds and
  - commercializing daptomycin

What is Required for Improving the Future

- Create a culture of cooperation between stakeholders
- Better communication with academia, regulatory authorities and industry
- Implementation of regulatory and other incentives

What is Required for Improving the Future

- Recognize and accept a balance between public health/medical needs and the commercial realities of drug discovery and development
- To achieve a reasonable return of investment restrictive price control has to be reconsidered
  - "premium price" is one option, but it only works if the new drug is not used as the "sunday's best"
  - recent evaluations in some EU countries to restrain from a restrictive price control for a certain time after MAA* is a good example
- Reimbursement of novel drugs should also consider access to best treatment and Health Economic benefits (reducing the days of illness)

*** MAA = Marketing Authorization Application**

What is Required for Improving the Future

- Create a culture of cooperation between stakeholders
- Better communication with academia, regulatory authorities and industry
- Implementation of regulatory and other incentives

What is Required for Improving the Future

- Close collaboration of industry scientists, clinicians and agencies on development strategies, trial design, supportive e.g. PK/PD and other preclinical models in order to speed up the development and approval process
- Receptive environment: the medical community and health authorities recognize the need for new antibacterial agents - but was not reflected by recent approvals of new antibiotics (label restrictions, requirement for more clinical data, additional studies etc.)

What is Required for Improving the Future

- Create a culture of cooperation between stakeholders
- Better communication with academia, regulatory authorities and industry
- Implementation of regulatory and other incentives

What is Required for Improving the Future
Current Incentives

- **Orphan Drug Designation (US and EU)**
  - not really helpful for antimicrobial agents
  - qualifying criteria not always affordable for anti-infectives

- **Benefits: close cooperation with regulatory authorities on protocol development for preclinical and clinical trials and guidance through the entire development**
  - market exclusivity (10 years EU, 7 years US, probably not sustainable)
  - increased probability for accelerated review
  - could be more attractive for small companies [Tax credits in the US (up to 50 % of clinical research expenditure) and in some EU countries]
  - fee waivers

What is Required for Improving the Future
Current Incentives

- **Fast Track Designation (US only)**
  - qualifying criteria could apply to new antibacterials
  - close cooperation with FDA during development including protocol assistance
  - “rolling NDA” possible, e.g. review of portions of the Dossier
  - accelerated approval
  - post-marketing studies may be required, not only if a conditional approval is obtained

What is Required for Improving the Future
Current Incentives

- **Accelerated Evaluation (EU)**
  Quality criteria:
  - seriousness of the disease (e.g. HIV, cancer) to be treated
  - absence of an appropriate alternative approach
  - anticipation/proof of exceptionally high therapeutic benefit

  ⟹ **Does not always fit for antibacterials**

What is Required for Improving the Future
Current Incentives

- **Scientific Advice from EMEA (EU)**
  - need if CPMP guidelines cover less than 40 % of specific issues, not sufficient patients for clinical trials
  - recommended in a very early phase of the development
    - takes 6 months
    - non-binding
    - no pre-evaluation of existing data
    - scientific follow-up possible at any time

What is Required for Improving the Future
New Incentives

- **Reliable label expectations - based on a company's successful completion of the preclinical and clinical package**
  - could be achieved by guidance of regulatory authorities (continued scientific advice)
- **Application of current incentives**
  - e.g. Fast Track designation in EU?
  - more flexibility in terms of number of trials per indication
  - development of criteria based on bridging concepts of PK/PD and clinical data to support clinical trials in related indications

What is Required for Improving the Future
New Incentives

- **Recently new initiative of the FDA:**
  Continuos Marketing Application (CMA) is a highly appreciated step in the direction "guidance as an incentive" and "accelerated evaluation"

- **Could this be in option for the EU as well based on increasing the collaboration between FDA and EMEA as announced in their information-sharing agreement last year?**

What is Required for Improving the Future
New Incentives

- **Extended Market Exclusivity**
  - e.g. for another prescription drug owned by the manufacturer ("wild-card" exclusivity)
  - or for another antimicrobial agent owned by the manufacturer (modified "wild-card" exclusivity)
- **Both would have high potential impact**
  - currently no legal prerequisite

What is Required for Improving the Future
New Incentives

Summary

- Even there are notable exceptions like Novartis, Pfizer, Bayer and Abbott, but large Pharmaceutical companies have abandoned or cut-back their research and development of antibacterial agents

- Investment and human resources have been shifted to the more attractive field of chronic (viral) diseases

- Small Biotech Companies, if they remained focused on antibacterial research, run the risk of going alone due to the lack of finding a large Pharmaceutical Partner for the clinical development and approval process

What is Required for Improving the Future
New Incentives

Conclusion

- **There is an urgent need for improvement by**
  - close collaboration and communication with expert societies, academia, clinicians, regulatory authorities and industry to identify points of medical and scientific debate and clarify the medical needs to be addressed in further development of antibacterial agents
- **Regulatory guidance or continuous scientific advice to reduce label uncertainties and accelerate the approval process**
- **Consider new incentives like Market Exclusivity via “Wild-Card” or “Modified Wild-Card”**
- **Explore public - private partnerships for antibacterial drug research and development as it has been implemented for HIV, Tuberculosis and Malaria**