

**LACK OF DEVELOPEMENT OF NEW ANTIBIOTICS:
WHO SHOULD BE BLAMED AND WHAT CAN BE
DONE?**

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Earlier Opinions

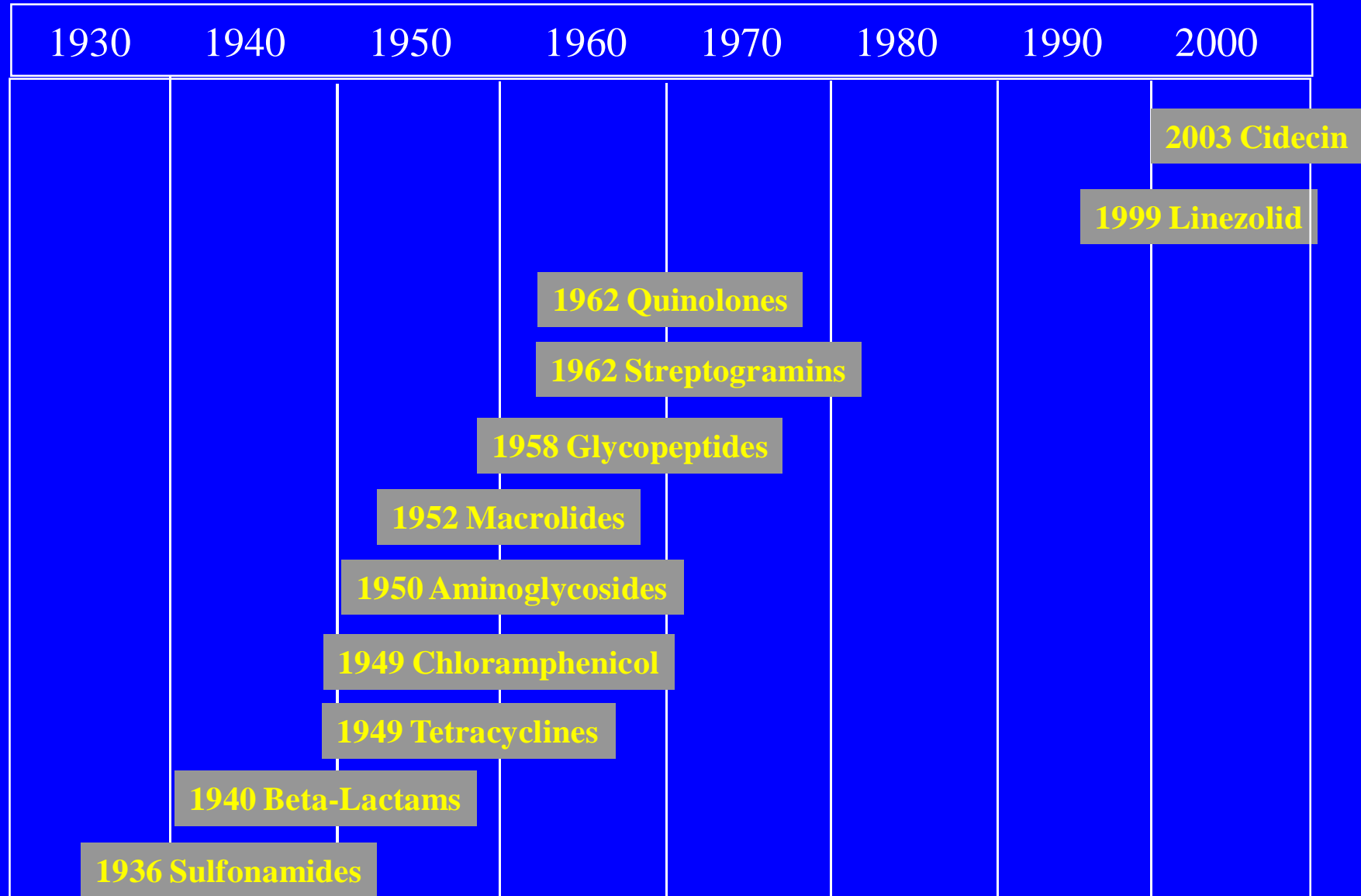
*“The book of infectious diseases
can now ultimately be closed!”*

US Ministry of Health, 1972

*„Everything that can be
invented has been invented.“*

*Charles H. Duell, Commissioner,
U.S. Office of Patents, 1899*

Development of Novel Antibiotic Classes



Pharmaceutical Companies and Antibiotic R & D

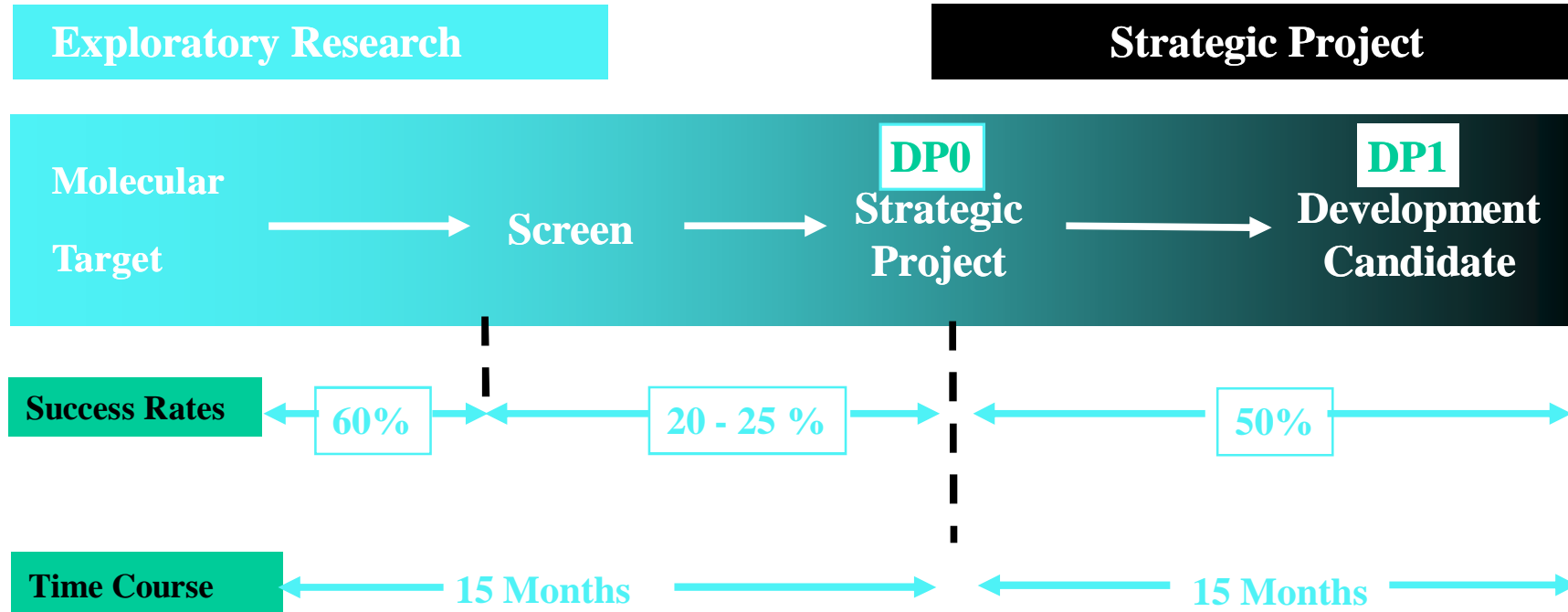
- Lilly, Wyeth, Roche, BMS, Aventis, (GSK), AstraZeneca: left or drastically reduced
 - High failure rate in research, lack of pipeline compounds
 - Preference for chronic vs. acute treatments
 - Increasing generic competition and high regulatory hurdles
 - High development costs (many indications)
 - Promises of genomics have not delivered

Pharmaceutical Companies and Antibiotic R & D (cont:d)

- Cubist: changed their strategy
 - Development of a few compounds took all resources, no more research
 - Partnerships on targets, screens and technologies difficult to achieve
- Novartis, Pfizer, Bayer, Abbott: step in or remain committed
 - High medical need, resistance
 - Higher succes rates in development

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

Newly Licensed Antibiotics

- New quinolones; improved Gram-positive activity
- New carbapenems, e.g. ertapenem; no spectrum improvements
- New macrolides, e.g. Synercid and telithromycin; improved Gram-positive activity

Newly Licensed Antibiotics (cont:d)

- New lipopeptide, daptomycin; improved Gram-positive activity
- New oxazolidinone, linezolid; improved Gram-positive activity
- Tigecycline; improved Gram-positive spectrum **but also important Gram-negative activity, e.g. against *Acinetobacter* spp.**

MRSA, VRE and PRP are important pathogens but so are multiresistant Enterobacteriaceae *Pseudomonas* spp., *Acinetobacter* spp, *Burkholderia* spp. and *Stenotrophomonas* spp.

No. of Targets in Well Known Target Areas

Target area	No. of known essential genes	No. of marketed antibiotics
DNA replication	19	3
Divison	5	0
Transcription	6	1
Translation	54	7
Fatty acid biosynthesis	7	1
Cell wall biosynthesis	11	2
Nucleotide biosynthesis	8	0
Co-enzyme biosynthesis	4	2



< 20% of well known essential targets are exploited

Which are the hurdles in the development of new antibiotics?

Lack of industry incentives

- Infections normally require short-term Rx and constant marketing efforts
- Normally many indications – drive phase III costs
- Small chances to become billion dollars products

Hurdles (cont:d)

Regulatory requirements

- Increasing demands for special safety studies, e.g. ECG and photosensitivity for quinolones
- Demands for documentation of all types of infections, often in at least 2 trials and also for a minimum number of pathogens (FDA)

Hurdles (cont:d)

The prescribers

- "Save the new ones for special situations"
- "New antibiotics too expensive"
- "Let's wait and see what others do"

Hurdles (cont:d)

Academia

- Limited research on identification of new antibiotic targets (where academia is equal to or better than industry)
- Quite a lot of research on alternative strategies, e.g. cytokines, which are often very far from clinical trials and, sometimes, of very limited commercial interest.

Hurdles (cont:d)

Biotech Companies

- Not enough capital to take products through clinical development

Can we overcome the hurdles?

Industry

- Create good relations with academia and small biotech companies on research dealing with pathogenesis and target identification.
- Be prepared to take over products prior to phase I/II
- Look in the crystal ball for future problems in bacterial infections, e.g. multi-resistant Gram-negatives

Overcoming the hurdles (cont:d)

- Prices: either low for drugs which are likely to be widely used, e.g. routinely for LRTIs and URTIs, or very high for drugs against resistant organisms where the profession might want to reserve the antibiotic. Dialogue needed prior to decision.
- A couple of hundred million dollars is also money!

Overcoming the hurdles (cont:d)

Regulators

- Allow extrapolations between indications, e.g. otitis-sinusitis and gynaecological-intraabdominal infections
- Allow data to be generated in small explanatory pk/pd studies of selected patients
- Seek continuous endpoints.

Overcoming the hurdles (cont:d)

- Be realistic in the requirements for documentation of pathogens; if the MICs for MSSA and MRSA are the same there is no need to require documentation of infections caused by both types of organisms for a non- β -lactam
- Abandon (in most cases) indications by pathogens; statistically meaningless and difficult to find patients