Challenges in Antimicrobial Clinical Development

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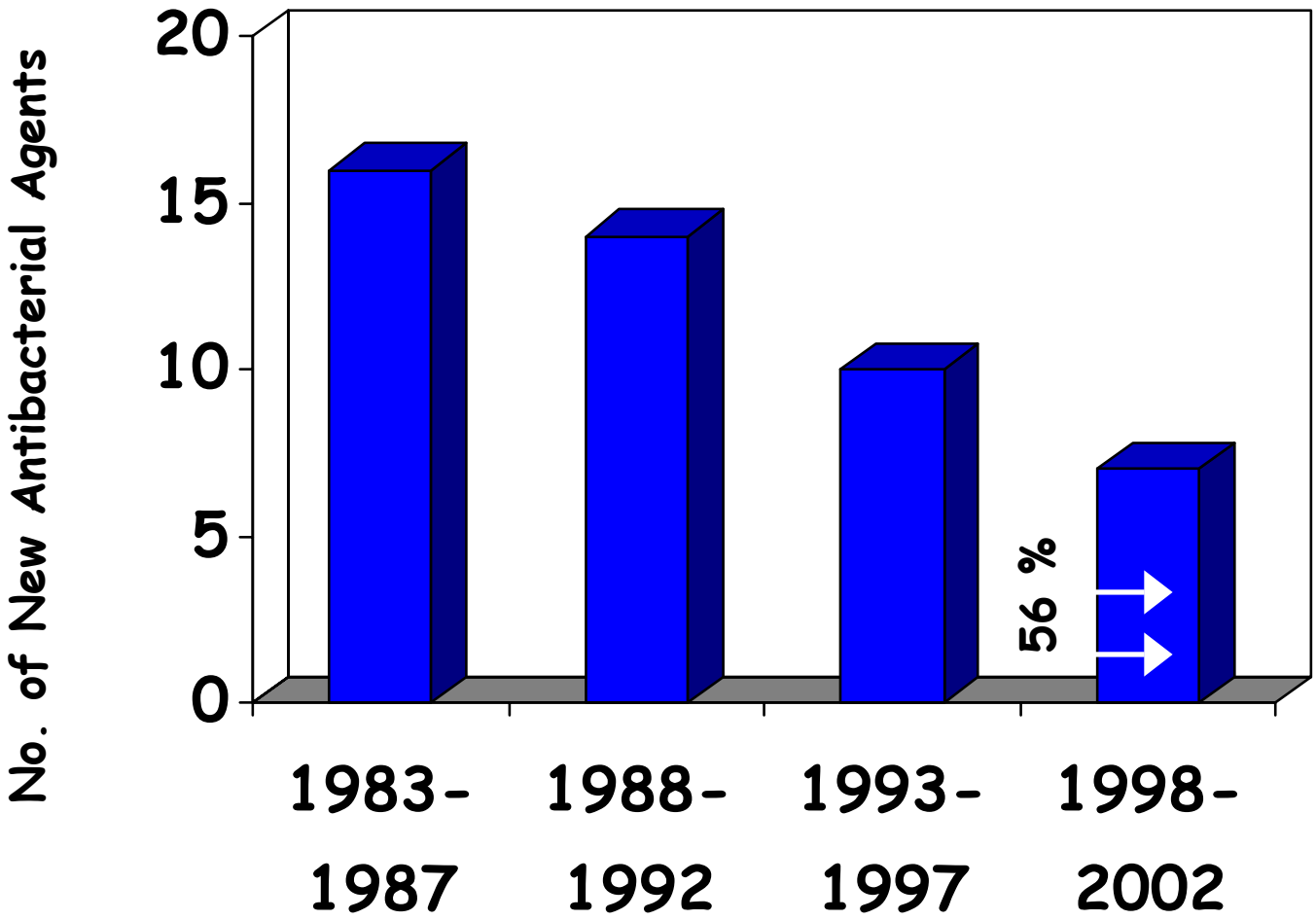
New antibacterial agents approved in the United States 1983 - 2002



Spellberg, CID May 01,2004; 38

Challenges for Antibiotic R & D in 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

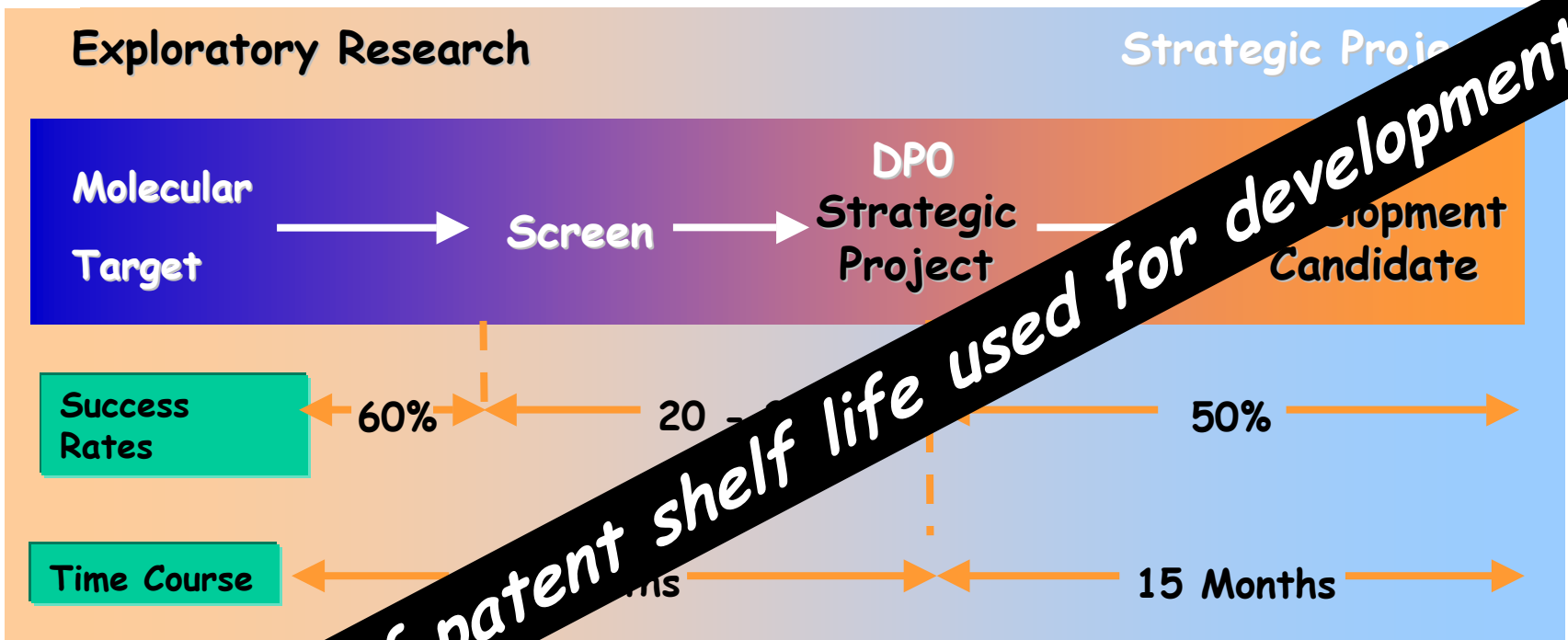
Highly promising approach to genomic based new agents has failed to date

Research focus in favour 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

From Target to Drug / Patent life time

I) Research Phase



-> ~ 50% of patent shelf life used for development

II) De… Phase

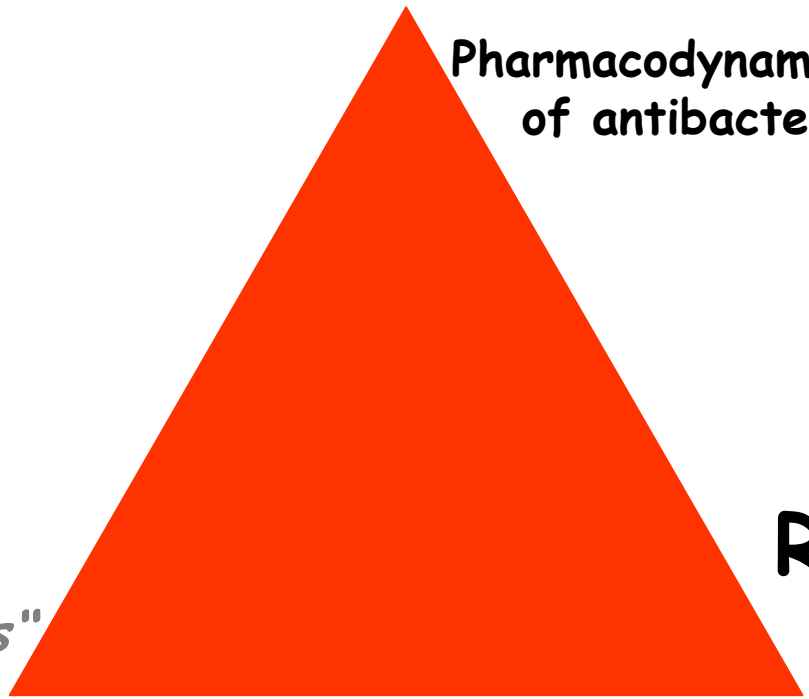
…P1 to Market: 6 Years, 800 mio Euro

DP0= decision point 0: Decision about novel strategic project
DP1= decision point 1: Decision about start of development

Challenges in the Development of Anti-infectives

Regulatory

Pharmacokinetics and Pharmacodynamics in the development of antibacterial medicinal products CPMP/EWP/2655/99



Strategic

„Superiority Claims"
„Time to Market"
in a very competitive environment

R&D

Discovery of and proof of concept for „Improved Candidates"
„Patents"

Role of Clinical Pharmacology in tackling the Challenges in the Development of Antimicrobials

- Classical safety and PK
  (frequent and less frequent AEs)
- PK/PD Defining the dose for clinical studies
  -> 'mechanistic' PK/PD approaches
- Sources and of PK variability (e.g. interactions) and their impact on antimicrobial activity
  -> population ('probabilistic') PK/PD approaches
- Justify the dosing regimen for the patient population based on PK/PD -> population PK/PD approaches
- Dosing recommendations for clinically relevant *drug drug interactions* and *patients at risk*

General Strategy to Define and Validate the Clinical Dose by PK/PD

Scientific knowledge

regulatory guidelines

Development Candidate → Proof of Concept → Approvable Drug

~ 3 years

‚Mechanistic' approach

PK:
non-compartmental
compartmental

Physiology Based PK (PBPK)

PK/PD:
In vitro/ in vivo/in silico
based on lead organisms

‚Probabilistic' approach

PK:
Population methods in patients

Modeling and Simulation

PK/PD:
statitistical tools based on epidemiological data,

e.g. Monte Carlo Simulations

PK/PD Tools I

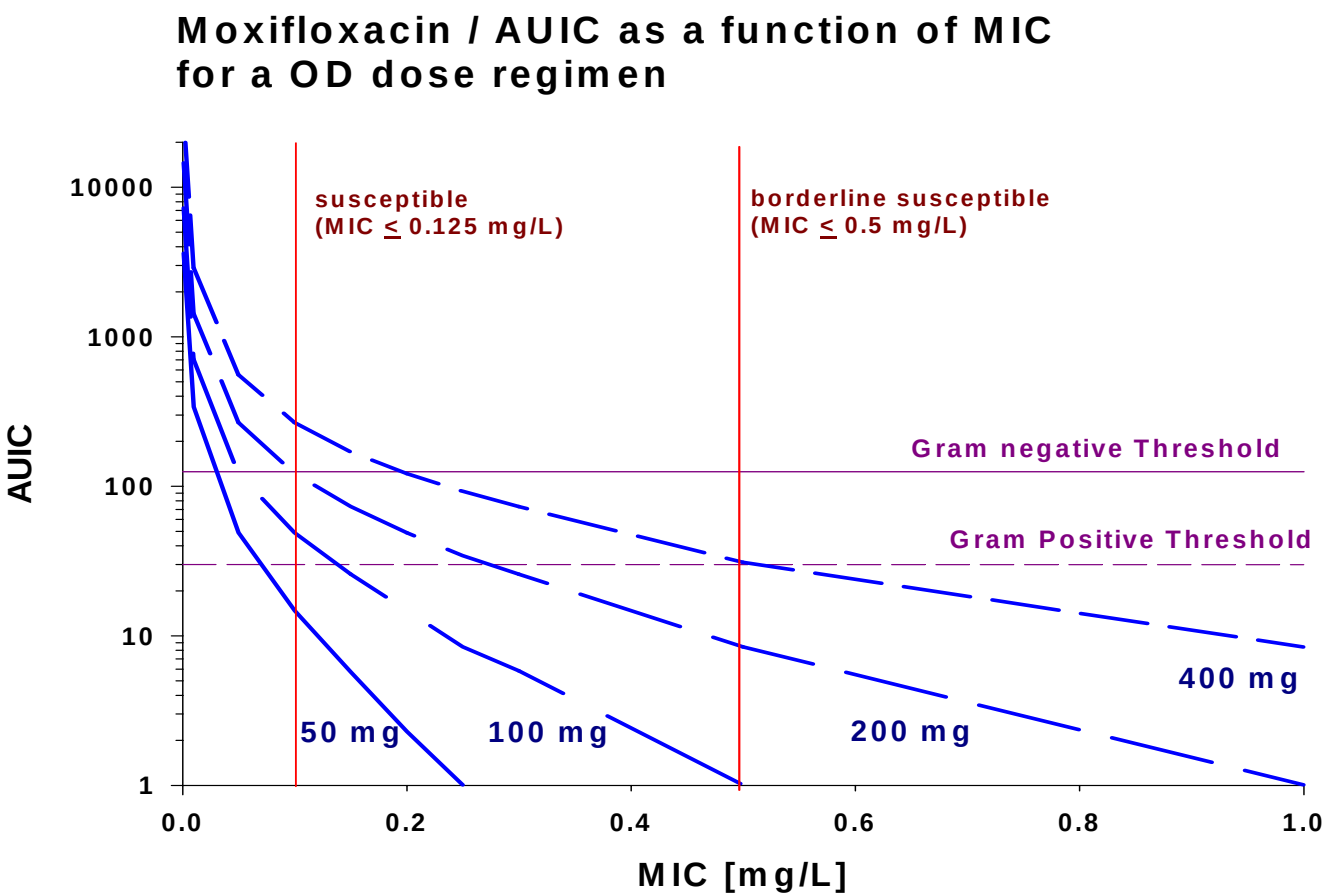
Mechanistic:

Physiology Based PK	Interspecies scaling of PK Target tissue concentrations
Tests of antibacterial effects:	static in vitro models -> MIC
Determination of the dominant PK/PD index driving the effect:	animal models, dynamic in vitro models (-> time to kill; change in viable counts; maximum reduction in viable counts; I_E; AUBC, AABC AUC/MIC, Cmax/MIC, t>MIC, $AUBKC_{norm}$
Determination of the magnitude of the PK/PD Index	-> PK/PD cut off points,

Target Concentration Strategy / Phase I-II

Deterministic PK/PD in early Phase I

Decision on target dose for MFX based on PK/PD from single dose escalation

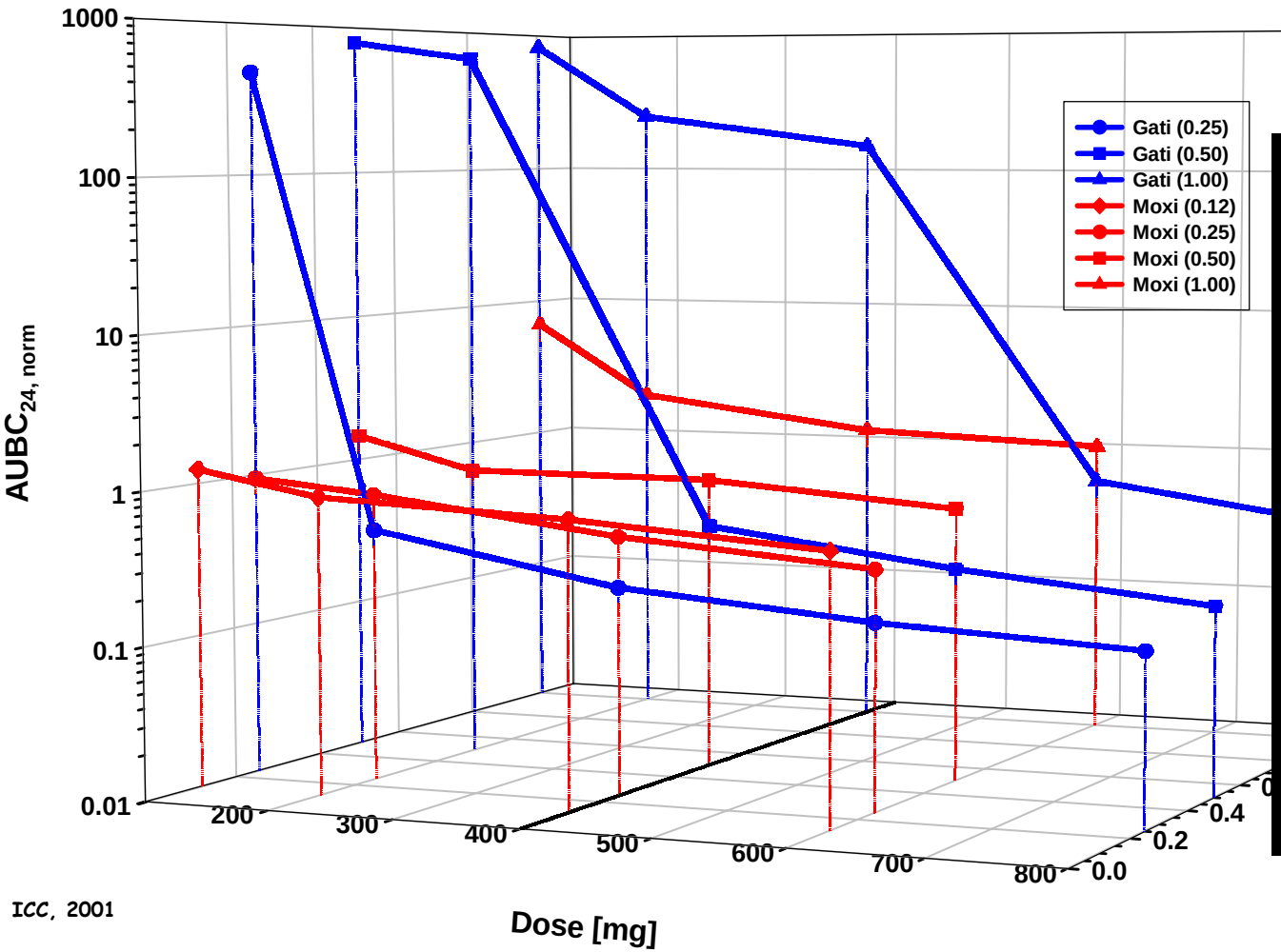


Use:

- Early dose estimation based on good knowledge of PK and PD properties of MFX
- Predicted dose: 400 mg once daily

Target Concentration Strategy / Phase II - III

Deterministic PK/PD mapping to characterize the effect of PK variability on the bactericidal effect of MFX



ICC, 2001

Use:

- Decision on clinical dose
- Predicted dose: 400 mg once daily
- Decision on necessity of dose adjustments (interactions, special populations)

PK/PD Tools II

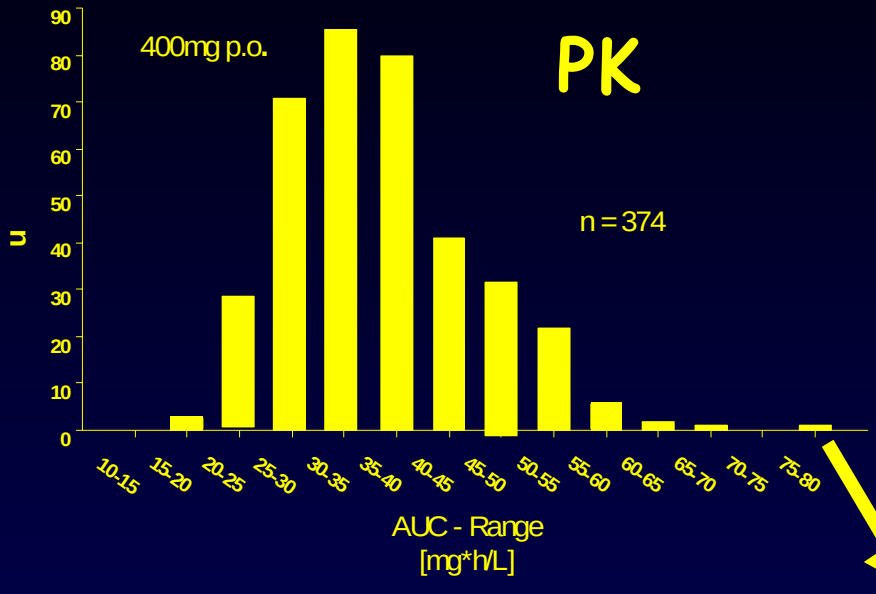
Probabilistic PK/PD methods

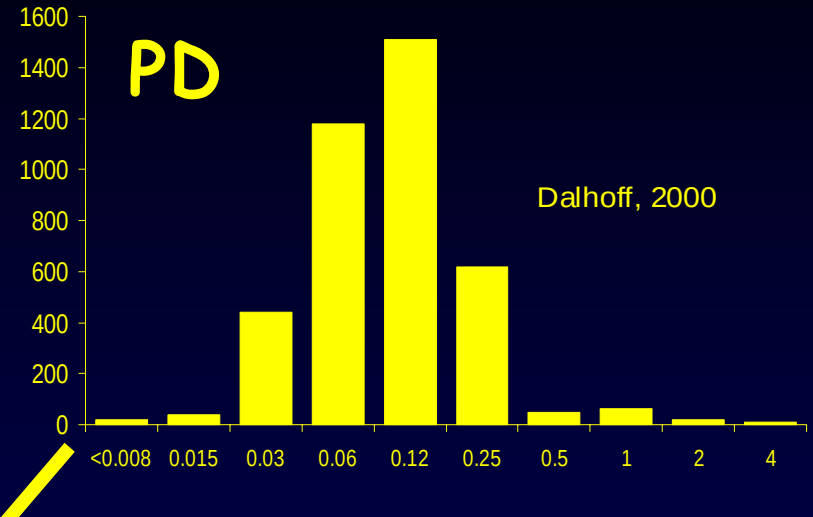
Principle: **Determination of the likelihood of clinical success by implementing information on PK variability and PD variability into PK/PD analysis**

Requirements: **Models describing the pharmaco kinetic variability in the target population using population PK methods**

Epidemiological distribution pattern of the target pathogens

PK/PD indices identified and quantified by mechanistic methods based on epedimiologic data on the targeted micororganisms
e.g. AUIC cut off, microbiological breakpoint

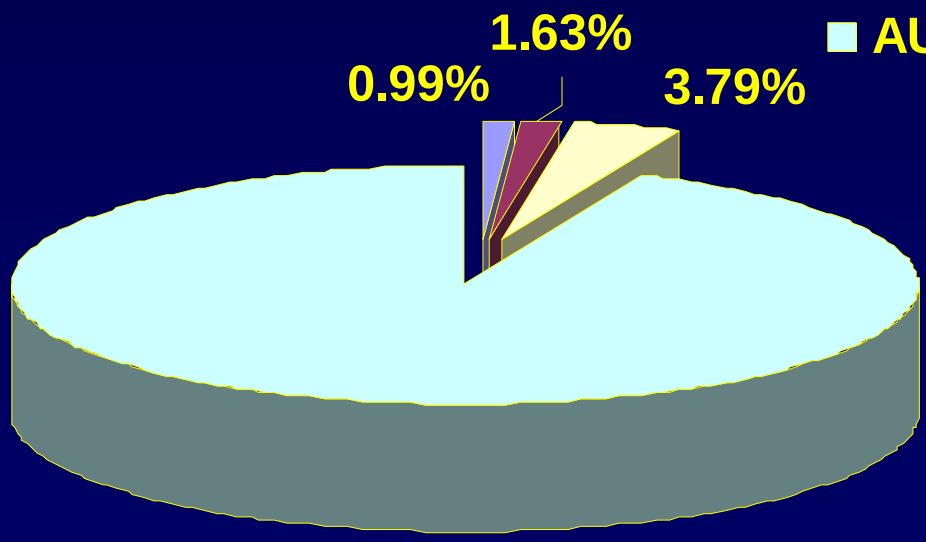




Monte Carlo Simulation

PD-Index

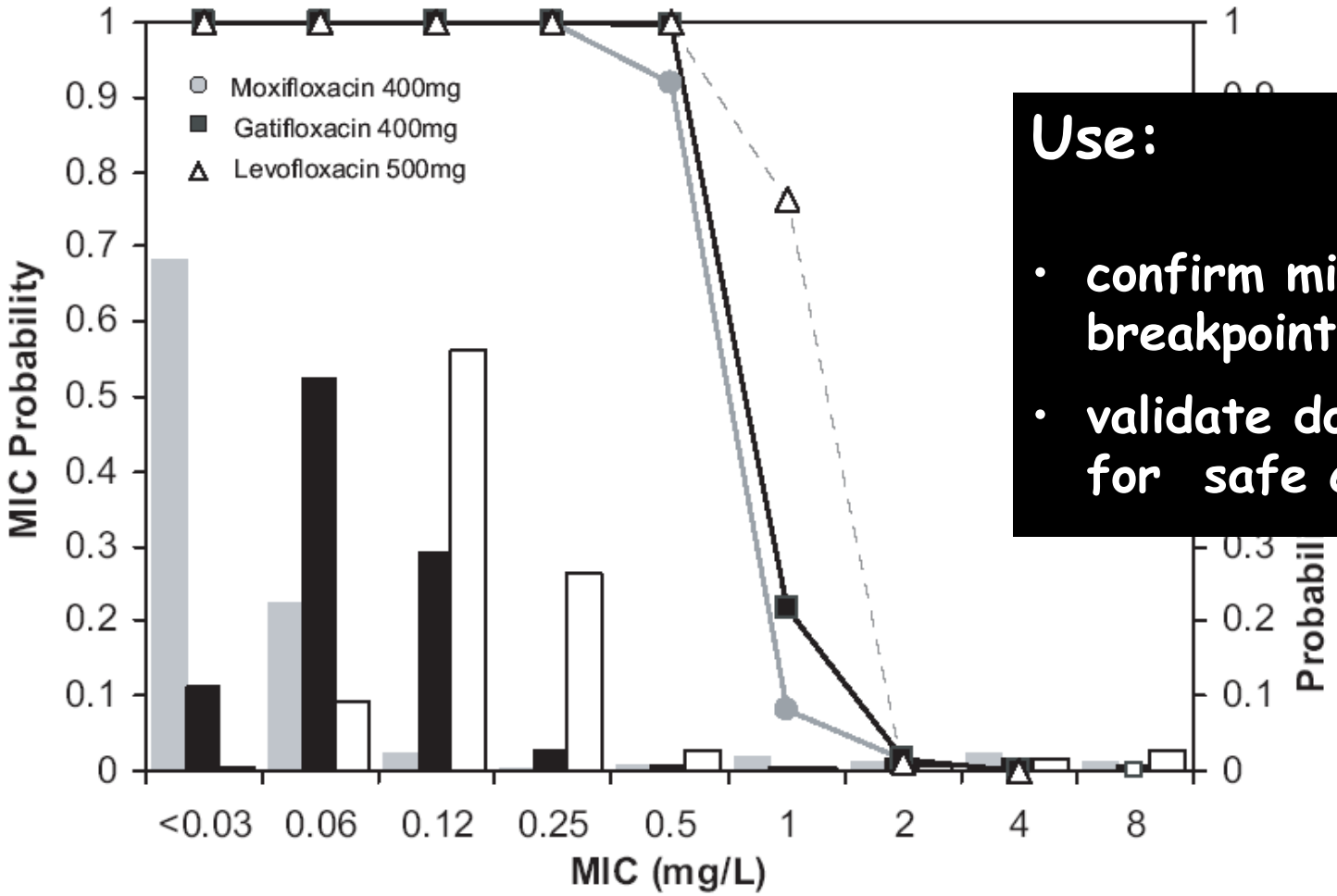
- AUIC<30
- 70>AUIC>30
- 125>AUIC>70
- AUIC>125



PK/PD

Probabilistic PK/PD Approaches in Phase III

Target hit rates based for 3 FQs based on unbound concentrations for 5000 simulated patients with *S. aureus* infection



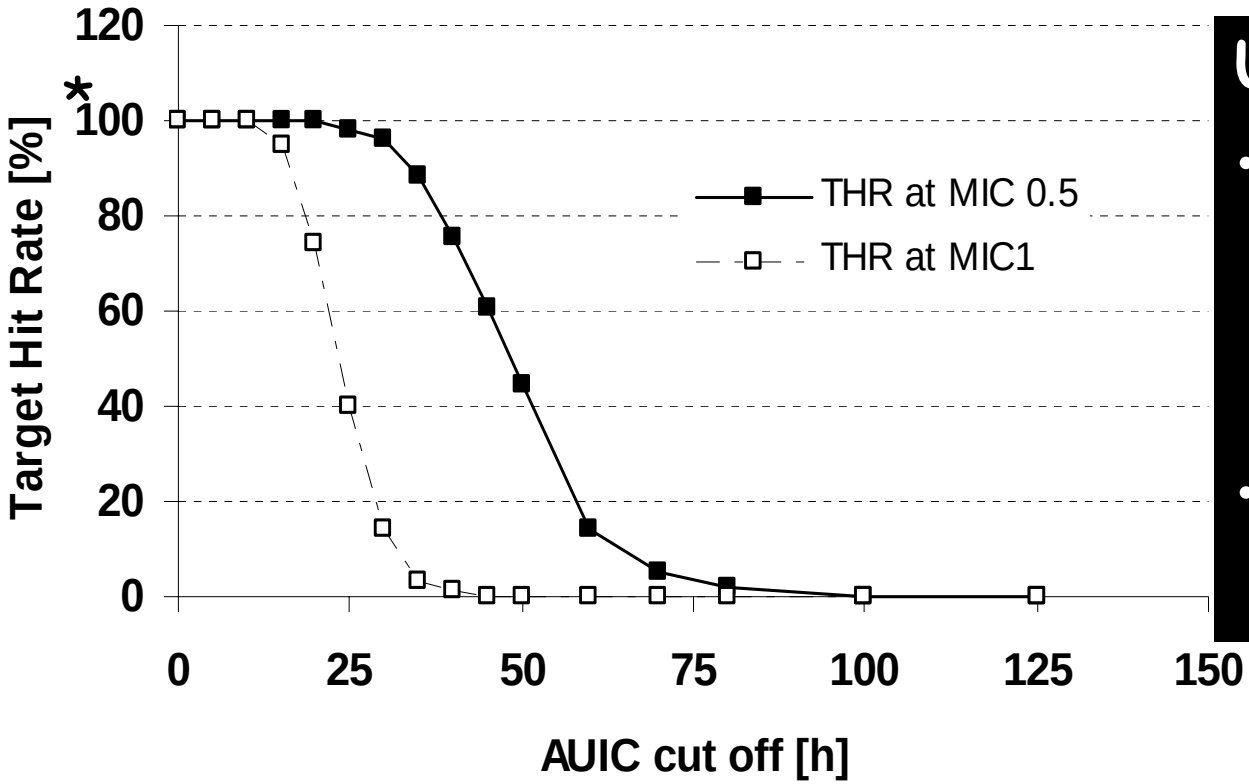
Use:

- confirm microbiological breakpoints
- validate dose regimen for safe clinical use

Ambrose et al., AAC 2004

Probabilistic PK/PD Approaches in Phase I

Sensitivity analysis of target hit rates for a drug candidate using population PK/PD methods for a given PK, dose regimen and PD distribution



Use:

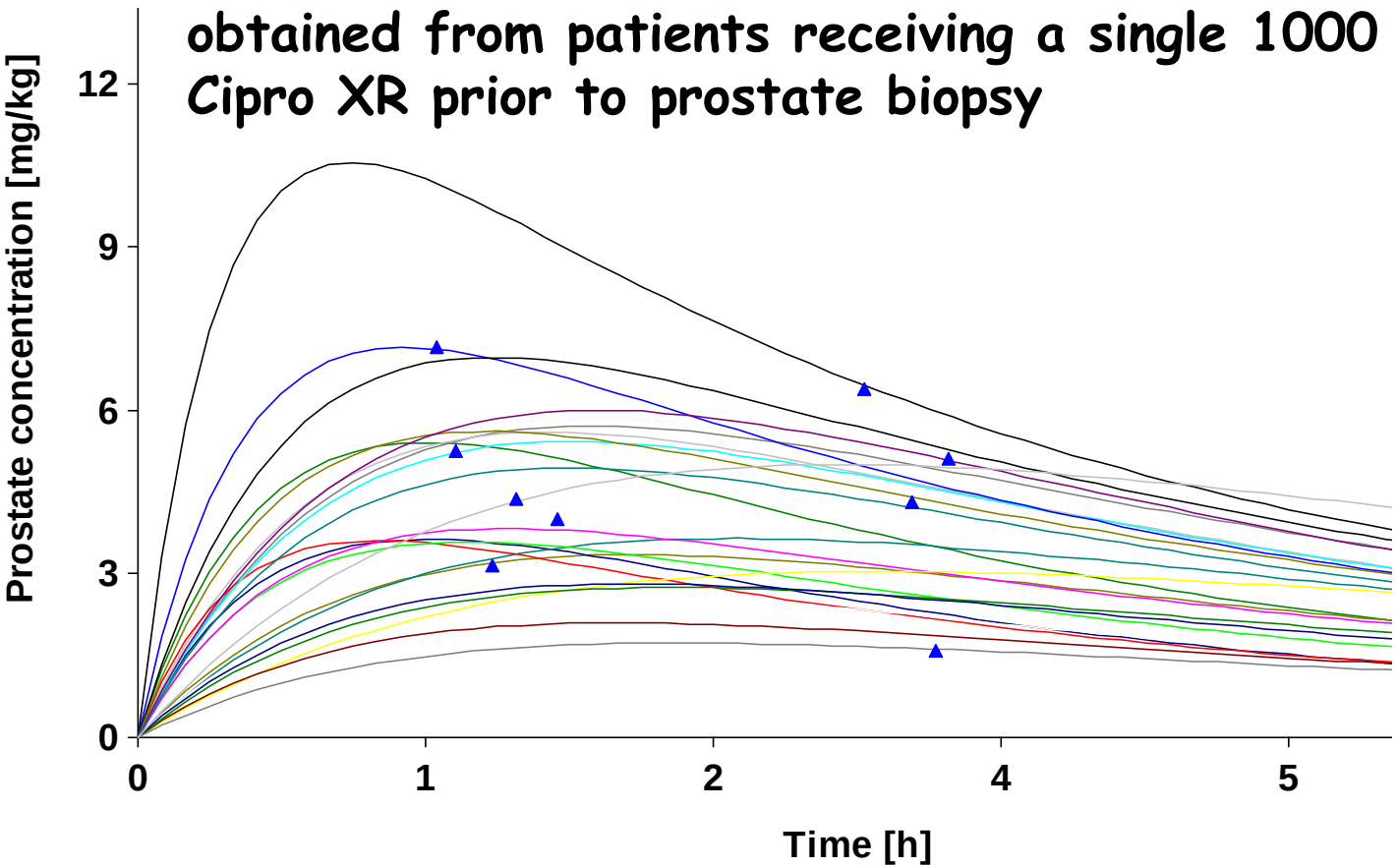
- **translate preclinical PK/PD results into clinical dosing regimen**
- **plan and optimize study designs**

*** each THR was obtained from a Monte Carlo simulation**

Probabilistic PBPK/PD Approaches in Phase I

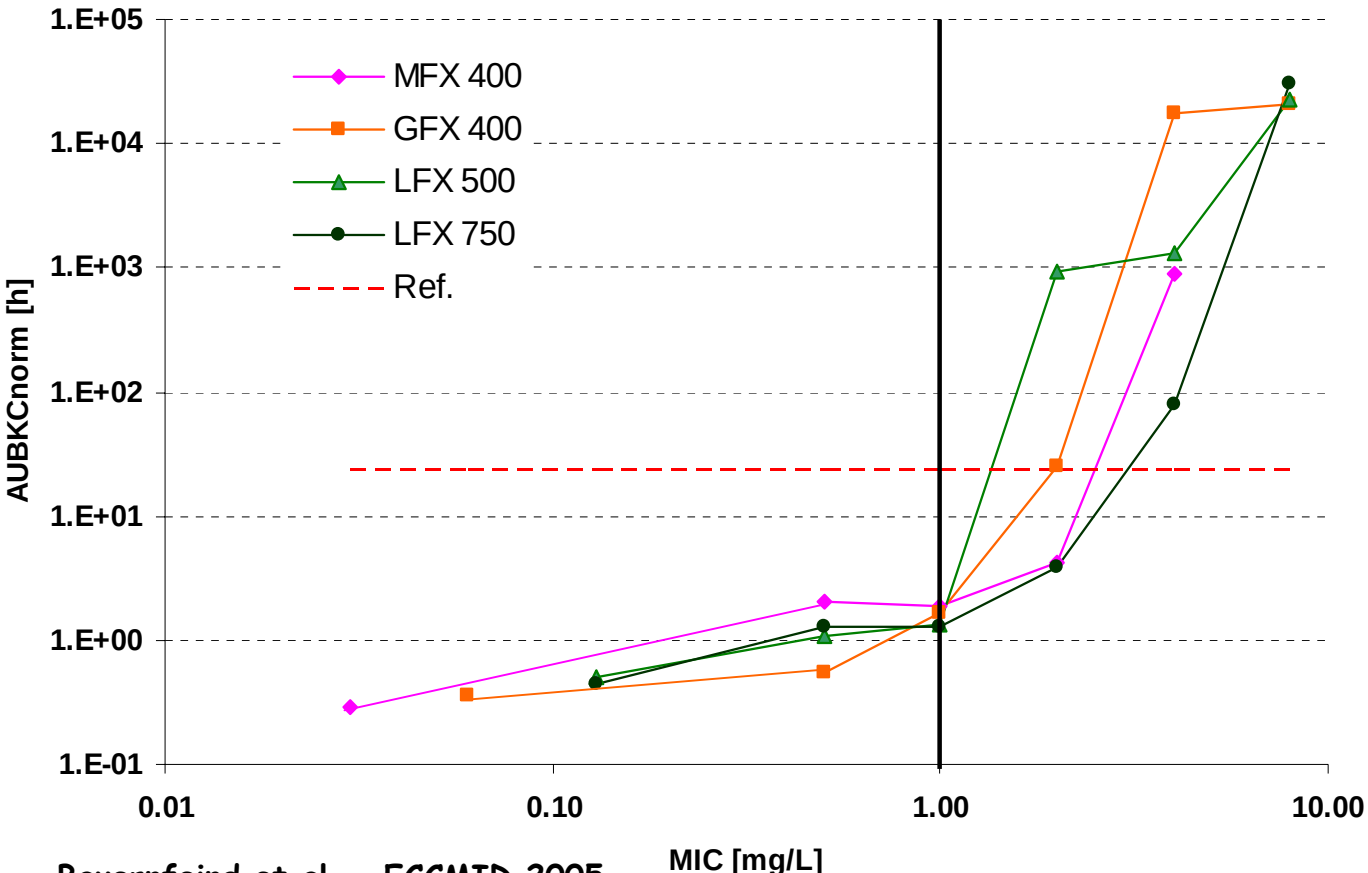
Planning of study designs using Modelling & Simulation based on literature data

Comparison between predictions and population PK results obtained from patients receiving a single 1000 mg dose of Cipro XR prior to prostate biopsy



PK/PD - where are we?

PK/PD methodology is a very powerful instrument to plan development and validate clinical findings and beyond ...



Bauernfeind et al., ECCMID 2005

In vitro PK/PD experiments suggest that compounds from one class (FQs) behave similar (vs S. aureus),

but...

PK/PD - where are we?

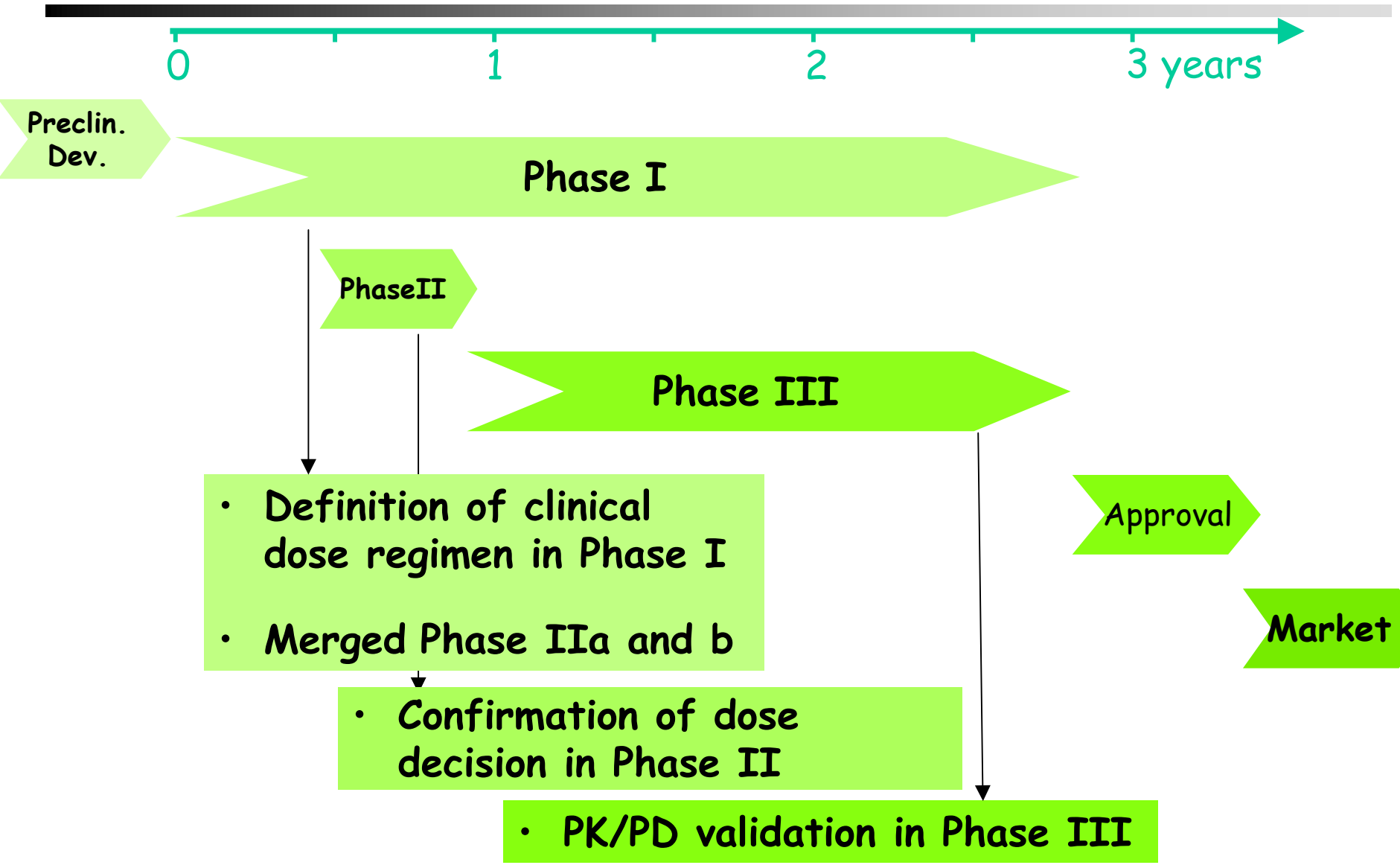
AUIC cut off	FQ	Indication	Ref.
> 125	Cipro	Gram - severe RTI, elderly patients	Schentag et al.
> 75	Grepa	Gram+ community acquired RTI, elderly patients	Pickerill et al.
> 30	Gati	Gram+ community acquired RTI, elderly patients	Ambrose et al.
> 12*	Levo	Gram+ community acquired RTI, cSSSI, Gram - UTI	Preston et al.

* peak/MIC cut off, (AUIC~100)

PK/PD - where are we?

- Open questions remain
  - individual PK/PD indices or per compound class/disease/patient population.... ?
  - applicability to various patient groups given ?
  - plasma or target tissue concentrations ?
  - ...
- for polymicrobial infections no clinically useful models exist to date
- However, wealth of different PK/PD methods available
- PK/PD indispensable to achieve 'lean' and smart development -> ...

PK/PD in Clinical Development of Moxifloxacin



PK/PD in Clinical Development of Moxifloxacin

Case study Moxifloxacin: development cost benefit

Consequences for development:		**Cost [T€]**
Phase I:	2 Phase I MD bracketing studies saved	**-250**
Phase II:	Condensed program (without separate 2B)	**-300**
Phase III:	Population PK/PD evaluations	**+ 50**
Total:		**-500** (< 1‰*)

***compared to total development cost**

Advantages

a) direct cost savings, but marginal compared to total development costs

b) expenses for development are postponed to later phases

c) -> financial risk reduction

PK/PD in Clinical Development of Moxifloxacin

Case study Moxifloxacin: strategic benefit

Consequences for development:		**Time savings**
Phase I:	2 Phase I MD bracketing studies saved	**3 months**
Phase II:	Condensed program (without separate 2B)	**9-12 months**
Phase III:	Population PK/PD evaluations	**+ 0**

Overall, development time reduced by ~ 1 year

PK/PD in Clinical Development of Moxifloxacin

Case study Moxifloxacin: economic benefit

Advantages

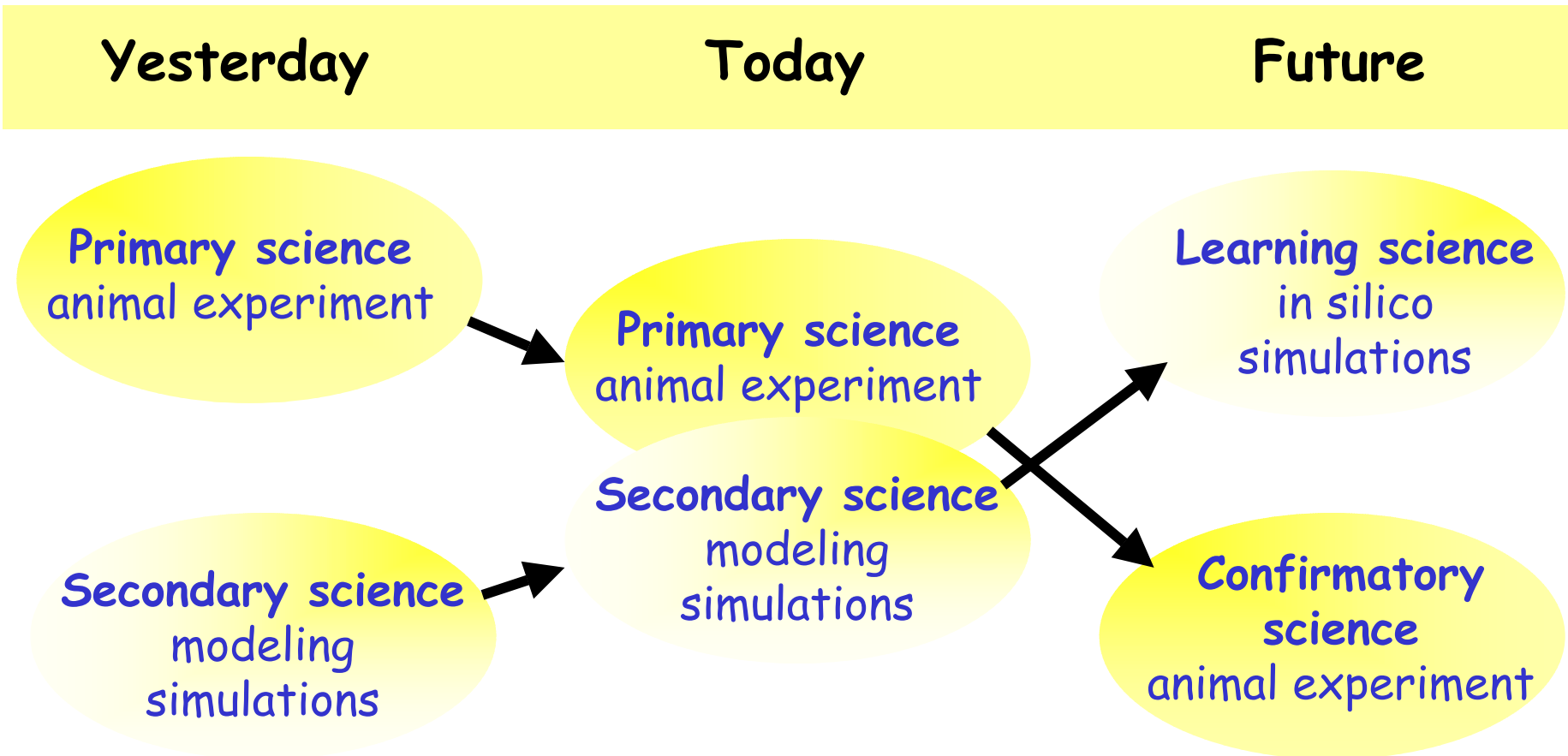
a) Market entry approximately 12 - 15 months earlier

b) Total savings of 10-50 Mio € (after discounting and risk adjustment)

c) Launch ahead of (potential) competitors,
thus stronger competitive positioning

d) One additional year of patent exclusivity ->
additional sales at peak sales level

Change of paradigms in drug development



modified from Pharma 2005, PricewaterhouseCoopers

Conclusion

Clinical Development of Antiinfectives is a challenging business, but ...

- In a competitive climate for clinical development modern PK/PD methods have evolved as a versatile tool to steer clinical development and to cope with these challenges
- While direct cost savings by use of PK/PD concepts are small in view of the total development costs, ...
- ... the strategic advances make the PK/PD tools a *mandatory* instrument of clinical development
- Scientifically, application of PK/PD concepts remains a fascinating field of research and development
- Few areas remain where application of PK/PD concepts is less supportive