Pharmacokinetic/ Pharmacodynamics in Antibiotic Evaluation, Clinical use, and Management of Resistance

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International Society of Anti-infective Pharmacology

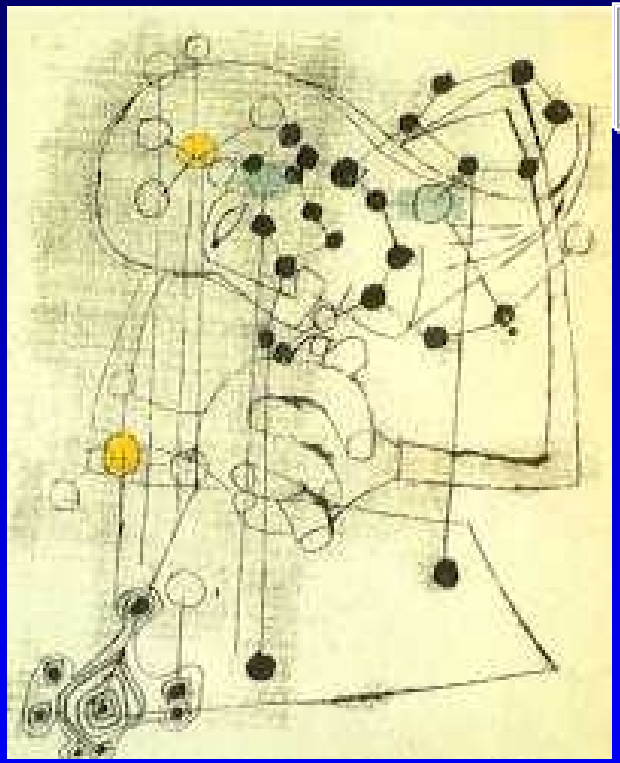
www.md.ucl.ac.be/facm

Fourth Annual
Conference of Infectious Diseases Pharmacotherapy
May 3d, 2001
Orlando, Fla,

www.isap.org

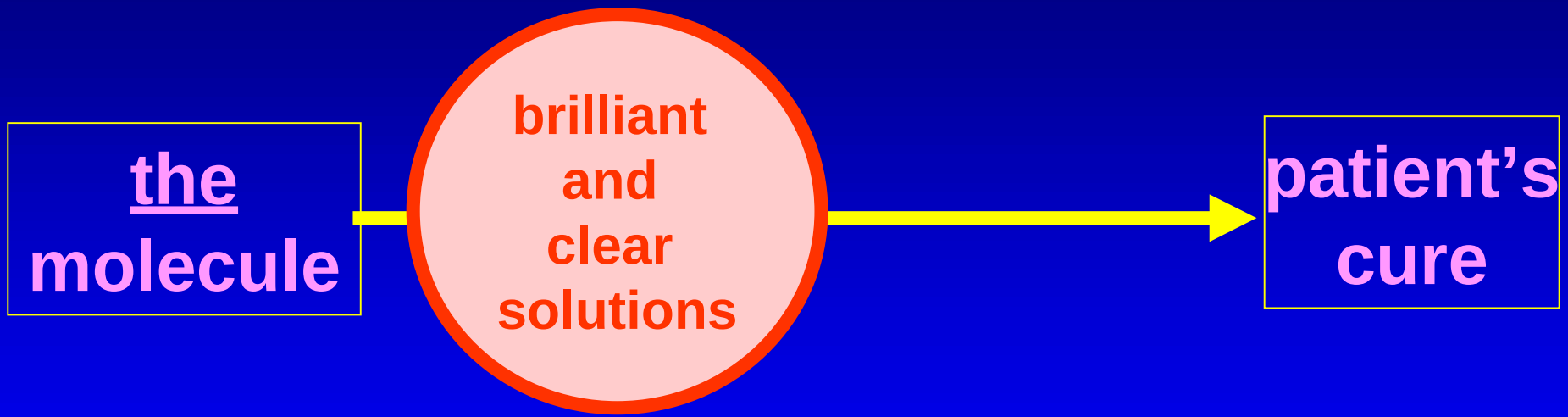
Should this be only magic ?

Magic ... or Science ?



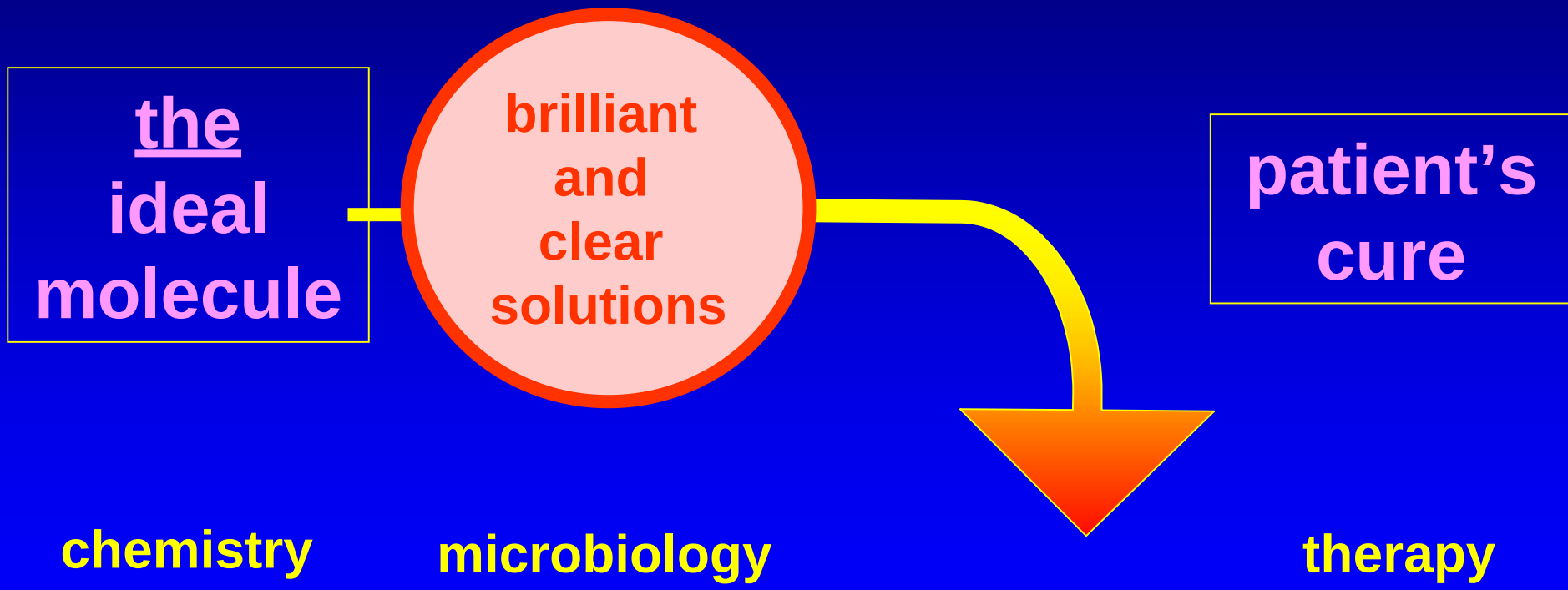
"Scientist" by Ben Shahn
New Jersey State Museum,
Trenton, N.J.

The ideal antibiotic ...



chemistry microbiology therapy

Will it always be ideal ?

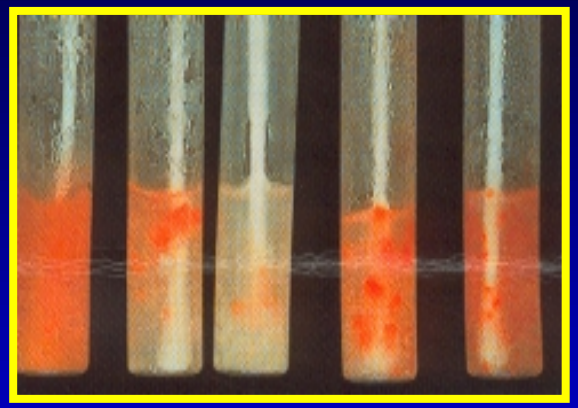


Main causes of antibiotic failures...

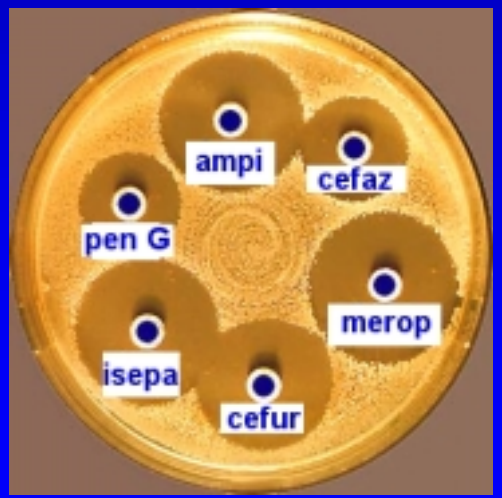
- **False failures**
  - erroneous diagnosis
  - underlying disease uninfluenced by antibiotics
  - unjustified lack of patience
  - inactivation of the antibiotic
- **Failures related to the patient**
  - compliance failure (broadly speaking)
  - inappropriate administration route (broadly speaking)
  - immunodepressed hosts
- **Pharmacological failures**
  - **unsufficient amount or drug inappropriately administered**
  - **unsufficient attention paid to pharmacodynamic parameters**
  - in situ inactivation or lack of drainage
- **Failures related to the micro-organism**
  - wrong pathogen
  - **resistance acquired during treatment**
  - **unsufficient bactericidal activity, bacterial persistence**
  - inoculum effect

Adapted from J.C. Pechère (*In* Schorderet e*t coll.*, 1988, 1993, 1998

Microbiological evaluation was (classically) static



identification

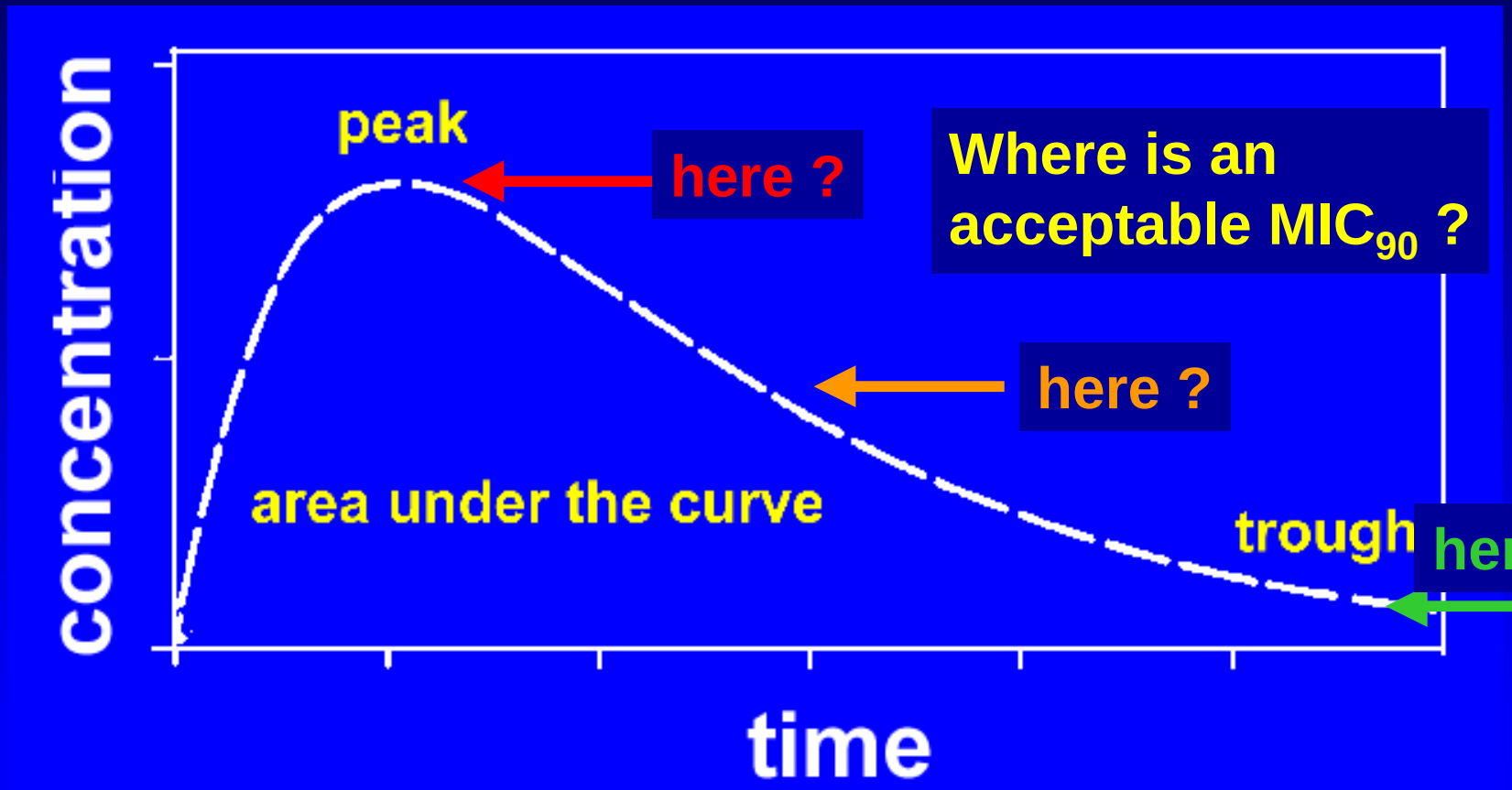


sensitivity → **MIC**

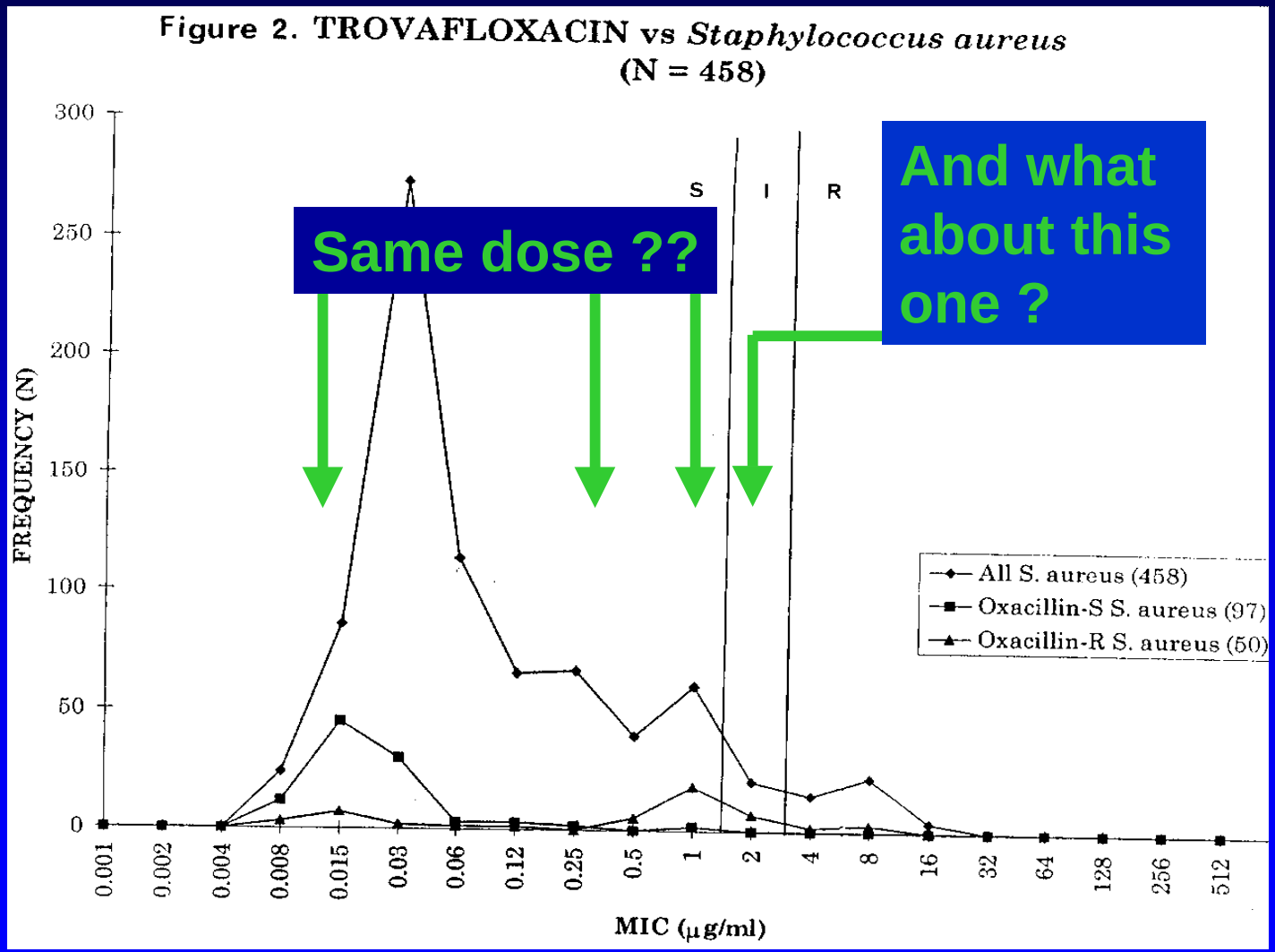
Breakpoints

by static techniques

Static techniques are (partly) inappropriate for *in vivo* projections of sensitivities



Breakpoints introduce artificial (and not always scientific) discontinuties in what is essentially a continuous distribution



PK / PD ...

- Pharmacokinetics

  What the body does to the drug …

  - **absorbtion**
  - **metabolism**
  - **elimination**

  → **C_{max}**, **AUC**, **half-life**

- Pharmacodynamics

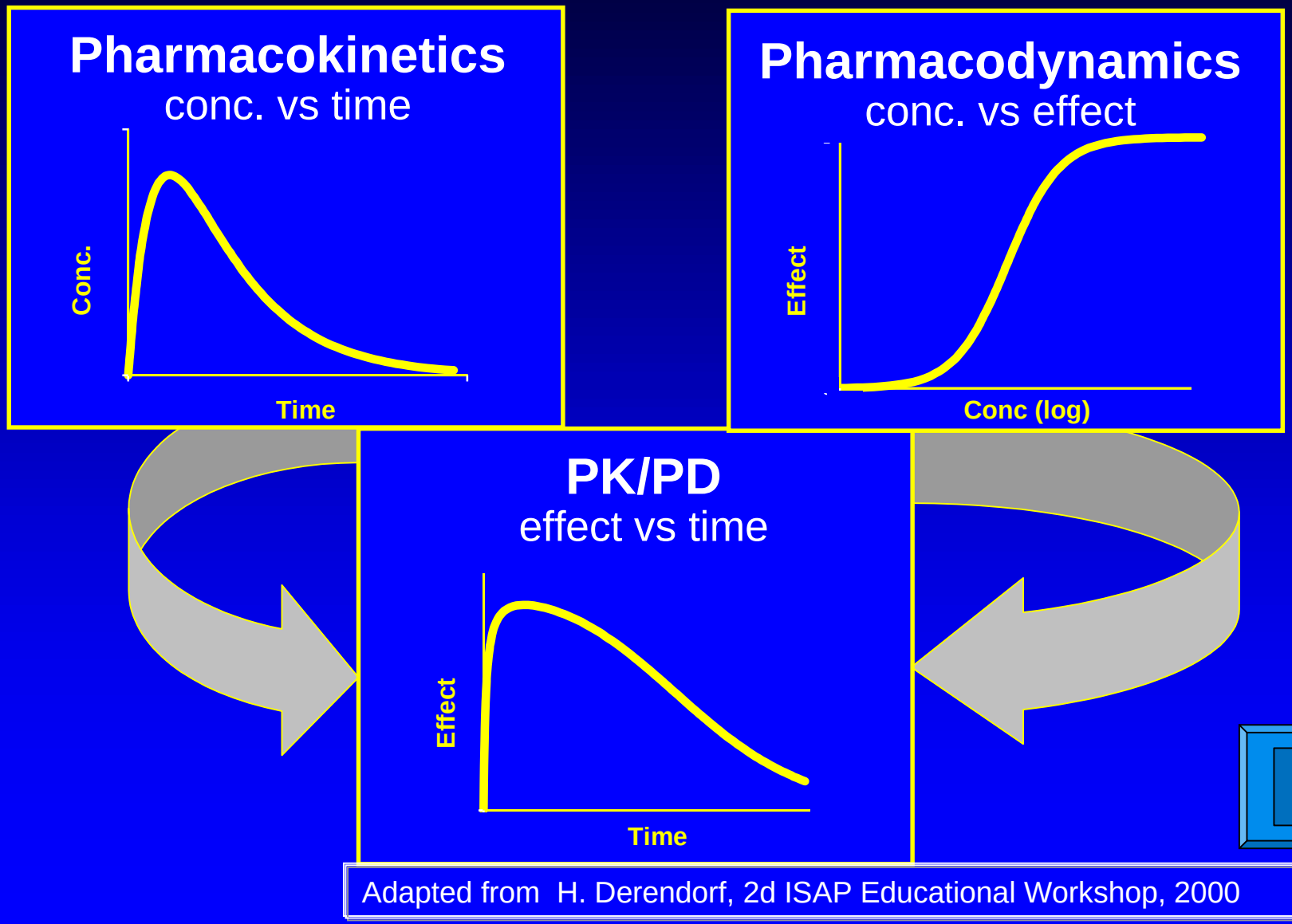
  What the drug does to the body …

  - **direct effects**
  - **post-drug effects**
  - **selection effects**

  → **E_{max}, rate of killing, ...**, **PAE, PASME, …**, **resistance**

Adapted from H. Derendorf, 2d ISAP Educational Workshop, 2000

From PK to PD ...



Adapted from H. Derendorf, 2d ISAP Educational Workshop, 2000

Pharmacokinetic/ Pharmacodynamics in Drug Development and Evaluation of Efficacy

The combination of

- **in vitro modeling,**
- **proper design of animal model experiments,**
- **pharmacokinetic information on patients in clinical trials**

allows an in depth understanding of which aspects of drug exposure are most closely linked to

- **therapeutic outcomes (successes as well as failures !!)**
- **quantifiable / predictable toxicity hazards**

1st ISAP Discussion Workshop with Regulatory Authorities, Rockville, MD, March 1st, 1999 (http://www.isap.org)

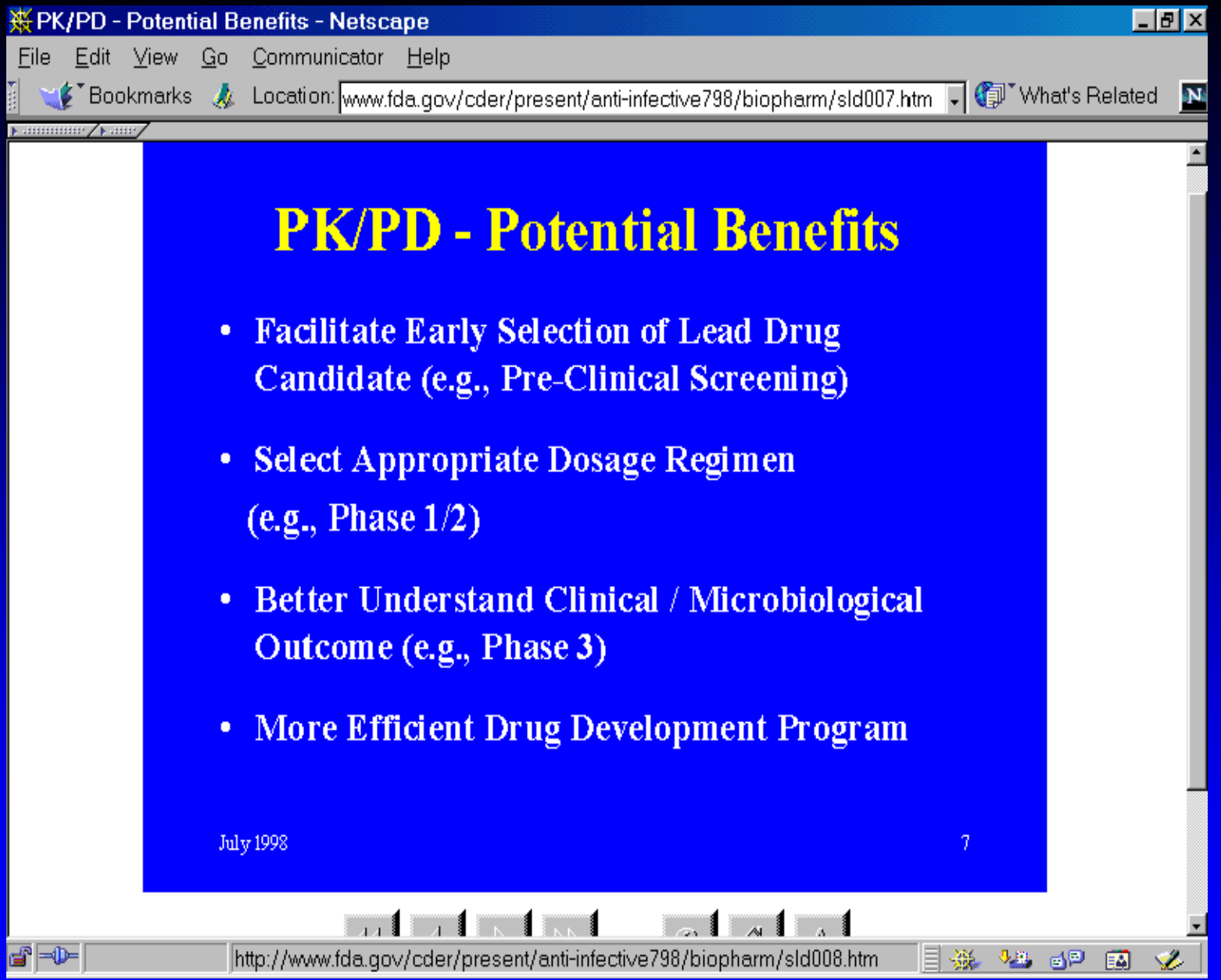
Are PK/PD important for efficacy / toxicity ?

- Medline search on March 25th, 2001 for:
  - **pharmacodynamics, *and***
  - **pharmacokinetics, *and***
  - **efficacy or toxicity, *and***
  - **antibiotic***

534 references...

PK/PD in drug develop-ment

A view from FDA



http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm

Pharmacokinetic/ Pharmacodynamics and antibiotic resistance...

Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance.

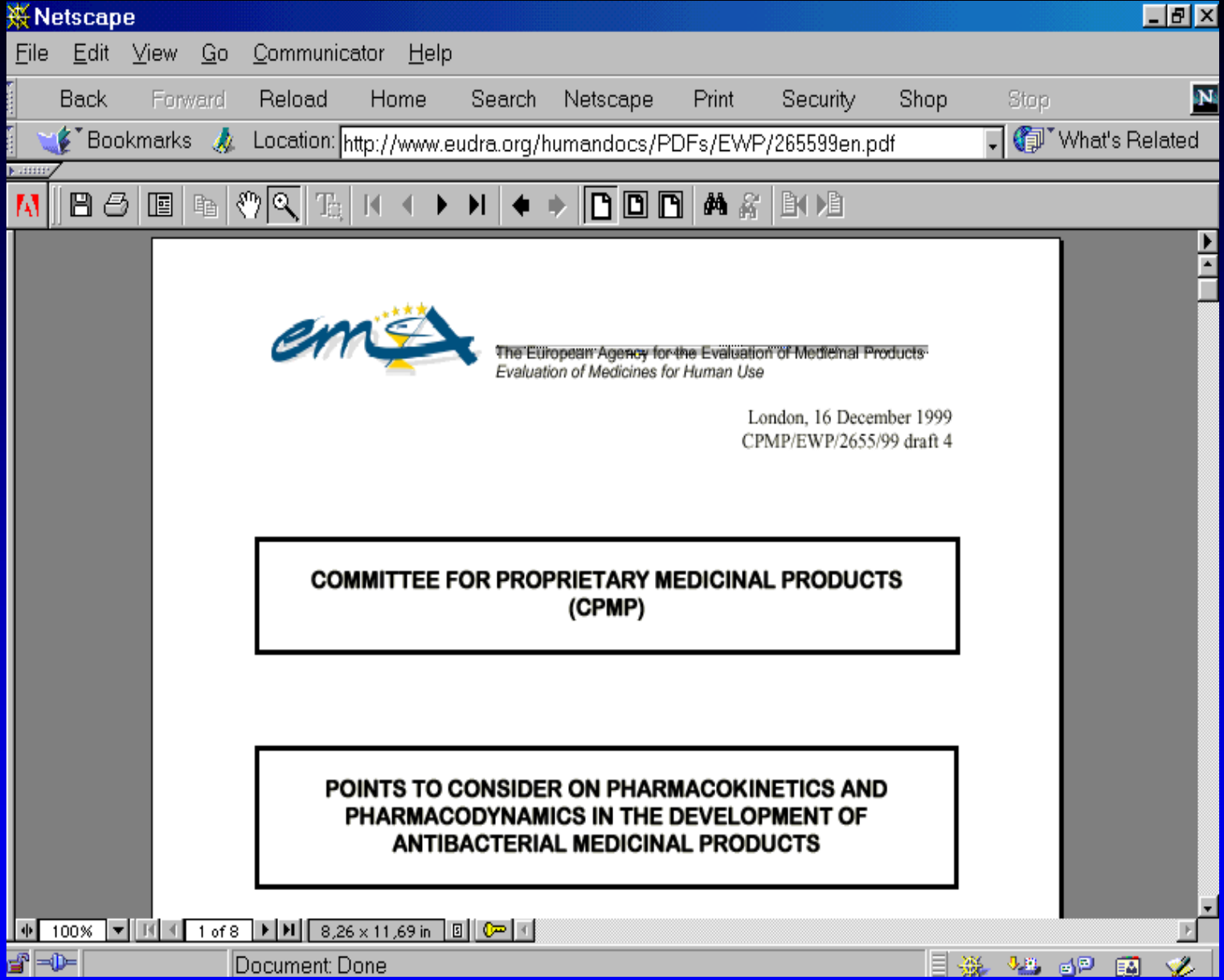
A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy.

The possibility to produce such a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP working parties…

EMEA discussion paper on Antimicrobial resistance, January 3, 1999 -- EMEA/9880/99

PK/PD and drug devlop-ment

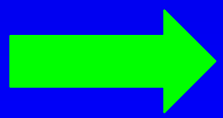
A view from EMEA



http://www.eudra.org/humandocs/PDFs/EWP/265599en.pdf
http://www.isap.org/1999/Uppsala/intro.htm

Are PK / PD important in resistance ?

- PubMed search on March 25th, 2001 for:
  - **pharmacodynamics, *and***
  - **pharmacokinetics, *and***
  - **resistance, *and***
  - **antibiotic***



1756 references...

Just a few of them…

- Eur Respir J 1999 Jul;14(1):221-9
  Pharmacokinetics and pharmacodynamics of fluoroquinolones in the respiratory tract.
  Wise R, Honeybourne D: **"Pharmacokinetic and pharmacodynamic features are important predictors of the therapeutic efficacy of an antibiotic"**.

- J Chemother 1999 Dec;11(6):426-39
  Antimicrobial action and pharmacokinetics/pharmacodynamics: the use of AUIC to improve efficacy and avoid resistance.
  Schentag JJ: **"Resistance is also predictable from these parameters, fostering a rational means of using dosing adjustments to avoid or minimize the development of resistant organisms".**

- Hosp Med 2000 Jan;61(1):24-30
  Clinical efficacy and antimicrobial pharmacodynamics.
  Wise R: **"Changes in the susceptibility of bacterial pathogens and the availability of new antimicrobial drugs mean that physicians need to understand the underlying pharmacodynamics of each antimicrobial therapy".**

Pharmacokinetic/ Pharmacodynamics in Drug Development and Evaluation

Who should take these points in consideration ?

1. Industry: surely !

➔ **efficacy both in short (efficacy) and long (emergence of resistance) terms**

this is what they already do at the research level …

2. Clinical pharmacists: more and more

➔ **optimizing therapy now and protect the future**

but they want to know exactly how to proceed ...

3. Regulatory bodies

➔ **to better appraise new drugs and set guidelines**

but they wish to be certain that this is the correct way !

Pharmacokinetic/ Pharmacodynamics: What are the goals ?

- **Effectiveness:** defining <u>prospectively</u>
  - the daily dose(s) that will be effective; **1st gen. FQ**
  - the optimal schedule; **AG**
  - the risk of emergence of resistance **FQ**
- **Lack or minimization of adverse effects:**
  - drug uptake characteristics at the target organs **AG**
  - influence of schedule and of repair between drug administration
- **Prevention of resistance:** evaluating propectively
  - the risk of low doses and/or to high bkpts **β-lactams**
  - the importance of the rate of bacteral killing **linezolid**
  - the potential for synergy **ampicillin x AG**
  - the doses needed for intermediate organisms **VISA strains**

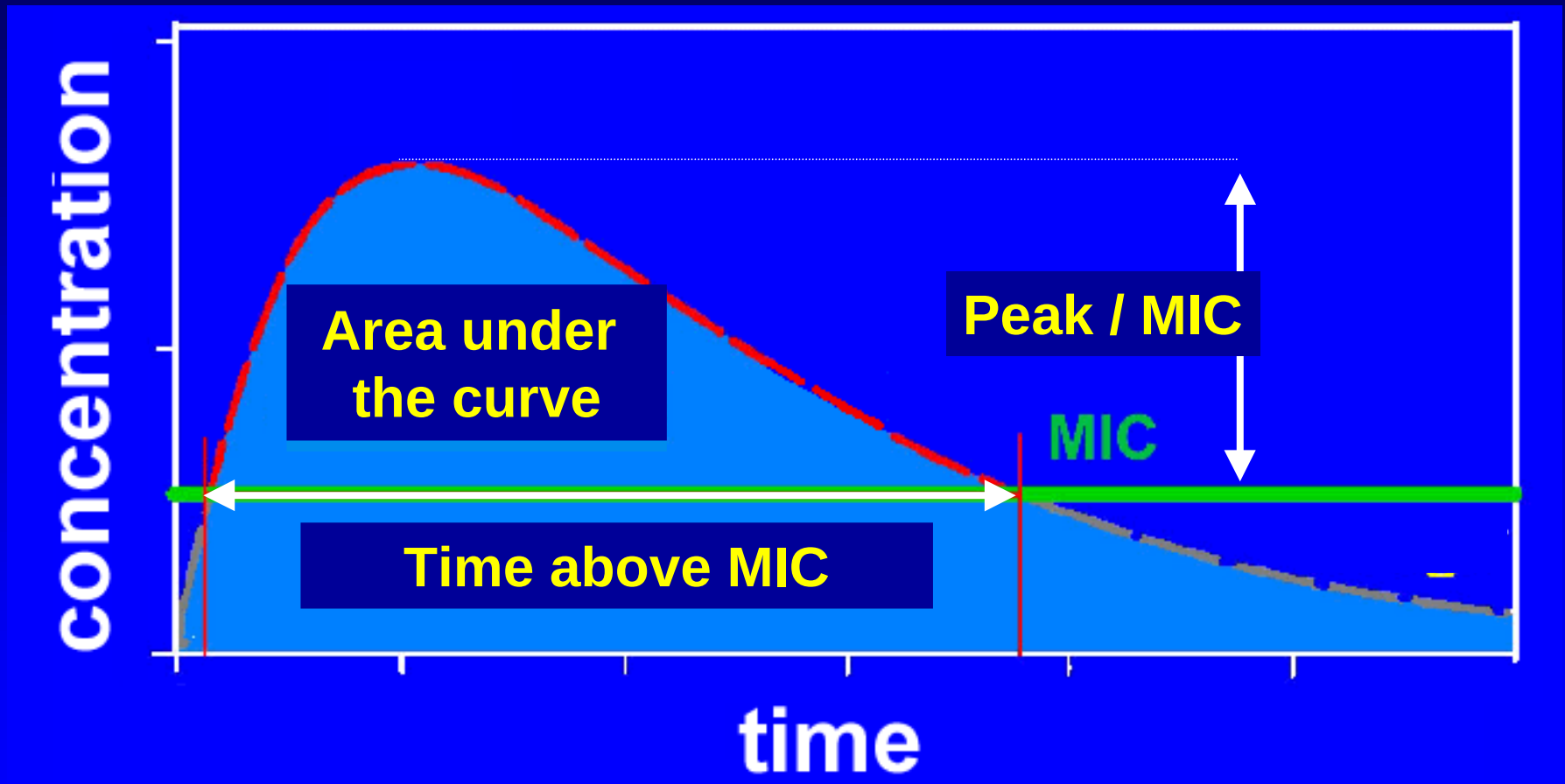
PK / PD of antibiotics in 2001 ?

- **Much Basic Science is already available**
  - **review articles**
    Craig, Drusano, Schentag, Dalhoff, Zinner, Carbon, …[1]
  - **chapters of books**
    Mandell, Armstrong, …
- **New drugs are being developed and registered with strong PK/PD bases**
  - moxifloxacin (fluoroquinolone)
  - ...
- **We need to apply the PK/PD principles to the existing drugs and/or to those wich have introduced recently without sound PK/PD bases**

Parameters controlling efficacy

- **concentration (peak / MIC)**
- **time above the MIC**
- **AUC / MIC ratio**
- **post-antibiotic and other persistent effects**
  - **sub-MIC effects;**
  - **post-exposure sub-MIC effects;**
  - **post-antibiotic (leukocyte enhancement effects)**

Pharmacokinetics ➔ Pharmacodynamics



The rest of the talk ...

- Methods use to determine which are the pertinent PK/PD parameters
- PK/PD parameters of existing antibiotics
- What does Industry do ?
- What can clinical pharmacists do ?

Methods use to determine which are the pertinent PK/PD parameters

- In vitro dynamic models
- Animal models
- Clinical trials
- Population pharmacokinetics

Methods

- In vitro dynamic models
- Animal models
- Clinical trials
- Population pharmacokinetics

In vitro dynamic models

- Dilution models
- Diffusion models
- Hybrid models
- ‘Physiologic models’
- Intracellular models

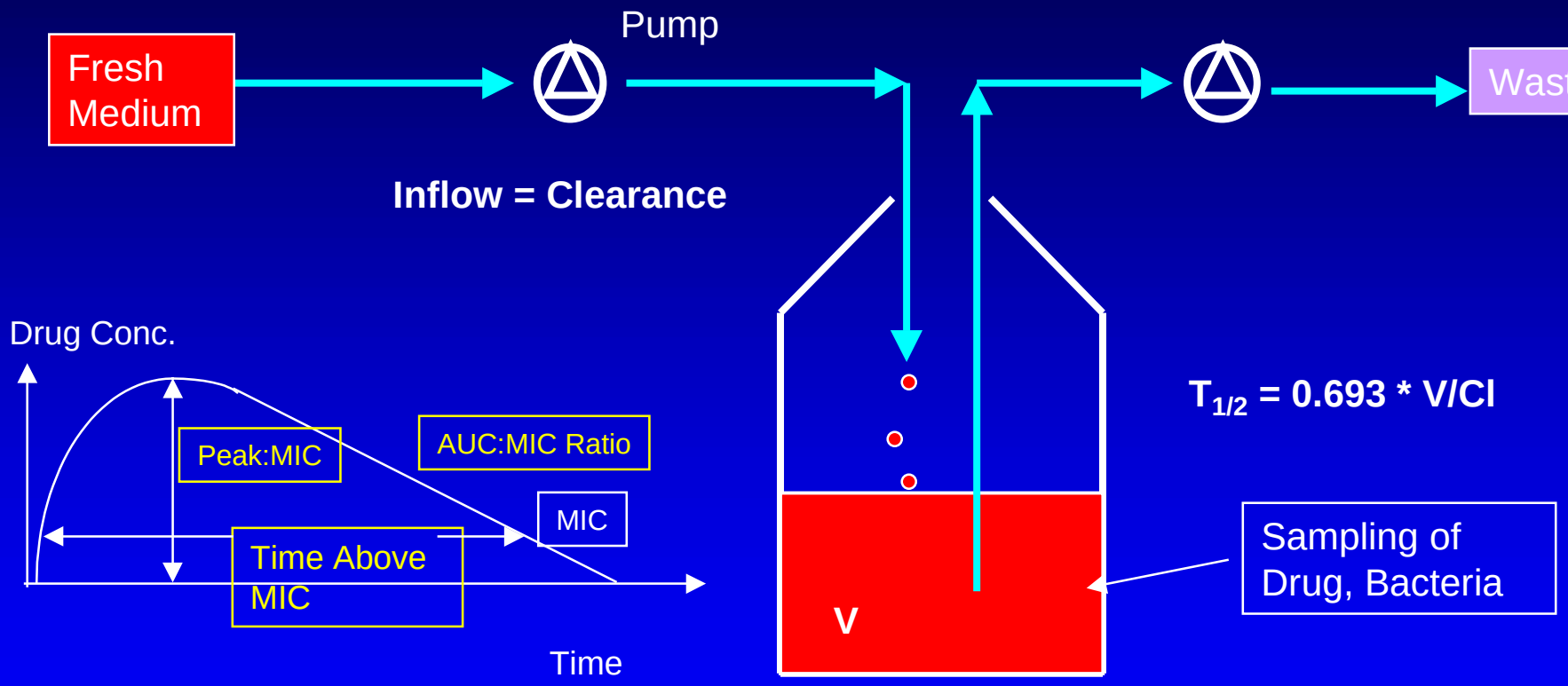
Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001

Dilution models

- Stepwise
  - simple dilution
  - sedimentation & resuspension
- Continuous, pump
  - without outflow
  - with outflow, retaining equal volume (filters)

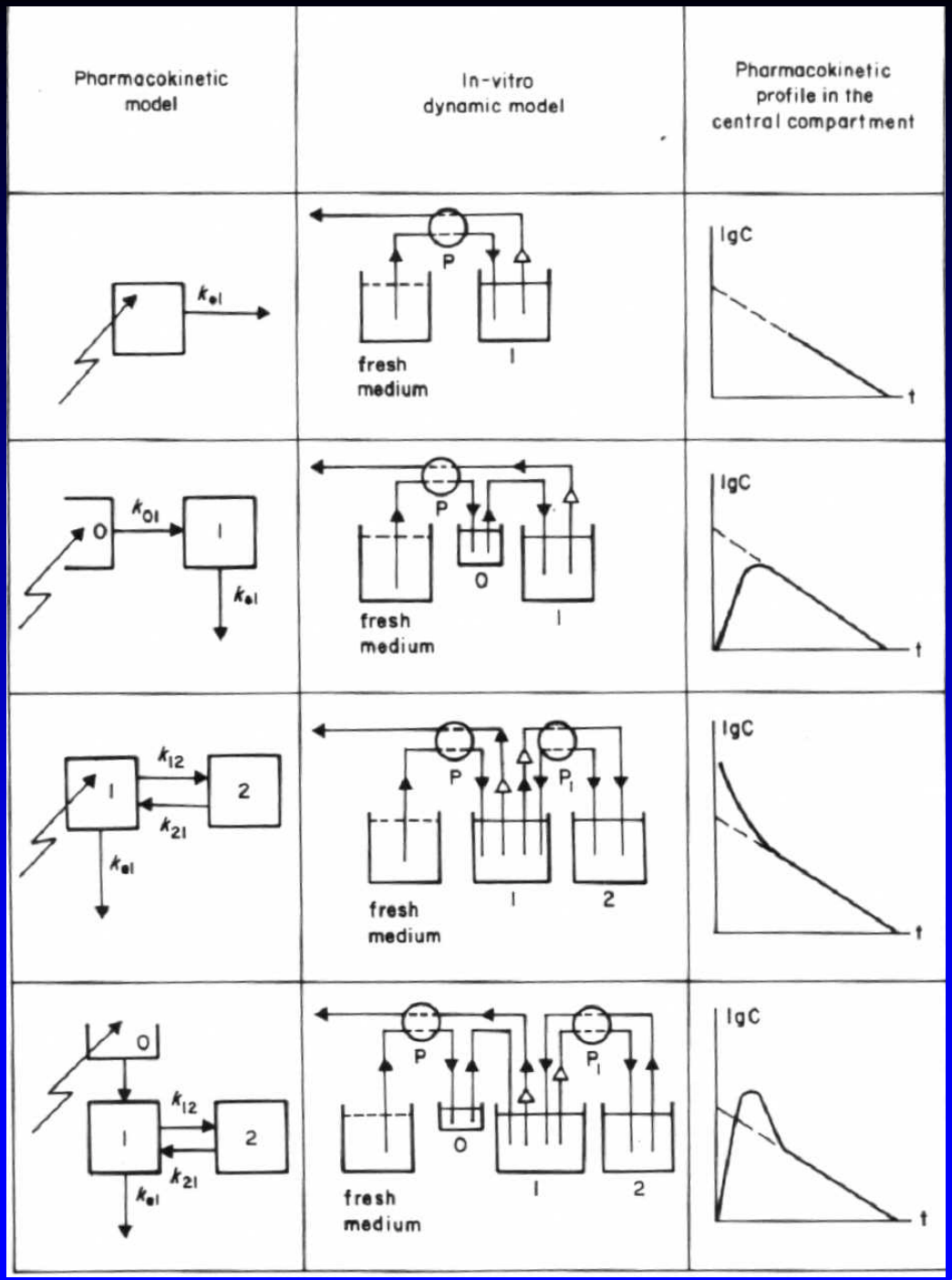
Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001

Dilution models: a simple, useful system ...



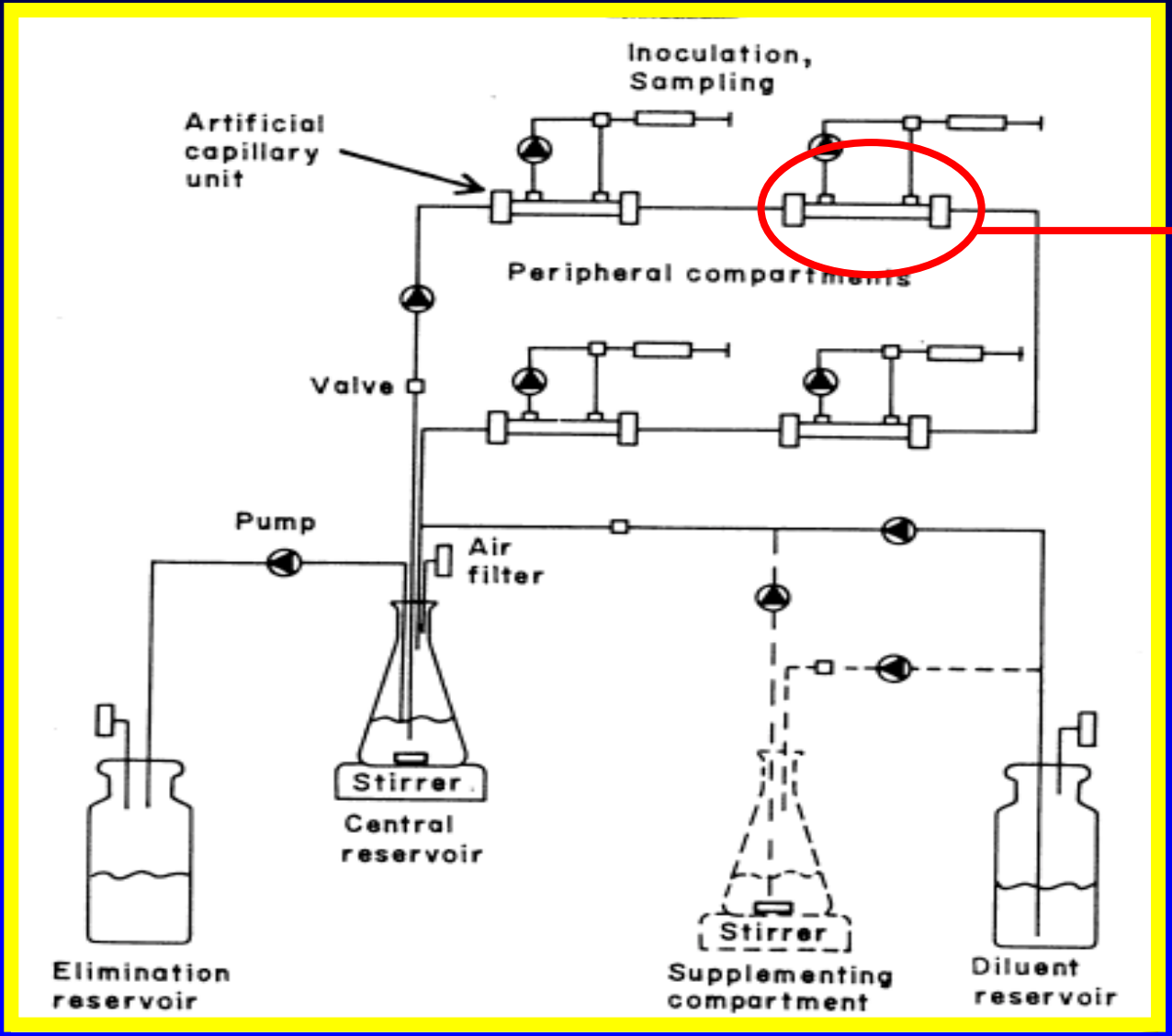
Adapted from M.N. Dudley, ISAP / FDA Workshop, March 1st, 1999

Dilution models: more sophisticated ones...



Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001

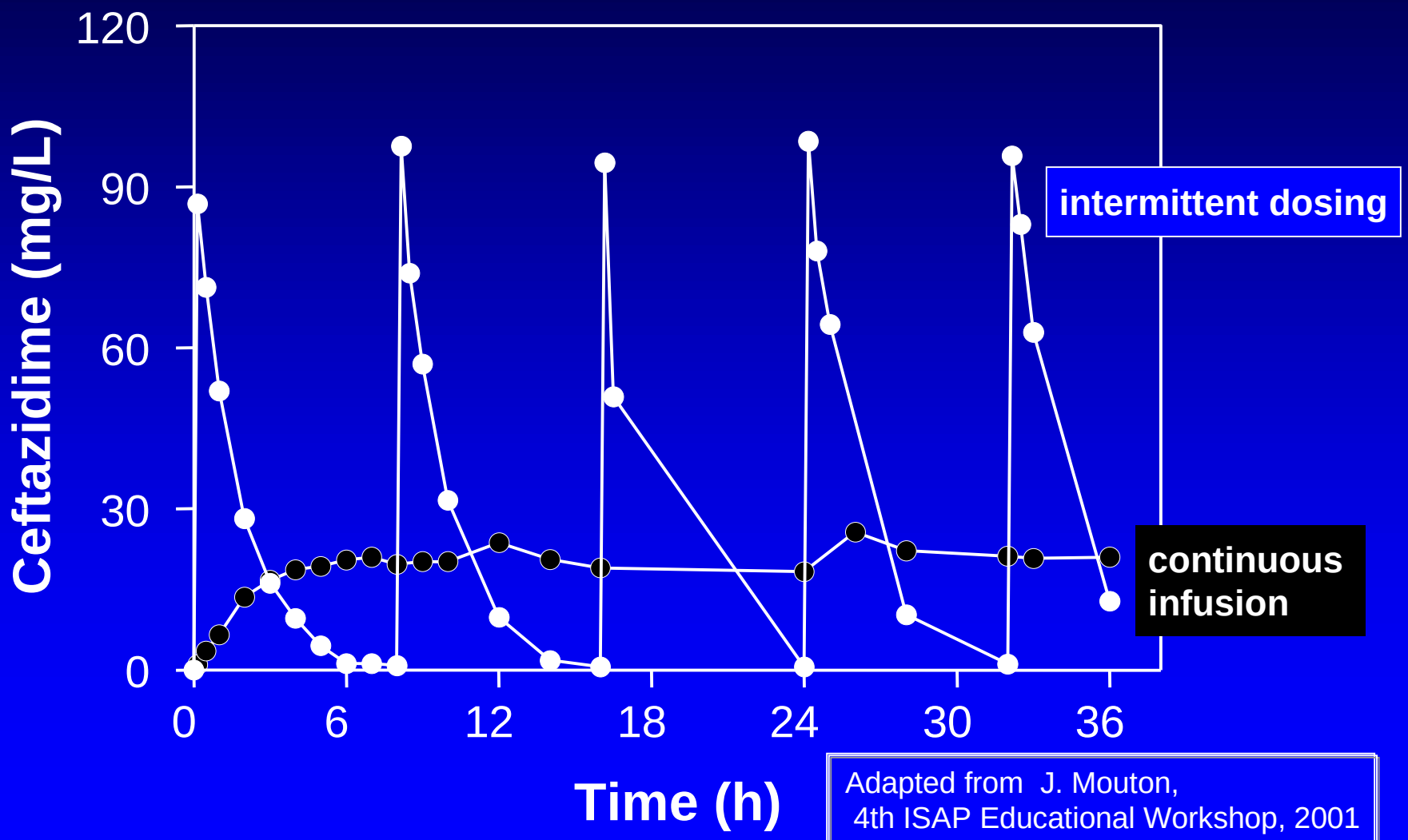
Diffusion models



- **Membranes** (hollow fibers)
- **dialyzers** (artificial kidneys)

Adapted from M.N. Dudley, ISAP / FDA Workshop, 1999

The goal is to mimic potentially useful and achievable serum concentration variations



Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001

Why *in vitro* dynamic models ...

- **The goal is to establish basic relationships between drug exposure (PK) and effect (PD)**
  - **PK:PD parameters for efficacy to apply across species, models, for combinations, etc...**
  - **Basis of dosage in phase II trials**

- **Limitations:**
  - **Experimental conditions (laborsome; contamination; …)**
  - **Usually only 1 or 2 days (effects 'fade' after 12-24 h)**
  - **Haag factor (biofilm…)**
  - **absence of host factors (includ. protein binding and metabolism)**
  - **...**

Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001

Methods

- In vitro dynamic models
- Animal models
- Clinical trials
- Population pharmacokinetics

Animal models

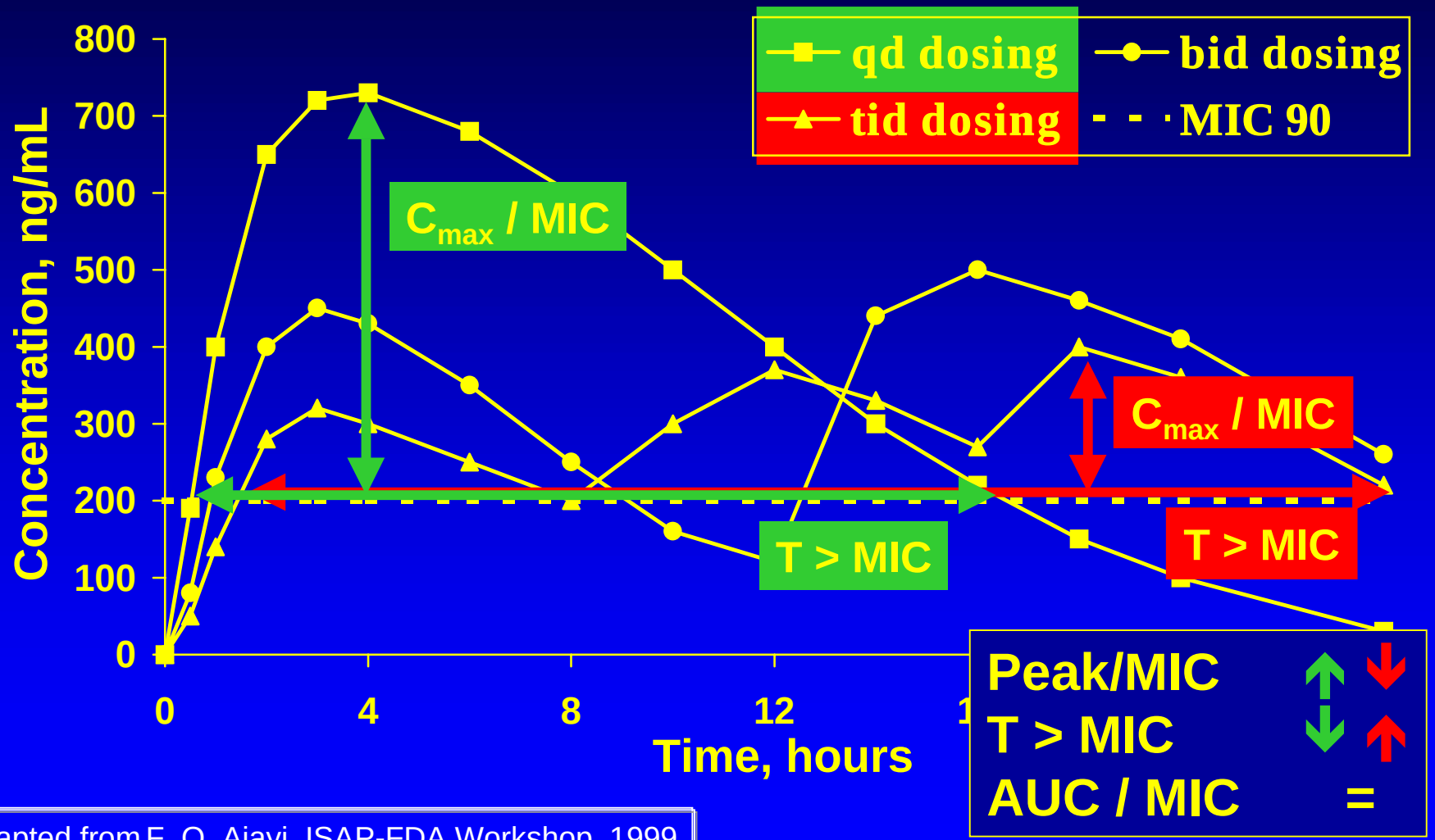
- Neutropenic mouse
- rabbit (endocarditis)
- rat, guinea pig, ...

The main advantage is the possibility to explore a VERY large array of dosing regimens so as

- **dissociate PK covariables (C_{max} vs AUC …)**
- **explore the PK "conditions of failure"**

Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000

Dissociating PK covariables



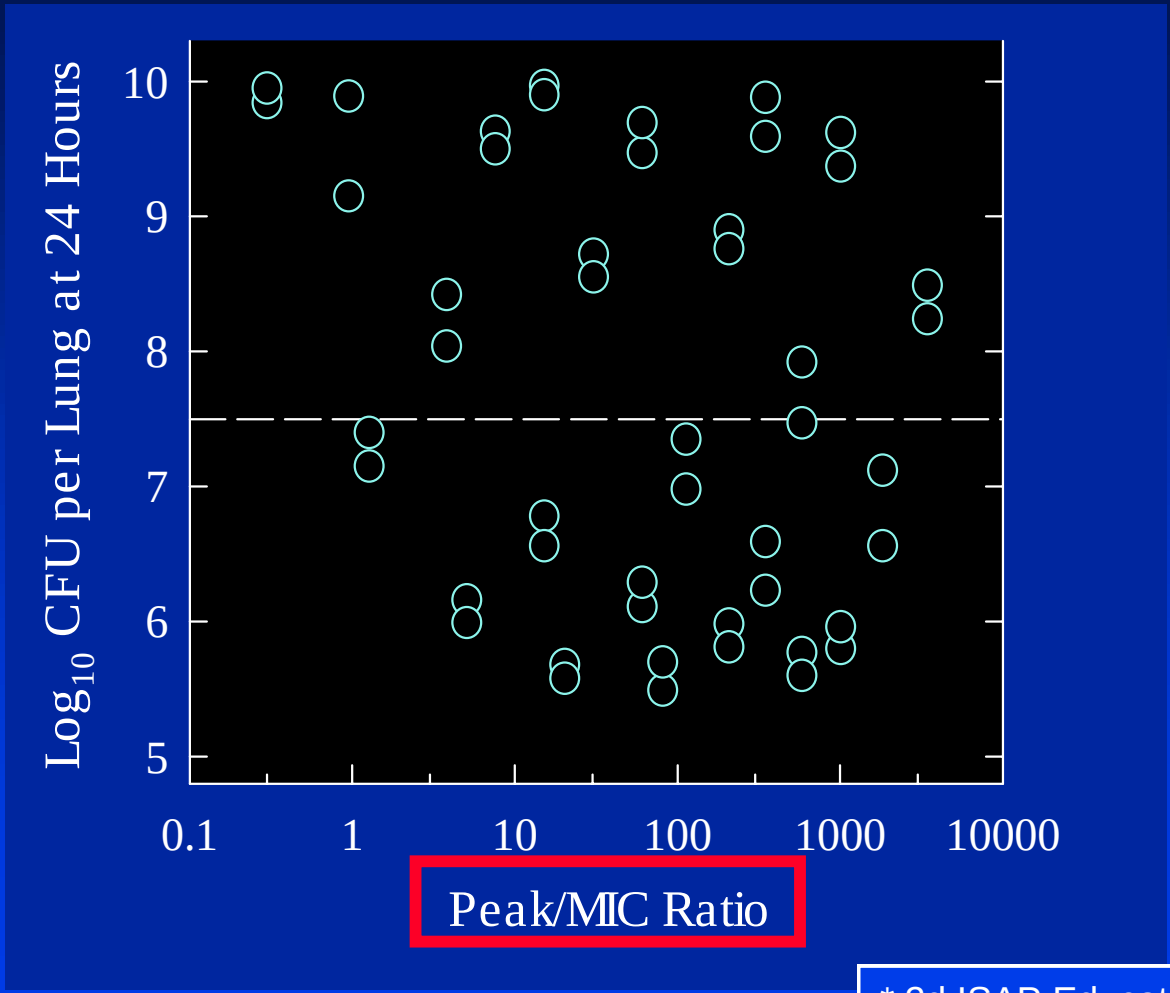
Adapted from F. O. Ajayi, ISAP-FDA Workshop, 1999

A typical animal model to establish which PK parameters is associated with efficacy

- **Use neutropenic murine thigh-and lung-infection models**
- **Evaluate 20-30 different dosing regimens (5 different total doses given at 4-6 different dosing intervals)**
- **Measure efficacy from change in Log_{10} CFU per thigh or lung at the end of 24 hours of therapy**
- **Correlate efficacy with various pharmacodynamic parameters (Time above MIC, peak/MIC, 24-Hr AUC/MIC)**

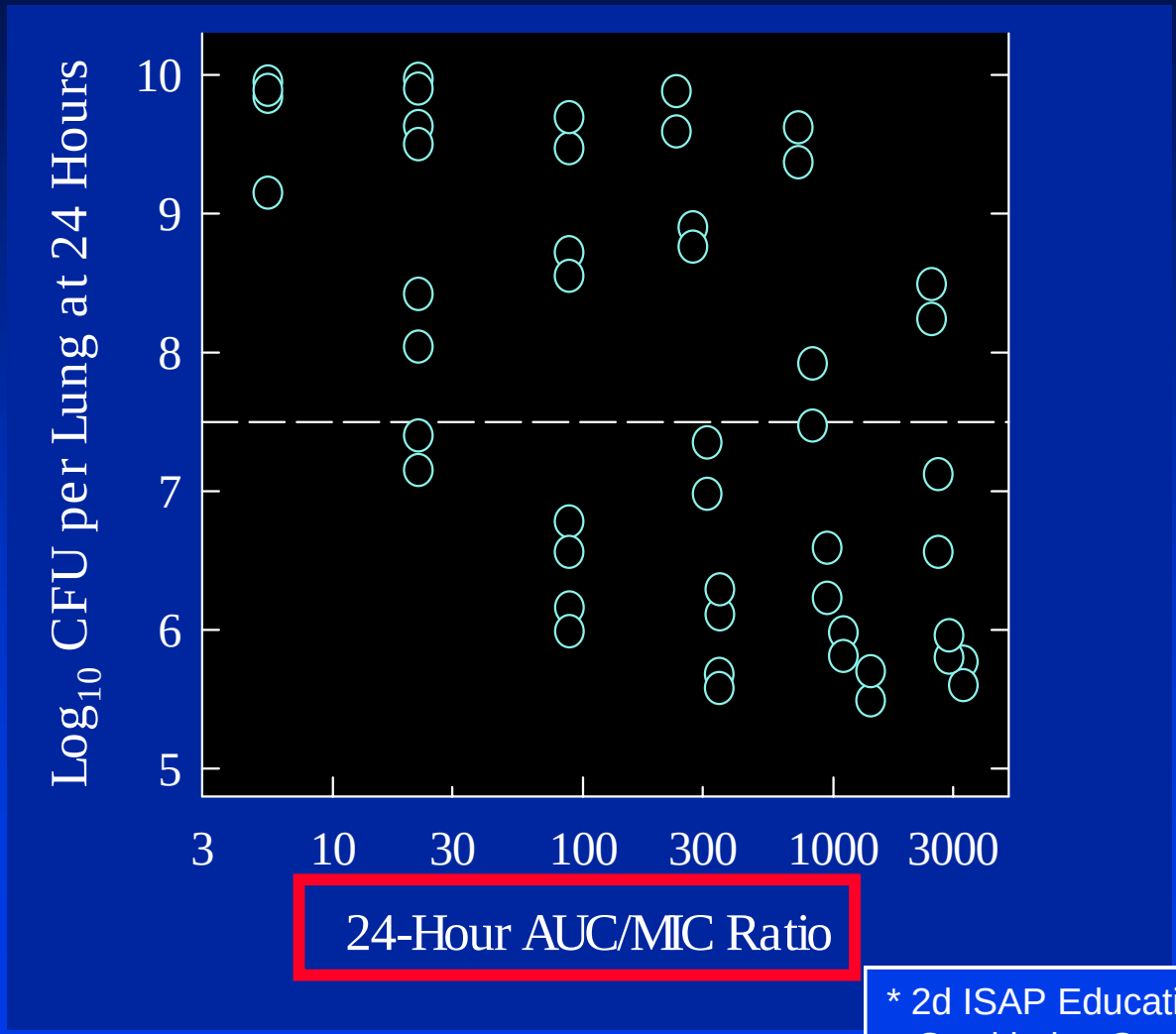
Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000

Relationship Between Peak/MIC Ratio and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)



* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Relationship Between 24-Hr AUC/MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)



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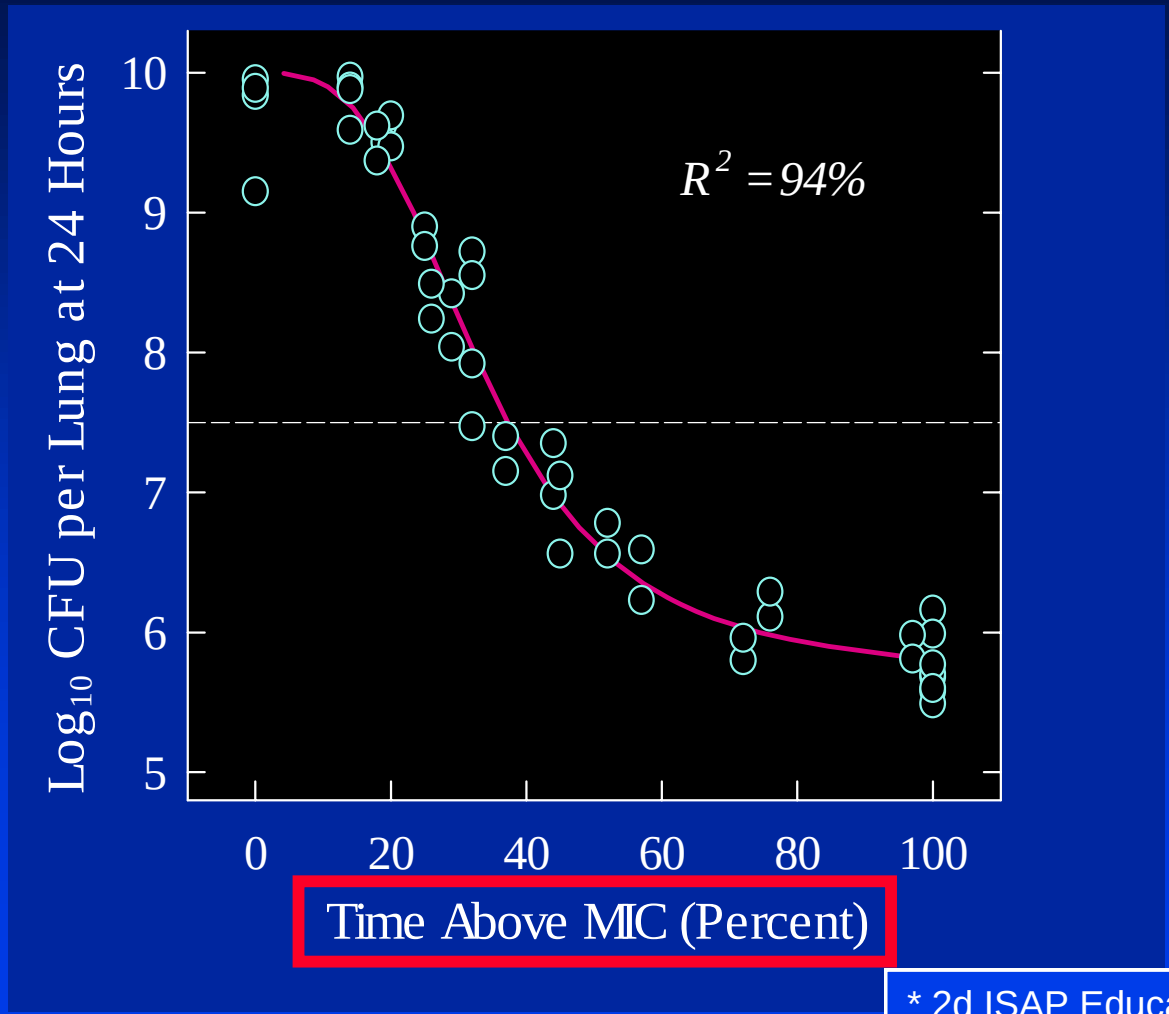
Relationship Between Time Above MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)



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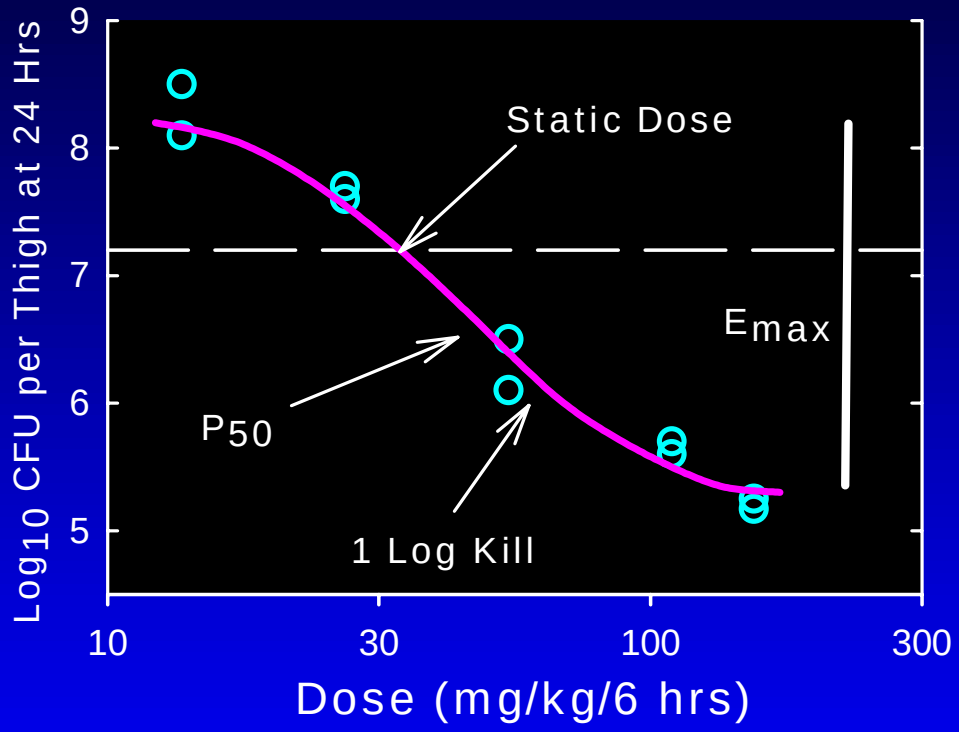
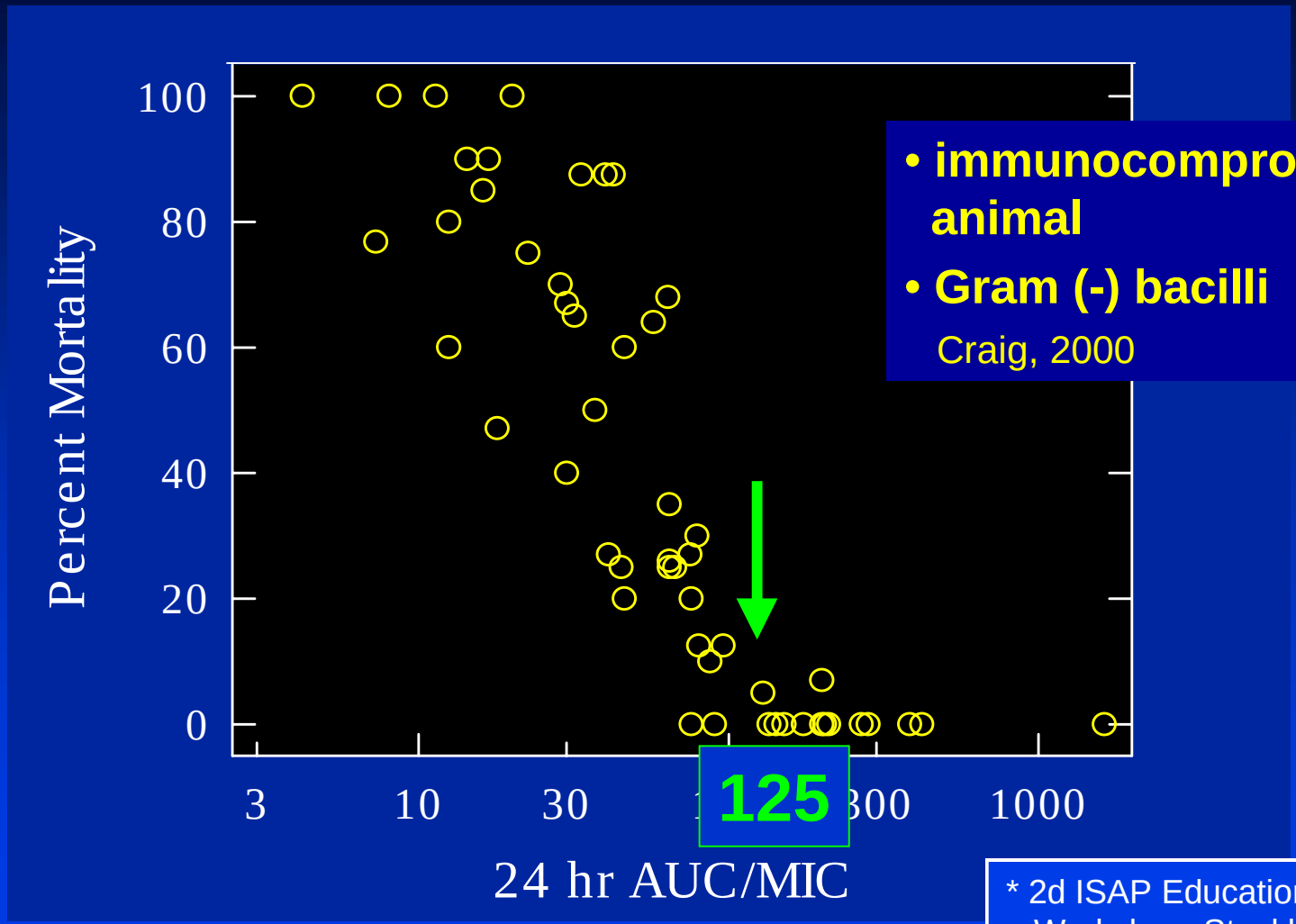
End-points of animal models

- Bacterial counts
  - static dose
  - 50 % effect
  - E_{max}
- Mortality
- Recovery of resistant bacteria



* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Relationship between fluoroquinolones 24 Hr AUC / MIC and mortality

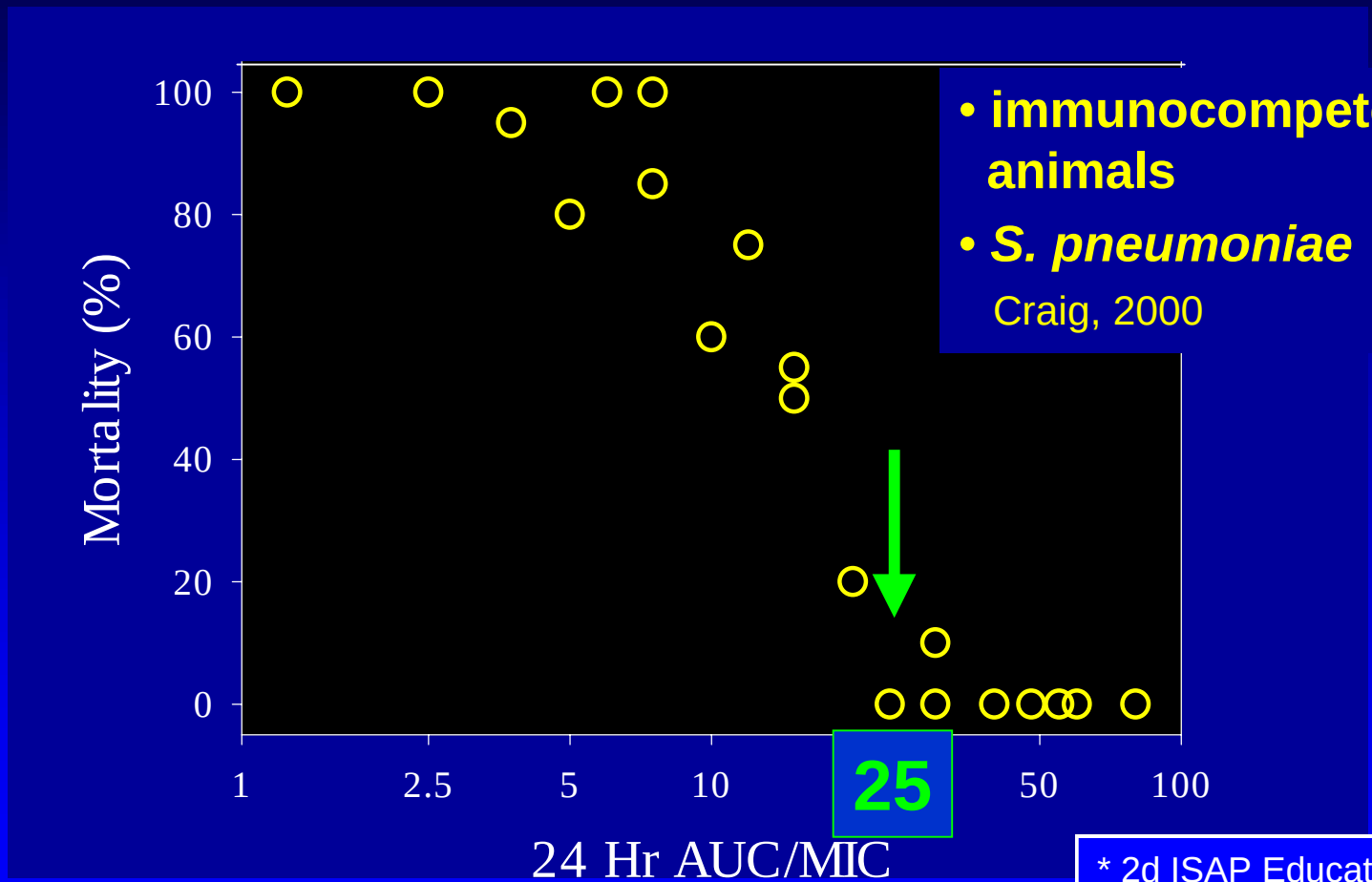


- **immunocompromised animal**
- **Gram (-) bacilli**

Craig, 2000

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Relationship Between 24 Hr AUC/MIC and Mortality for FQs in Immunocompetent Animal Models with *Str. pneumoniae* infection (Craig, 2000) *



* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Known PK problems (with solutions) linked with animal models

- Serum clearance of most antimicrobials is faster in animals than in man
- Serum protein binding is usually less in animals than in man
- The higher doses required for studies in animal models may result in non-linear kinetics
- Sensitive drug assays should be used to identify deep tissue compartments that could prolong activity against very susceptible organisms

Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000

Known PD problems with animal models

- short term, acute infections
- necessity to make the animal receptive to the infection
- difficulties to eradicate (subpopulations not dealt with by impaired host defenses)
- growth of bacteria influenced by local (artificial) conditions
- disagreements concerning the end points to consider (static dose, E_{max}, etc…)

Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000

Demonstrated advantages of animal models

- **Is the magnitude of the parameter required for efficacy the same in different animal species?**

YES

- **Does the magnitude of the parameter vary with:**
  1. **the dosing regimen? NO**
  2. **different drugs within the same class? NO**
  3. **different organisms ? Minimal**
  4. **different sites of infection (e.g. blood, lung, peritoneum, soft tissue)? NO, but ...**

Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000

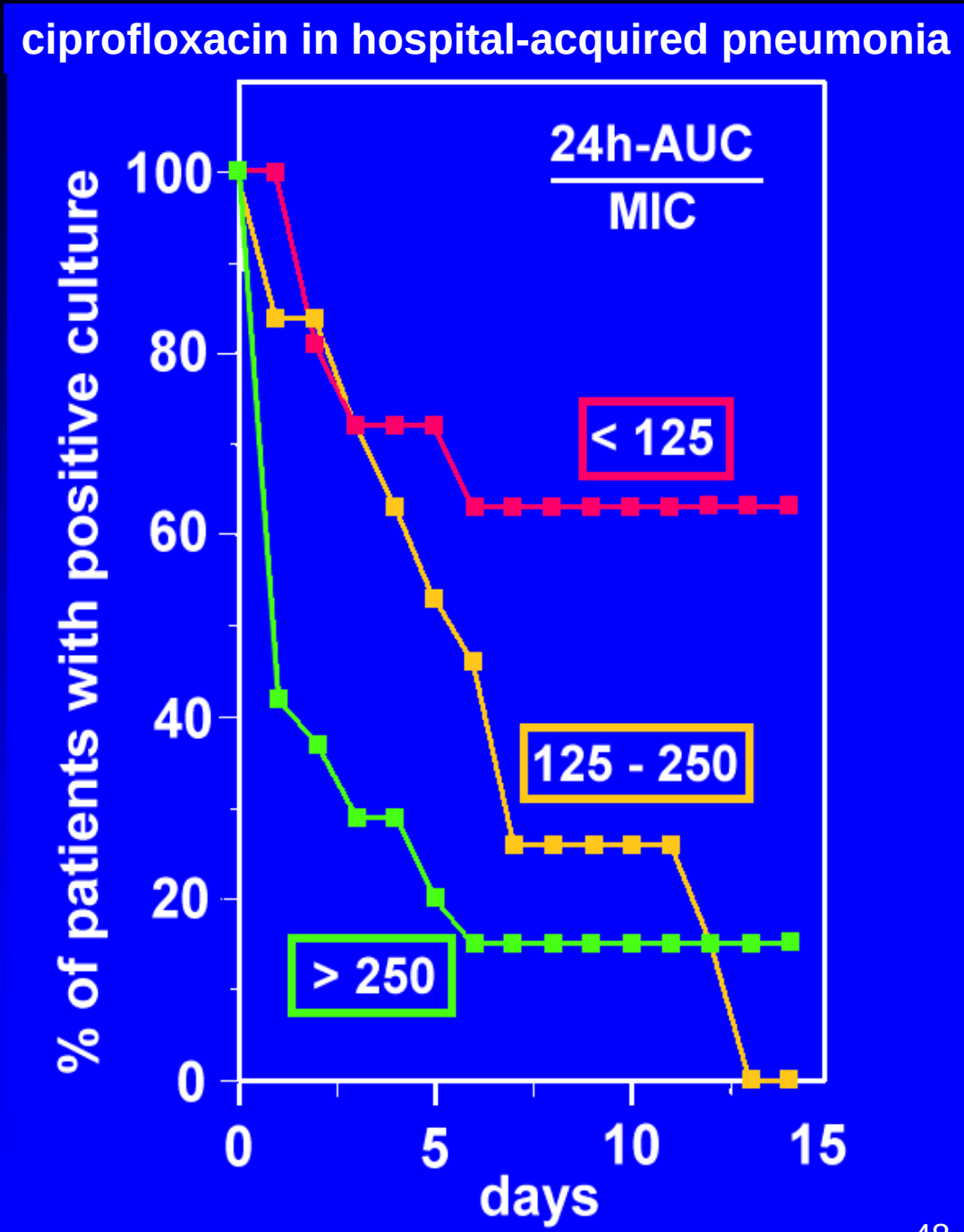
Methods

- In vitro dynamic models
- Animal models
- Clinical trials
- Population pharmacokinetics

PK/PD of fluoroquinolones in clinics

Demonstration of the role of the

24h-AUC / MIC ratio



Forrest et al., AAC, 1993

24h AUC / MIC : what were the data ?

Parameter	No.Pat.	% CureMicrob.		% CureClinical
MIC (mg/L)				
<0,125	28	82		79
0,125-0,25	13	75	success	69
0.5	14	54		79
1	9	33	failures	44
2	2	0		0

Forrest et al., AAC, 1993

24h AUC / MIC : what were the data ?

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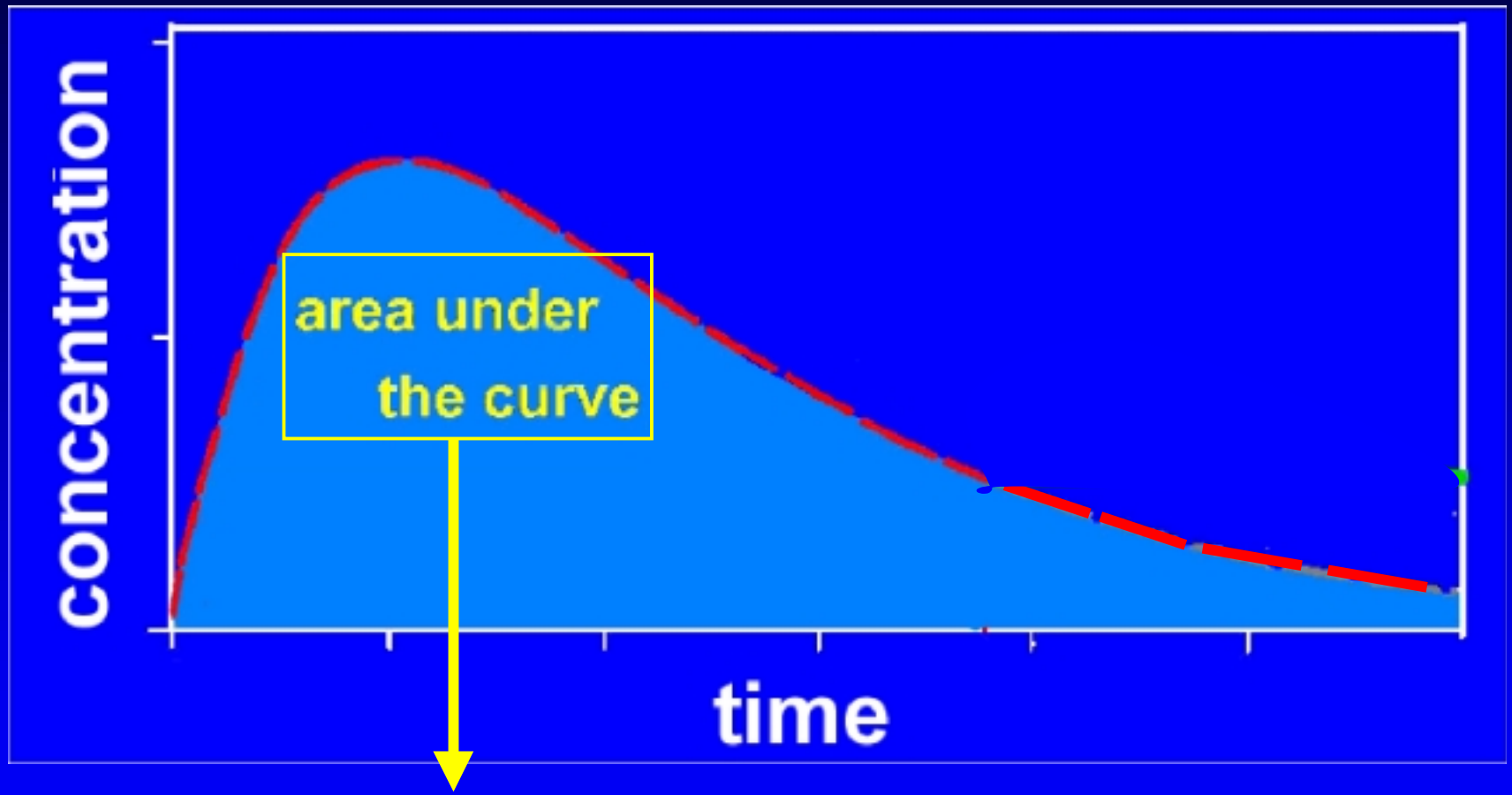
0.5	14	54		79
1	9	33	failures	44
2	2	0		0
24h AUC / MIC				
0-125	19	32	failures	42
125-250	16	81	success	88
250-1000	14	79		71
1000-5541	15	87		80

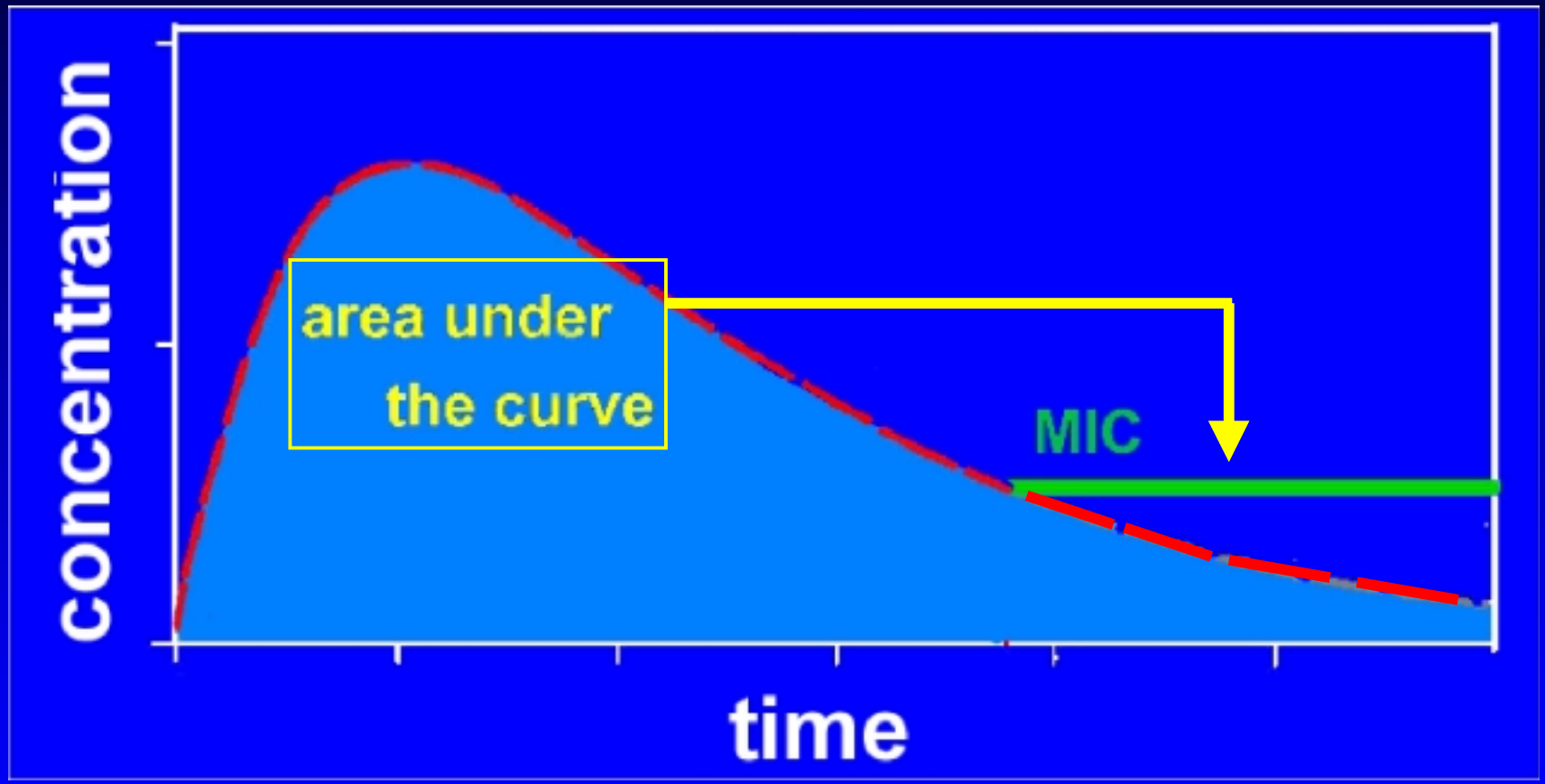
Forrest et al., AAC, 1993

What is the 24h-AUC / MIC ratio (AUIC) ?



$AUC_{24h} = dose_{24h} / clearance$

What is the 24h-AUC / MIC ratio (AUIC) ?



AUC_{24h} / MIC = 125 ⇒ 5 x MIC for 24h

Modeling of the clinical data

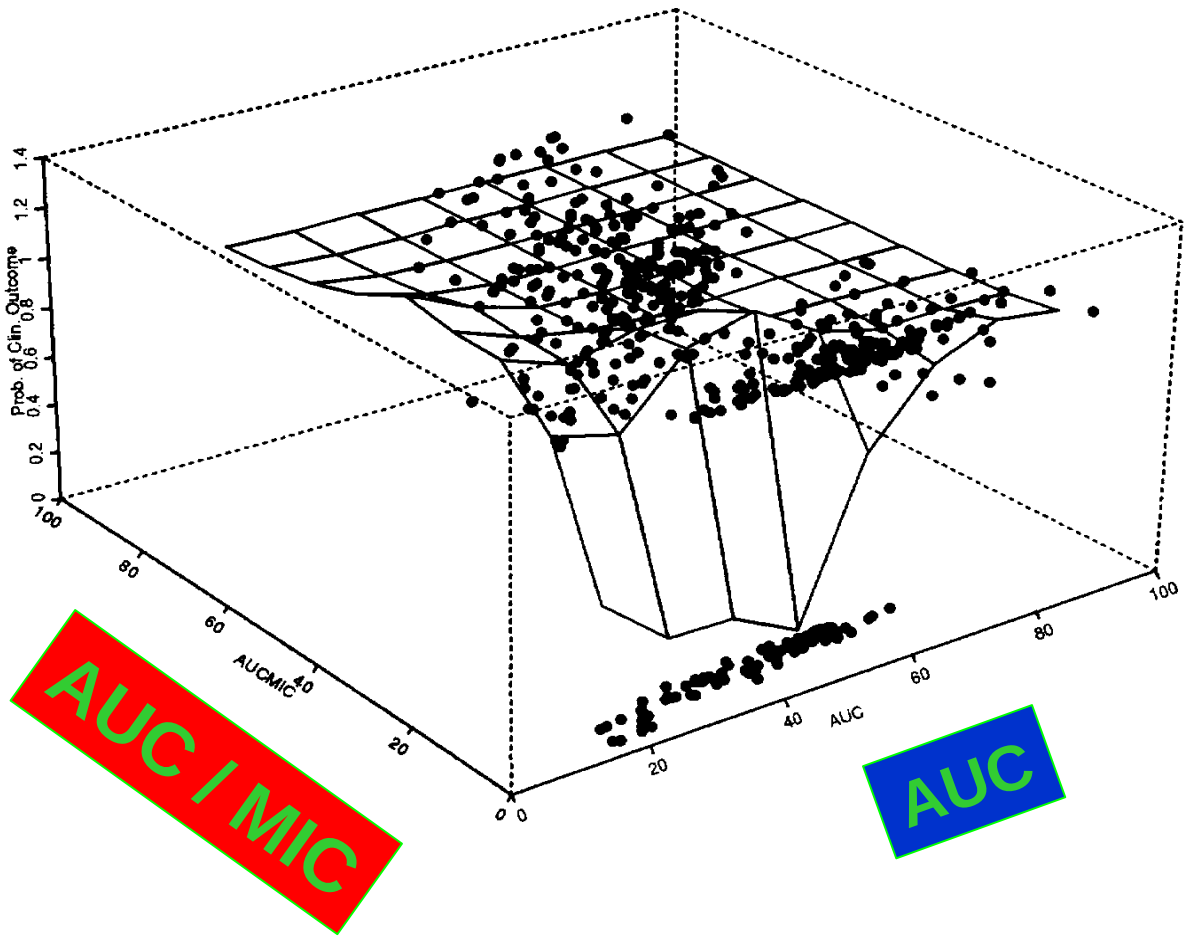
Associating successes and failures to PK parameters

- **Logistic Regression**
  - for evaluating the effects of covariates on outcome where the outcome measure is binary
- **Generalized Linear Modeling** (GLM)
  - multiple linear regression approach
- **Generalized Additive Modeling** (GAM)
  - models the dependence of outcome on the predictor variables
- **Tree based modeling**
  - An approach for understanding the predictive power of PD variables (clinical outcome, microbiological outcome)

F. O. Ajayi, ISAP-FDA Workshop, 1999

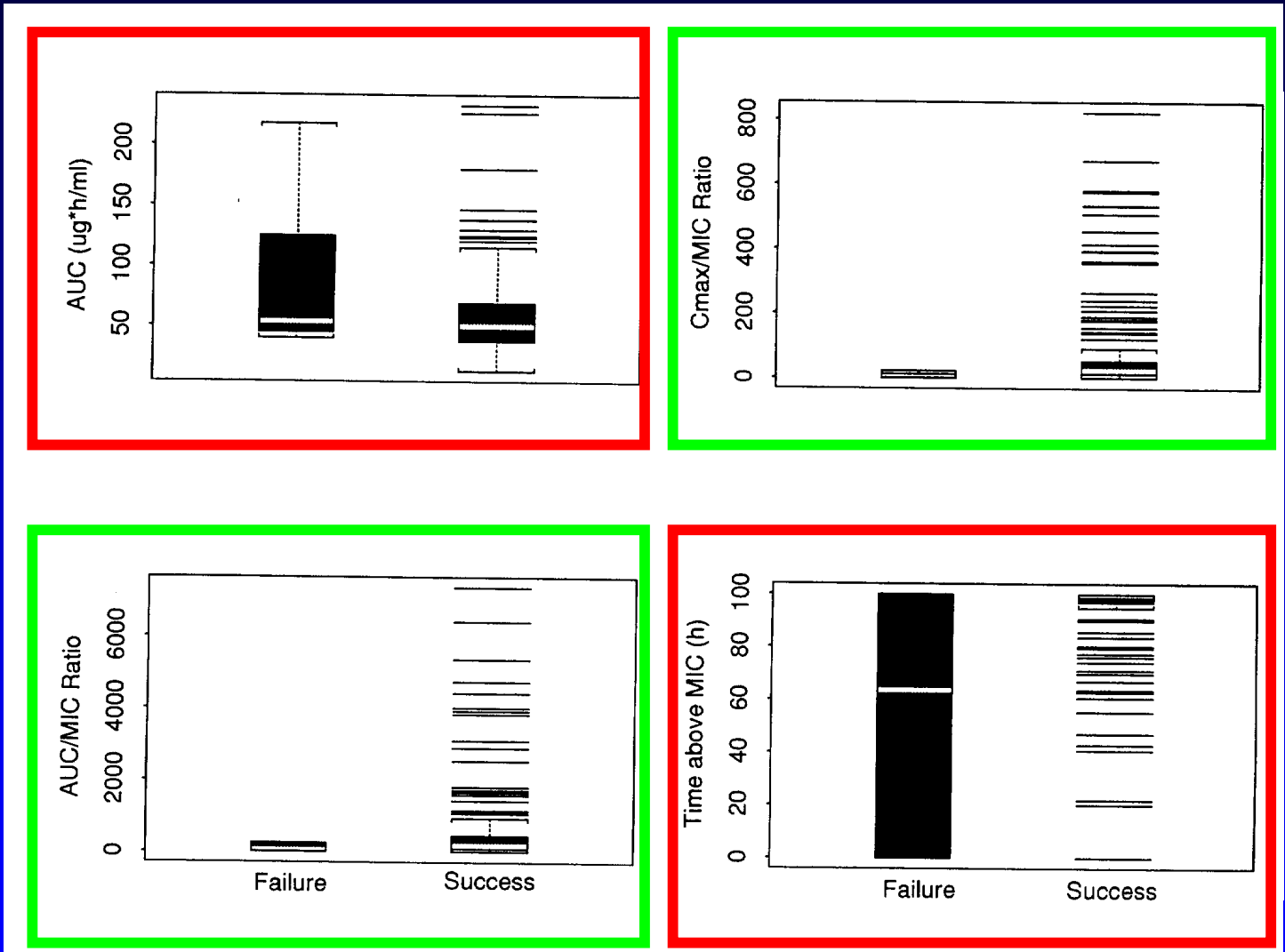
Medeling of fluoroquinolones clinical outcome

clinical outcome



F. O. Ajayi, ISAP-FDA Workshop, 1999

Modeling of fluoroquinolones successes and failures



F. O. Ajayi, ISAP-FDA Workshop, 1999

Why are the conclusions of the clinical trials apparently (sometimes and apparently) contradictory ?

- **insufficient separation of covariables**
  - only one or a few dosage regimens
- **not enough true failures**
  - self-limiting diseases
  - study design
- **intercurrent variables influencing outcome and not recognized as such**
- **unsufficient or inappropriate collection of PK data**
  - only “peaks” or troughs...

Correct but uncomplete conclusion

No conclusion possible

Conclusions of poor value (shed confusion…)

Methods

- In vitro dynamic models
- Animal models
- Clinical trials
- Population pharmacokinetics

Patient care or Drug assessment ?

- In clinical therapy, we would like to give an optimal dose to each individual patient for the particular disease

  → **Individualized therapy**

- In new drug assessement / development, we would like to know the overall probability for a population to show an appropriate response to a given drug and a proposed regimen

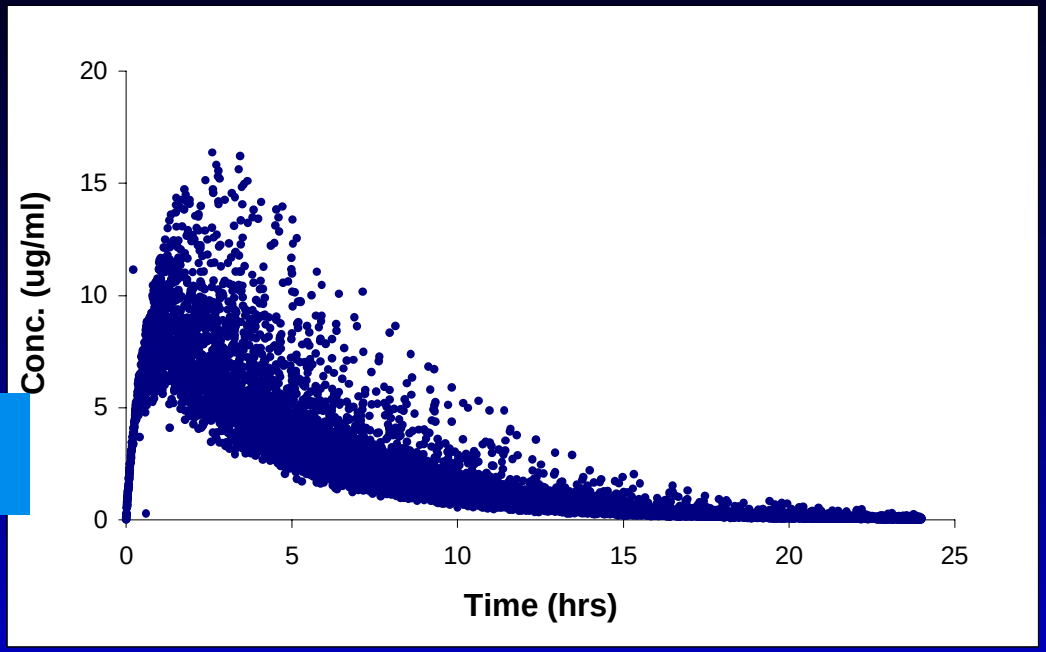
  → **Population-based recommendations**

H. Sun, ISAP-FDA Workshop, 1999

PK/PD and population-based recommendations : the issues

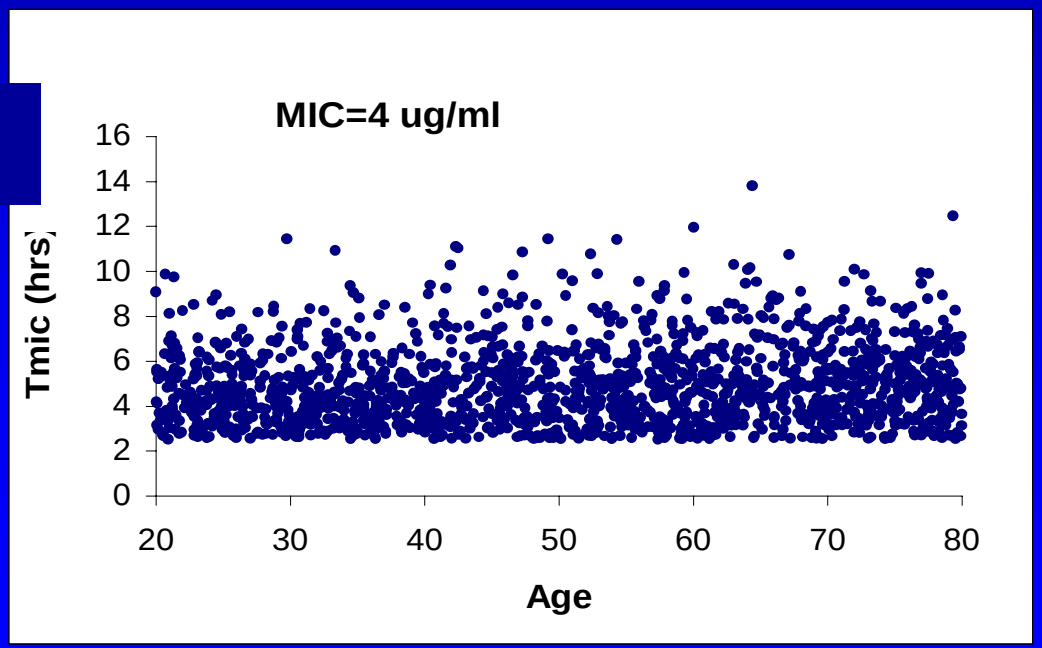
- PK parameters are variable among patients
- if PK / PD parameters predict outcome, then PK variabilities will have a significant impact on the overall rate of clinical responses
- then, you need to estimate what are the chances of reaching an appropriate level of the pertinent PK/PD parameter in a sufficiently high proportion of patients...

Examples of variations



C_{max}

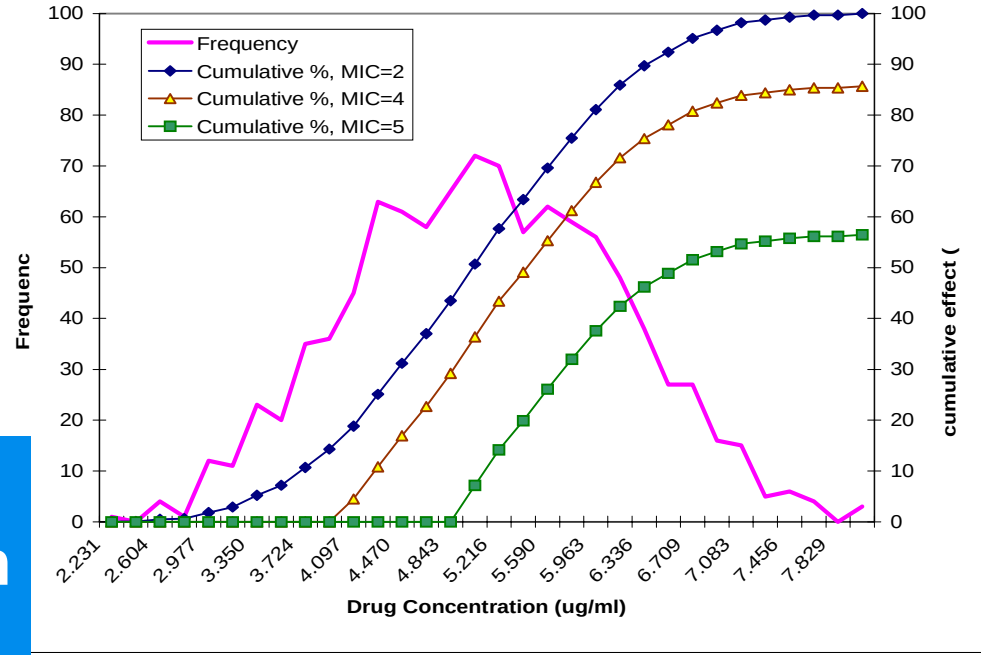
T > MIC



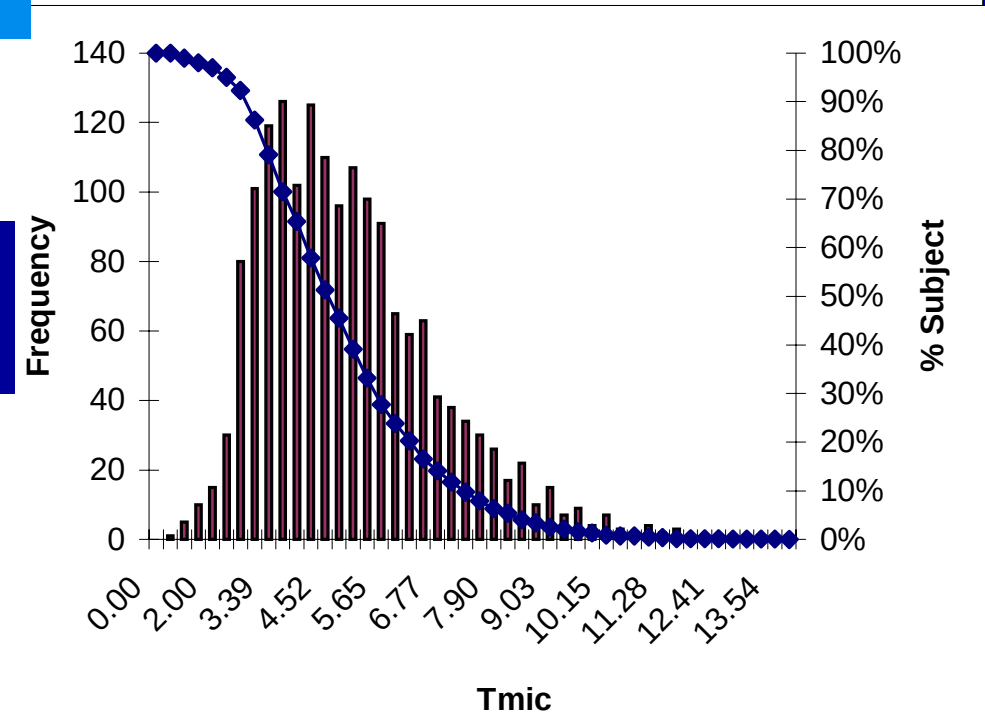
H. Sun, ISAP-FDA Workshop, 1999

Obtaining population cumulative frequencies

Quantal drug concentration effects

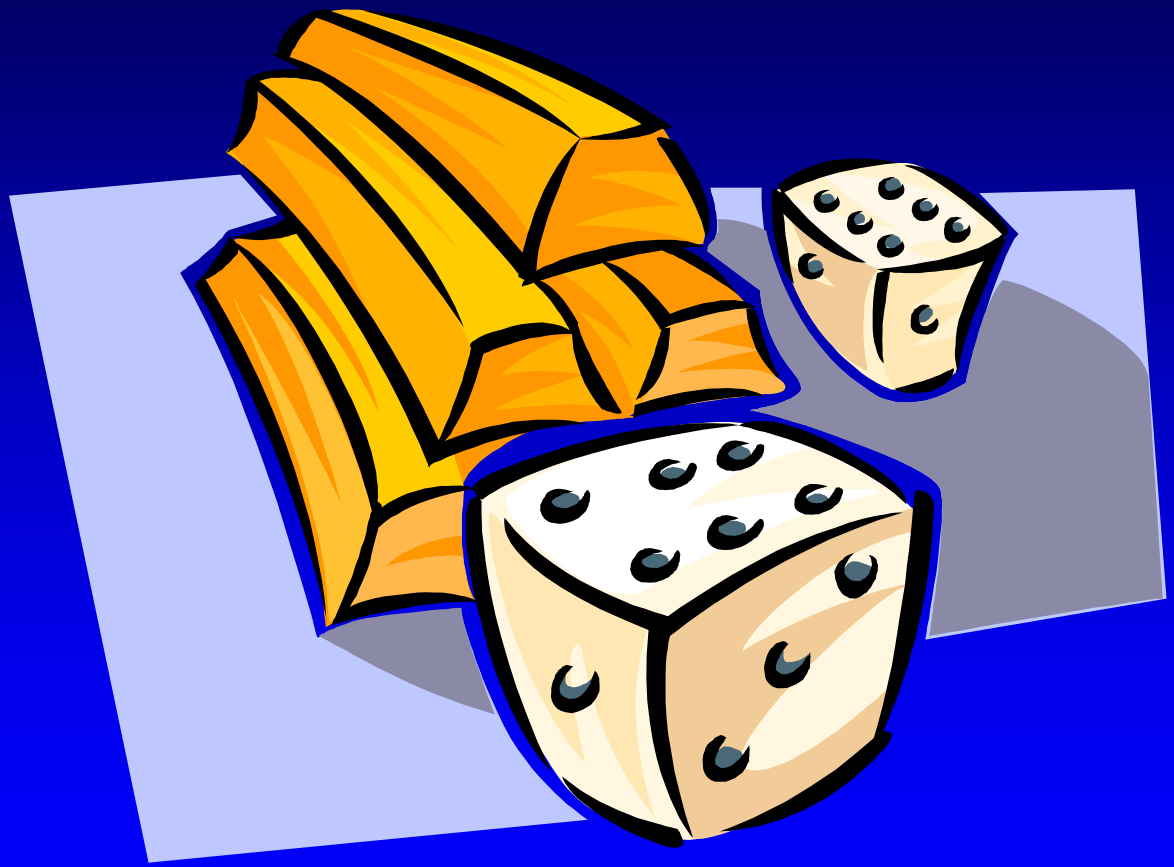


Quantal T>MIC plots

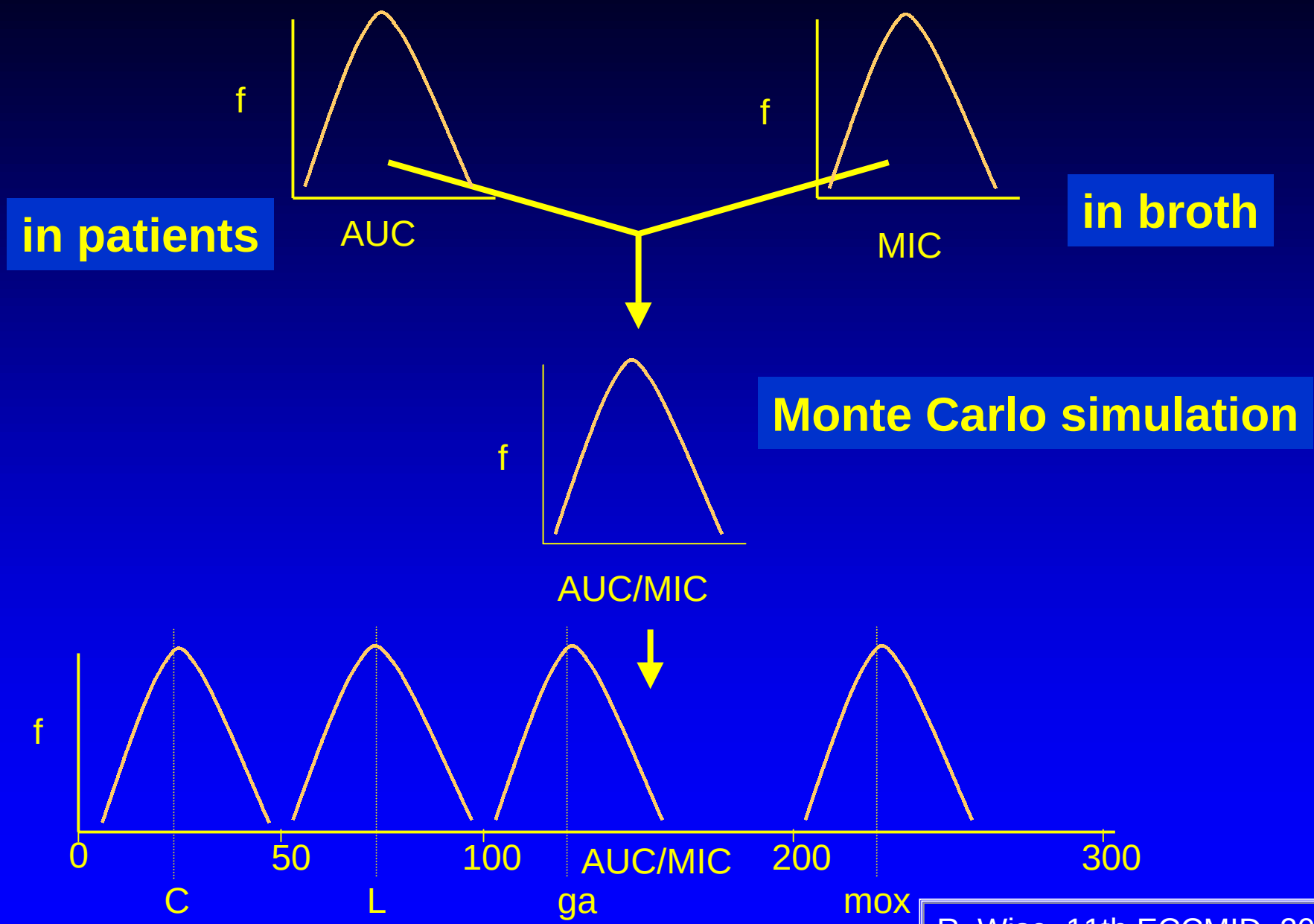


H. Sun, ISAP-FDA Workshop, 1999

Monte Carlo simulations

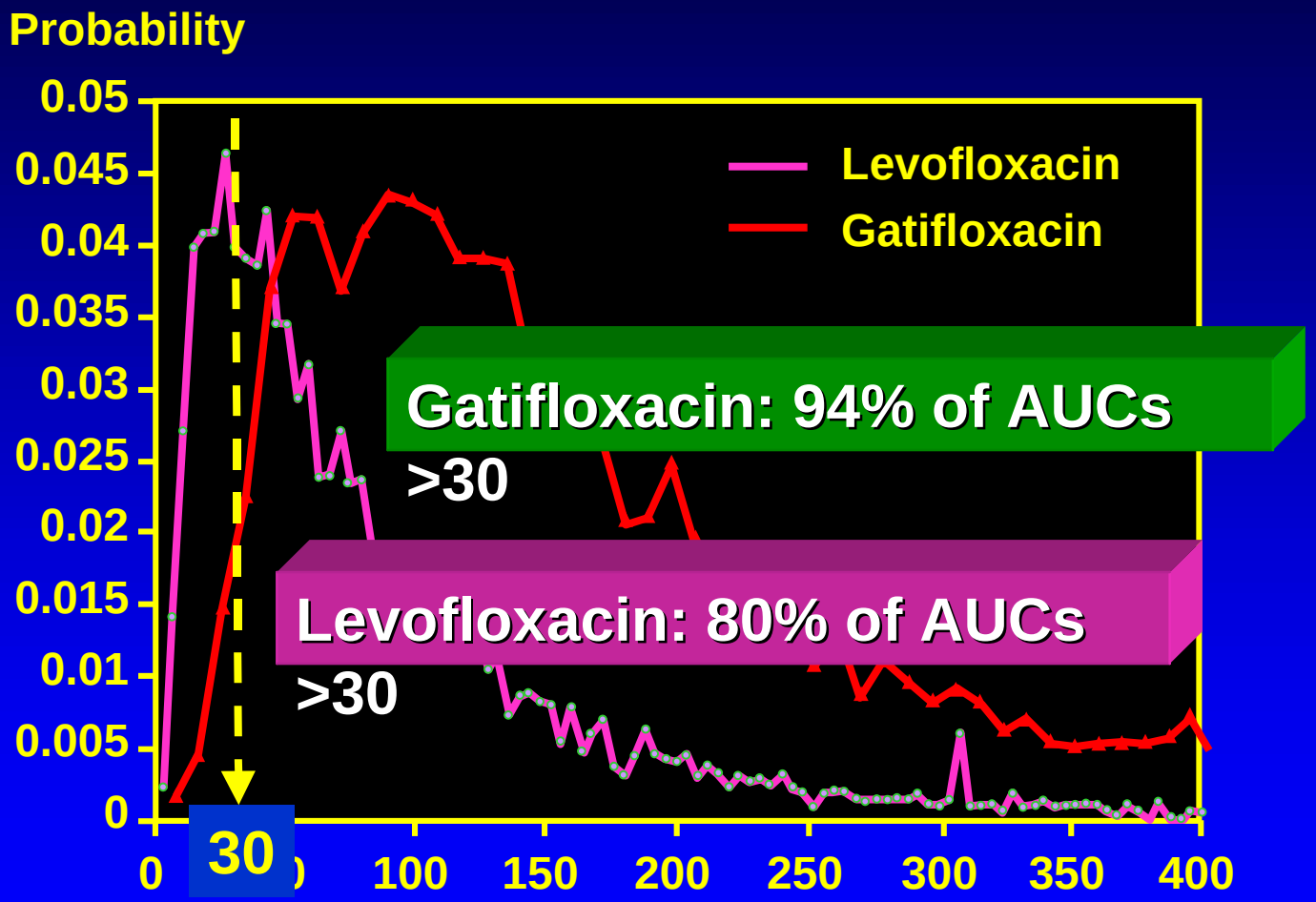


R. Wise, 11th ECCMID, 2001



R. Wise, 11th ECCMID, 2001

Distribution of AUC: MIC Ratios of Gatifloxacin and Levofloxacin Against *S. pneumoniae*: "Monte Carlo" analysis



Data from Ambrose PG, Grasela D. ICAAC 1999

M Jacobs, 11th ECCMID, 2001

Monte Carlo simulations of fluoroquinolone AUC / MIC against *S. pneumoniae*

- **Probability of achieving free drug AUC / MIC >30**
  - **levofloxacin 77.6±0.9%**
  - **gatifloxacin 97.5±0.4%**
  - **moxifloxacin 97.5±0.9%**

Owens *et al*, 2000

- **Probability of achieving total drug AUC/MIC ratio of…**

	>40	>80
– ciprofloxacin	4%	0%
– levofloxacin	56%	6%
– gatifloxacin	91%	33%
– moxifloxacin	100%	100%
– gemifloxacin	100%	100%

Atkins *et al*, 2000

The rest of the talk ...

- Methods to derive pertinent PK/PD parameters
- Data with selected existing antibiotics
- What does Industry do ?
- What should Clinical Pharmacist do ?

PK/PD patterns of antimicrobial activity

The existing antibiotics consistently show 3 type of dominant pattern:

- Time-dependency
- AUC / MIC - dependency
- AUC / MIC- and Peak / MIC -dependency

PK/PD patterns of antimicrobial activity (1 of 3)
(after WA. Craig, 2000)

1. Antibiotics with time-dependent killing, no or little effect of concentration, and minimal to moderate persistent effects

Drugs	Key PK/PD parameter	Goal
beta-lactams clindamycin oxazolidinones macrolides flucytosine	Time above MIC	Optimize the duration of exposure to drug

Relationship between time above MIC and efficacy For β-lactams, macrolides and TMP/SFX in otitis media

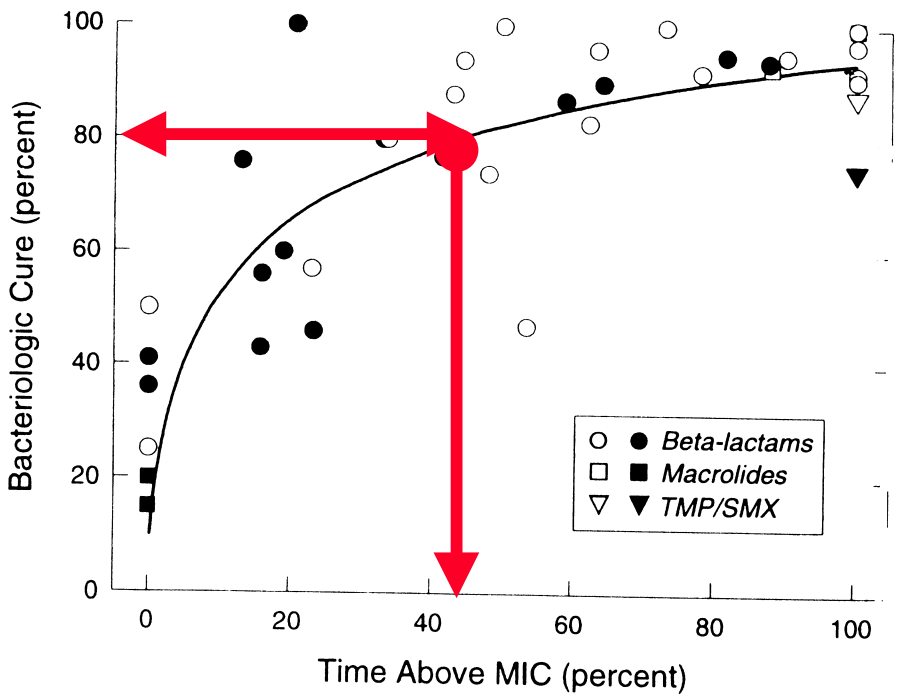
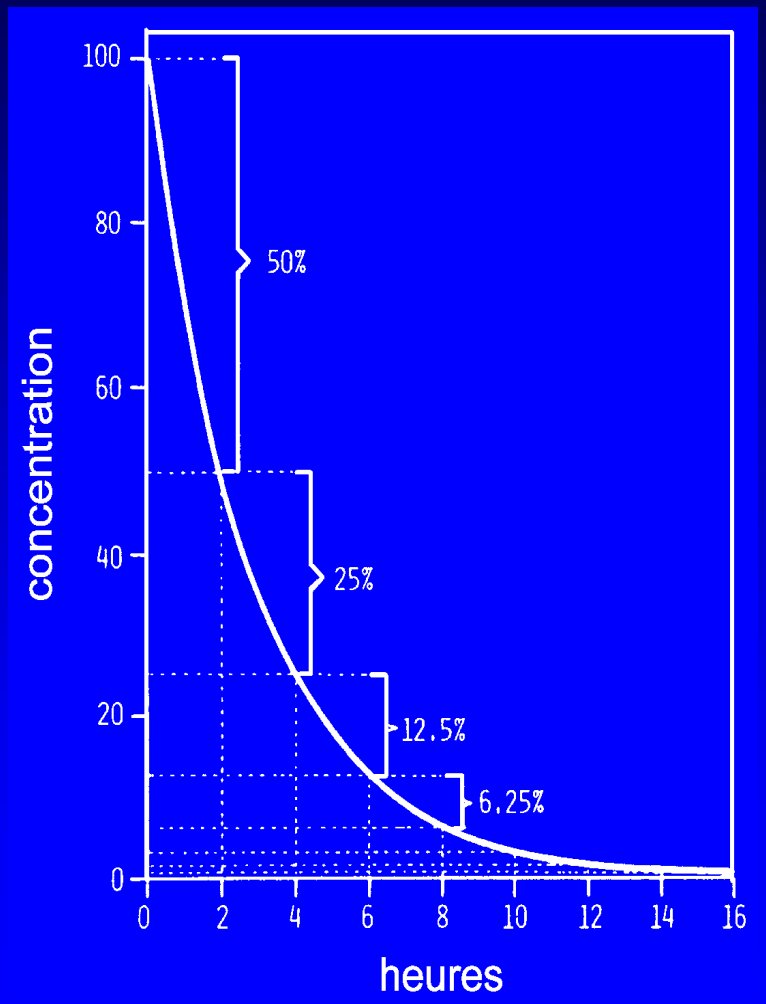


FIG. 1. Relationship between the percentage of time that serum levels exceed the MIC_{90} and the bacteriologic cure in otitis media caused by *S. pneumoniae* (*open symbols*) and beta-lactamase-positive and -negative *H. influenzae* (*closed symbols*). Data available for 10 beta-lactams, 2 macrolides and trimethoprim-sulfamethoxazole. The coefficient of determination was 0.57.

T > MIC must reach 50 %

β-lactams : at least 50 % of the time above the MIC...



<u>you must calculate the interval</u>

$$C_t = C_0 \times e^{-kt}$$

time between 2 administrations:

- **<u>dir.</u> proportionnal to the dose**
- **<u>inv.</u> proportionnal to the half-life**

Most betalactams have an half-life of approx. 2 h or less

PK / PD in action: what can you do with a model β-lactam *

time (hours)	concentr. (mg/L) for a dose of 0.5 g	1 g	2 g	if given every 12h
2	25	50	100	
4	12.5	25	50	
6	6	12	25	50 % coverage
8	3	6	12	66 % coverage
10	1.5	3	6	
12	0.75	1.5	3	100 % coverage

* adult 50 kg; single administration; 2h half-life; V_d = 0.2 l/kg; **free fraction !!**

Improving β-lactam efficacy by reducing the interval

time (hours)	concentration for 0.5 g	1 g	2 g	if given every 8 h
2	25	50	100	
4	12.5	25	50	50 % coverage
6	6	12	25	66 % coverage
8	3	6	12	100 % coverage
10	1.5	3	6	
12	0.75	1.5	3	

* single administration; 2h half-life; V_d = 0.2 l/kg; **free fraction !!**

β-lactam by continuous infusion ?

- Optimized PK/PD-based administration
- Reasonably stable serum concentrations around 20 to 40 mg/L can easily be achieved

BUT….

- Critical issues include
  - the stability of the β-lactam ring (temperature !!!)
  - physical and chemical compatibility with other drugs administered by continuous infusion (Intensive Care patients, e.g.)

Breakpoint issues:

NCCLS vs PK/PD (50 % time coverage) breakpoints of common β- lactams (µg/ml) *

	NCCLS		PK/PD
	S. pneumoniae	*H. influenzae*	all organisms
Amoxicillin	2	4	2
Amox-clav	2	4	2
Cefuroxime	1	4	1
Cefprozil	2	8	1
Cefixime	–	1	0.5
Cefaclor	1	8	0.5
Loracarbef	2	8	0.5

* conventional doses and schedules

M. R.Jacobs, 11th ECCMID, 2001

β-lactams PK / PD and resistance

- too low doses
- too long intervals
- too high breakpoints

"250 mg" ampicillin...

BID schedules...

cefaclor, some C4, ...

lead to suboptimal effects

➔ **delay in eradication**

➔ **selection of subpopulations with reduced susceptibility**

PK/PD patterns of antimicrobial activity (2 of 3)
(after WA. Craig, 2000)

2. Antibiotics with time-dependent killing, but also prolonged persistent effects

Drugs	Key PK/PD parameter	Goal
glycopeptides tetracyclines azithromycin streptogramins fluconazole	**24 h AUC / MIC ratio**	**Optimize the amount of drug administered**

AUC / MIC - dependent antibiotics and resistance

Evidence is mounting that resistance to

- **macrolides**
- **glycopeptides**
- **tetracyclines**

can be linked to

- **their slow and uncomplete bactericidal activity;**
- **the too low doses;**
- **their use in situations in which eradication is impossible to achieve.**

AUC / MIC - dependent antibiotics and resistance

Examples:

- **glycopeptides :**
  - **eradication of MRSA colonization**
  - **selective decontamination of the digestive tract**
  - **primary treatment of antibiotic associated colitis (AAC)**
  - **topical application or irrigation**
- **macrolides**
  - **otitis media**
  - **“good for all respiratory tract infections” promotion**
- **tetracyclines**
  - **low doses for fear of toxicity**
  - **treatment of acne**

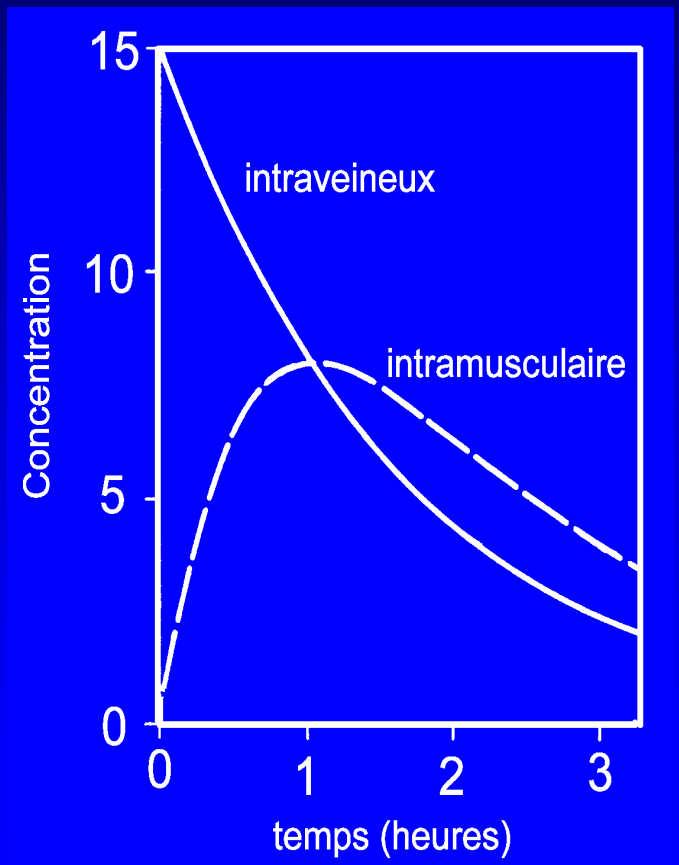
PK/PD patterns of antimicrobial activity (3 of 3)
(after WA. Craig, 2000)

3. Antibiotics with concentration-dependent killing and prolonged persistent effects (post-antibiotic effects)

Drugs	Key PK/PD parameter	Goal
aminoglycosides fluoroquinolones daptomycin ketolides amphotericin B	**Peak and 24 h AUC / MIC ratio**	**Optimize concentrations and drug amount**

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000

Aminoglycosides : obtain a peak !



1. adequate mode of aministration

i.v. administration

2. calculate the peak you need

minimal peak = MIC / 8

3. calculate the dose you need

peak = dose / Vd

dose = peak x Vd

PK / PD in action ...

Aminoglycosides :

increase the unit dose to get the appropriate peak !

MIC = 1 mg/L ➡ C_{max} = 8 mg/L ➡ 3 mg/kg

MIC = 2 mg/L ➡ C_{max} = 16 mg/L ➡ 6 mg/kg ← limit for G, T, N

MIC = 4 mg/L ➡ C_{max} = 32 mg/L ➡ 15 mg/kg ← limit for A, I

PK /PD in action ...

Aminoglycosides 1st rule of thumb…

anything with an MIC < 1 (within the indications…) will be treatable

efficacy will become a problem for organisms with MIC's

- **> 2 for G, T, N (up to 6 mg/kg)**
- **> 4 for A, I (up to 15 mg/kg)**

PK / PD "safe" breakpoints for AG

- **G, N, T : 2 µg / ml**
- **A / I : 4 µg / ml**

PK PD in action ...

Aminoglycosides 2d rule of thumb...

give them once-a-day to reduce toxicity

- **1h peaks of 12-18 mg/L for G, T, N**
- **1h peaks of 20-30 mg/L for A, I**

Increase interval (→ 36h, → 48h) in case of renal failure before reducing the unit dose...

Once-daily dosing of aminoglycoside antibiotics

Fisman, DN; Beth Israel Deaconess Med Ctr; Div Infect Dis; Harvard Univ, Sch Publ Hlth, Infectious-Disease-Clinics-of-North-America. Jun 2000

Fluoroquinolones : get both a peak and an AUC !

- **24h-AUC / MIC must be ≥ 125 *** (Schentag, ...)
- **24h-AUC is proportional to the daily dose**
  - ➔ **adjust the daily dose**

- **peak must be ≥ 10 *** (Drusano, ...)
- **peak is proportional to the unit dose…**
  - ➔ **adjust the unit dose**

*** you may like to consider only the free fraction !!**

24h-AUC / MIC = 125 as a guide to determine acceptable sensitivities to standard doses of FQ

Drug	Dosage (mg/24h)	24h-AUC (mg/L x h)	**PK/PD Bkpt [AUC/MIC = 125]**
norfloxacin	800	14 *, #	**0.1**
ciprofloxacin	500	12 *	**0.1**
ofloxacin	400	31 to 66 *, +	**0.2 - 0.4**
levofloxacin	500	47 *	**0.4**
gatifloxacin	400	35 *	**0.3**
moxifloxacin	400	48 *	**0.4**

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN® and AVELOX®; # litterature data; + first dose to equilibrium

Peak /MIC = 10 as a guide to determine acceptable sensitivities to standard doses of FQ

Drug	Dosage (mg/24h)	C_{max} (mg/L)	**PK/PD Bkpt** [C_{max} / 12] (mg/L)
norfloxacin	800	2.4 *	**0.2**
ciprofloxacin	500	2.4 *	**0.2**
ofloxacin	400	3-4.5 *, +	**0.3 - 0.4**
levofloxacin	500	5-6 *, +	**0.4 - 0.5**
gatifloxacin	400	4.2 *	**0.4**
moxifloxacin	400	4.5 *	**0.4**

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, TEQUIN®, LEVAQUIN®, and AVELOX®

\+ first dose to equilibrium

Combining it all …

Peak/MIC = 10 and 24h-AUC / MIC = 125 as predictors of efficacy standard doses of FQ ...

Drug	Dosage (mg/24h)	PK/PD Bkpts (mg/L) AUC/MIC (24h)	peak / MIC
norfloxacin	800	0.1	0.2
ciprofloxacin	500	0.1	0.2
ofloxacin	400	0.2-0.4	0.3 - 0.4
levofloxacin	500	0.4	0.4 - 0.5
gatifloxacin	400	0.3	0.4
moxifloxacin	400	0.4	0.4

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN® and AVELOX®

Breakpoint issues ...

Drug	Dosage (mg/24h)	PK/PD Bkpts (mg/L) AUC/MIC (24h)	peak / MIC	NCCLS Bkpts*
norfloxacin	800	0.1	0.2	< 4
ciprofloxacin	500	0.1	0.2	< 1
ofloxacin	400	0.2-0.4	0.3 - 0.4	< 2
levofloxacin	500	0.4	0.4 - 0.5	< 2
gatifloxacin	400	0.3	0.4	< 2
moxifloxacin	400	0.4	0.4	< 2

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN® and AVELOX®

Which patient and which value of AUC / MIC ?

An example with levofloxacin 500 mg qD

creatinine clearance (mg/l)	AUC (mg/L X h)	PK/PD Bkpt (mg/L)	
100	56	**0.5**	**2**
50	98	**0.8**	**4**

But the peak remains unchanged at ~ 5 mg /L

AUC / MIC = 125

AUC / MIC = 25

To increase efficacy of FQ, you need to increase both the AUC and the peak …

An example with levofloxacin (qD)

dosage qD	AUC * mg*h/L	**AUC/MIC** Bkpt**	Peak * mg /L	**Peak/MIC** Bkpt***
250	28	1	2.5	0.25
500	56	2	5	0.5
1000	112	4	10	1

* based on normal half-lifes; CL ~ 100 mg/dl; dos

** **for a 24h AUC / MIC = 25**

*** **for a peak / MIC = 10**

but the MIC of *S. pneumoniae* ~ 1-2 mg/L

Breakpoints of FQ: two problems ...

Classical breakpoints of older FQs and of levofloxacin have been probably set too high and will correspond to 24h AUC / MIC - based PK/PD breakpoints only if

- **clearance is lower than in normal subjects**
- **accepting an 24 AUC / MIC ratio of 25 as being sufficient…**
- **considering total drug concentrations**

Classical FQ breakpoints almost never correspond to a peak / MIC ratio ≥ 10 !

Resistance...

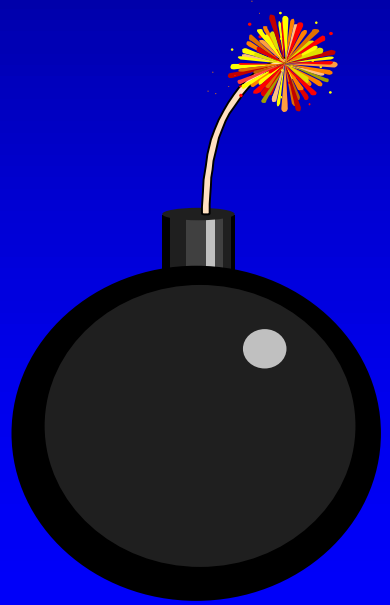
Pharmacokinetics / Pharmacodynamics in action ...

Fluoroquinolones: 3d rule of thumb...

Do not trust (*too much*) NCCLS, and do not try to treat with <u>conventional</u> doses <u>serious</u> infections caused by organisms with MIC's > 0.5 !!

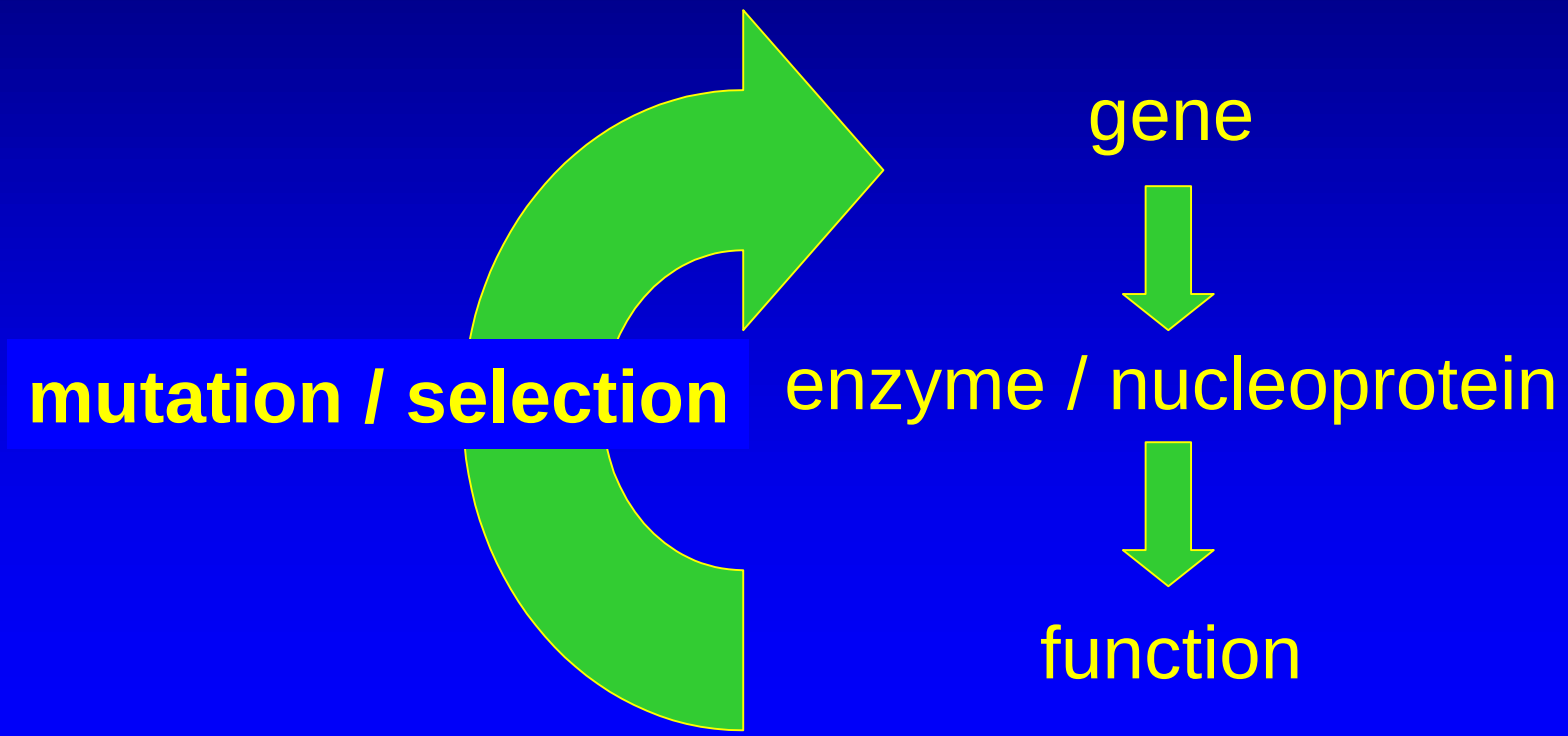
Why should you NOT use low doses ?

A bacteria which does not get killed is a collection of genes that can mutate !!

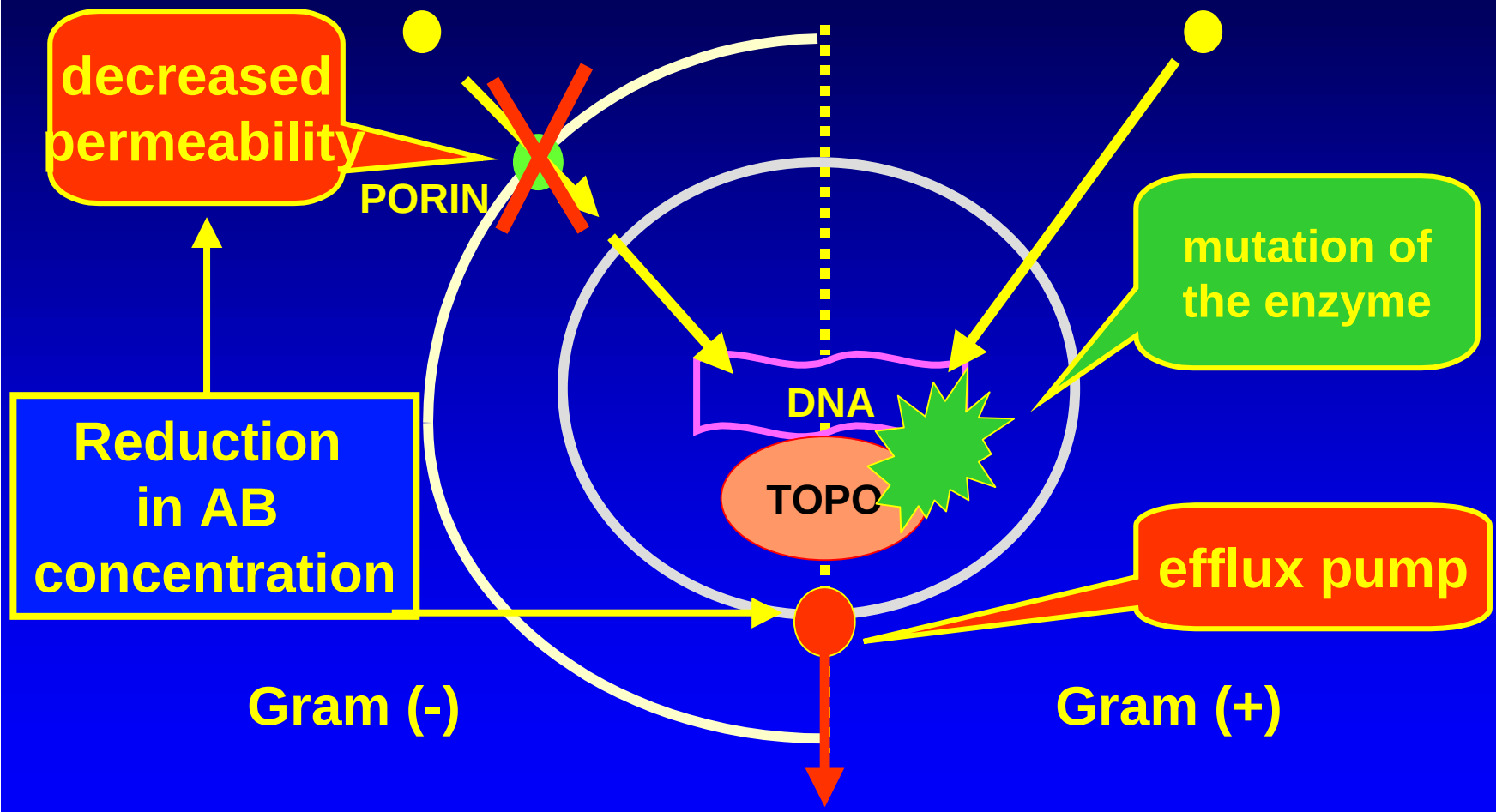


Resistance: a global overview...

Favored by exposure to sub-MIC concentrations



Mechanisms of resistance to fluoroquinolones



PK/PD and antibiotic efflux pumps...

Efflux pumps -

Co-operate with other mechanisms of resistance

→ ***high level resistance phenotypes***

show rapidly increased effectiveness by point mutations

→ ***easy adaptation to new environment***

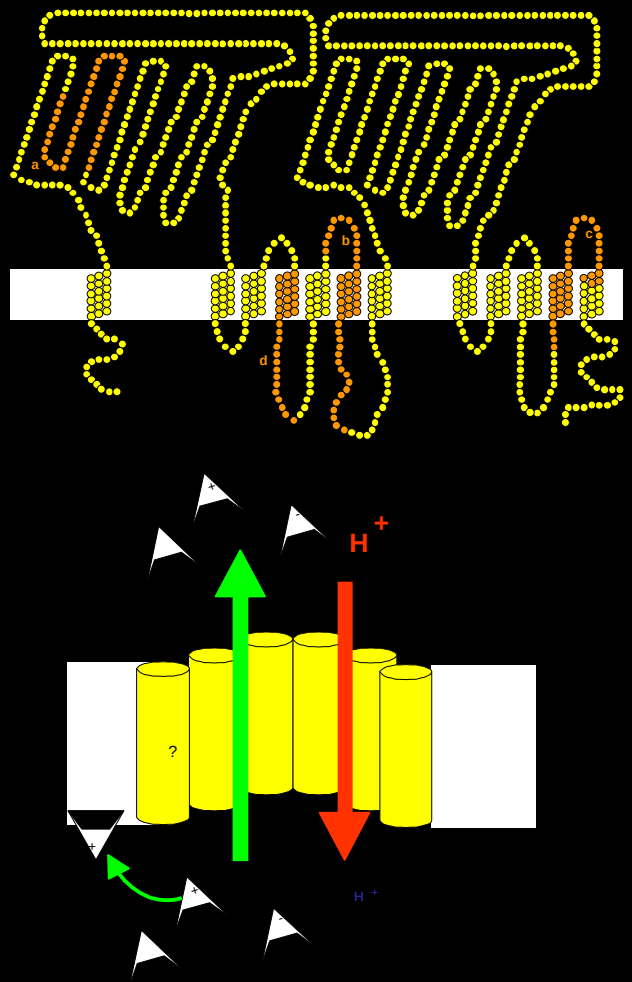
are under control of regulatory genes

→ ***multi-antibiotic resistance phenotype***

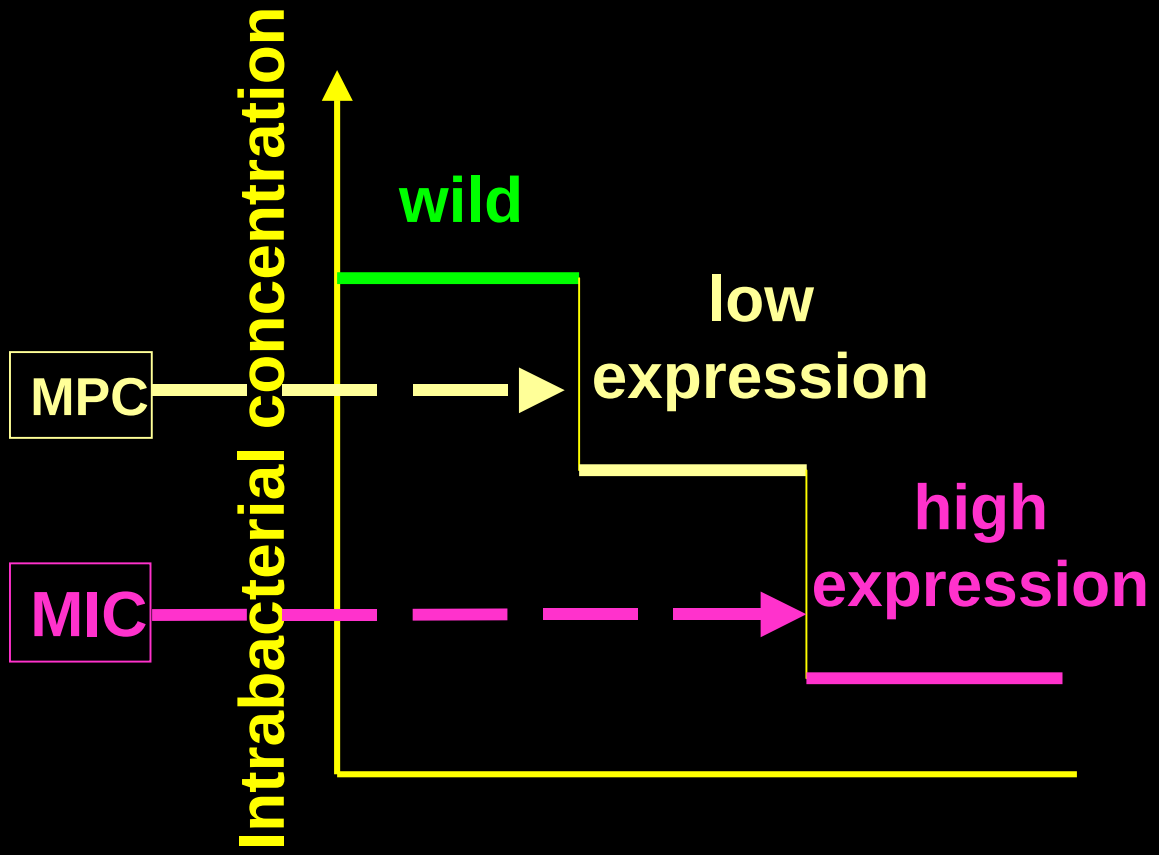
are unspecific but also very “selective” in substrate recognition

→ ***possibility of large variations among related drugs***

PK/PD and antibiotic efflux pumps… an example with RND...

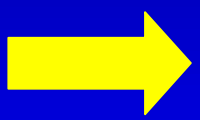


Van Bambeke et al., 2000



Pharmacokinetics / Pharmacodynamics in action ...

Fluoroquinolones: 4th rule of thumb...



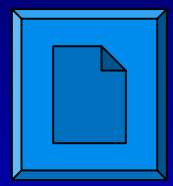
Try to have a peak above the MPC ...

The rest of the talk ...

- Methods to derive pertinent PK/PD parameters
- Data with selected existing antibiotics
- What does Industry do ?
  (but they may not tell you…)
- What should clinical pharmacists do ?

What does (serious) Industry do ?

- Preclinical studies examine the PK/PD parameters related to efficacy (in vitro and animal models), to help in selecting lead candidates with desired properties
- Phase I studies examine if the human PK properties of the drug candidate are compatible with sufficient activity
- Phase II trials are designed with an optimized dosage



And look at the FDA registration dossier * of a new fluoroquinolone...

Moxifloxacin Pharmacokinetics/Pharmacodynamics

PK/PD Parameters that best correlate with Quinolone Efficacy*

- C_{max} / MIC_{90} > 8-10
- AUC / MIC_{90} > 100
- Post Antibiotic Effect (PAE)

*Craig, 1998

AUC/MIC_{90}* Data for Selected Quinolones

	MXF	LEV	CIP	SPFX
S. pneumoniae	192	47.5	11.6	17.0
H. influenza	1600	1583	387	17.0
M. catarrhalis	800	1583	193	623

For optima antimicrobial effect and to minimize resistance, AUIC be > 125 (Craig 1998)

MXF Based on NDA Data on File; Levofloxacin, Ciprofloxacin, Sparfloxacin, Grepafloxacin Data from PDR and MRL Surveillance Study RTI Isolates 1997-1998

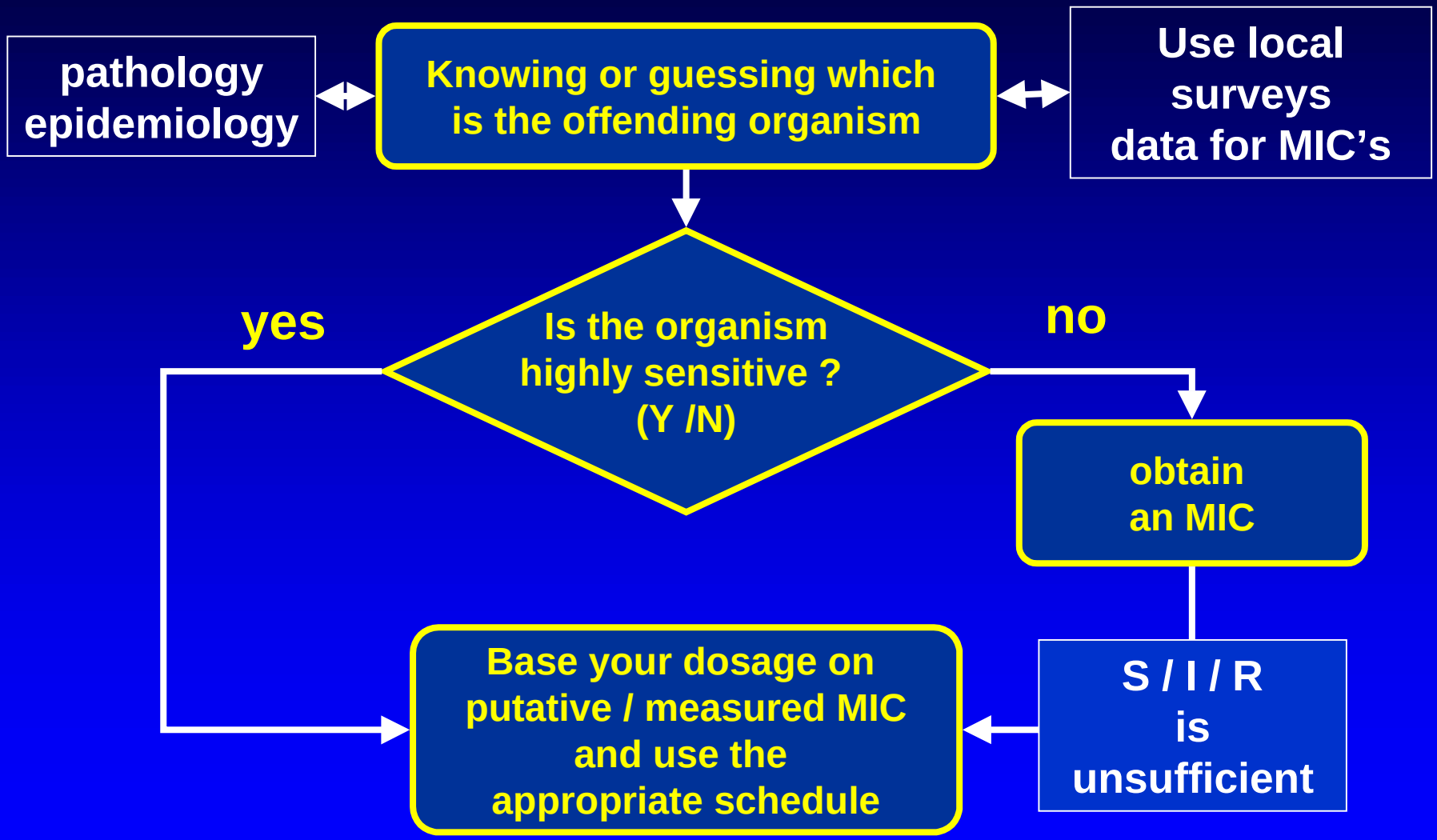
400 mg qD

* **Avelox® (moxifloxacin) FDA hearing committee 1999**

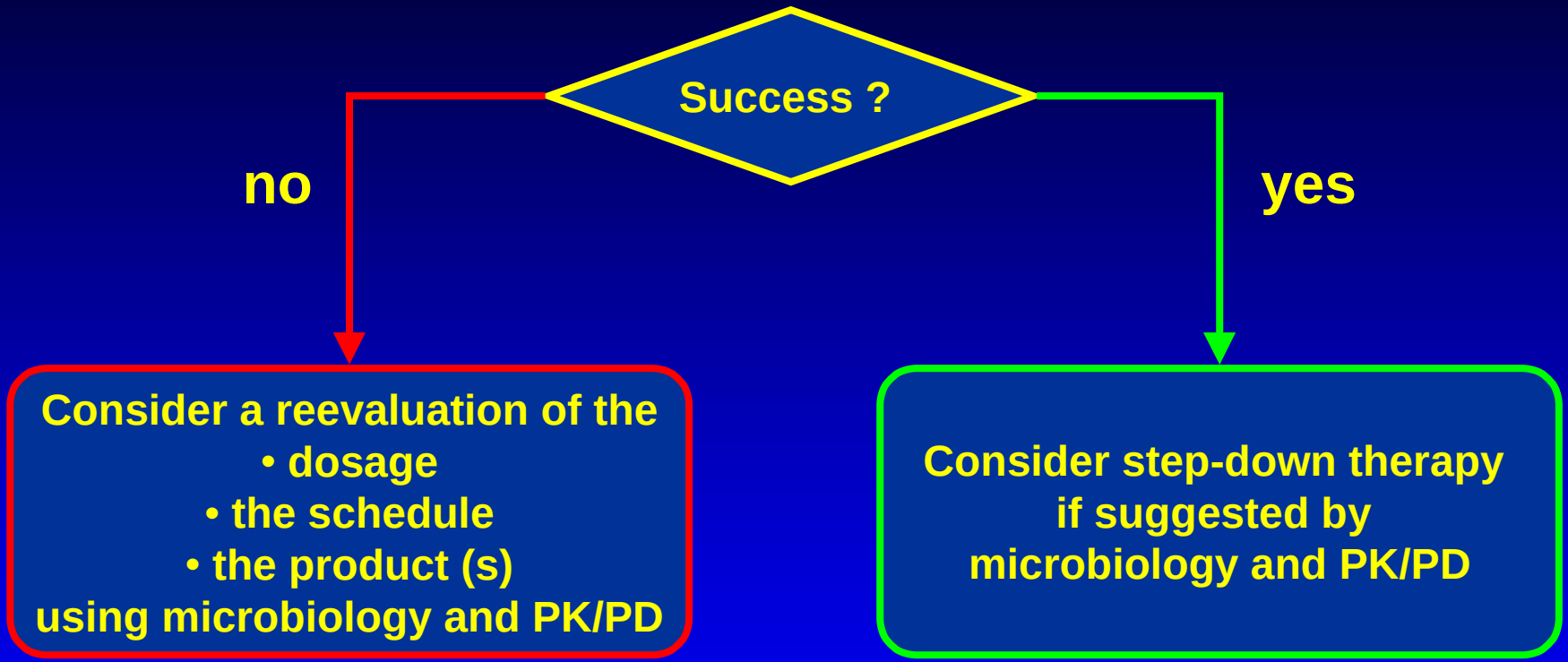
The end of the talk ...

- Methods to derive pertinent PK/PD parameters
- Data with selected existing antibiotics
- What does Industry do ?
  (but they may not tell you…)
- What should Clinical Pharmacists do ?

PK / PD in action ...



PK / PD in action ...

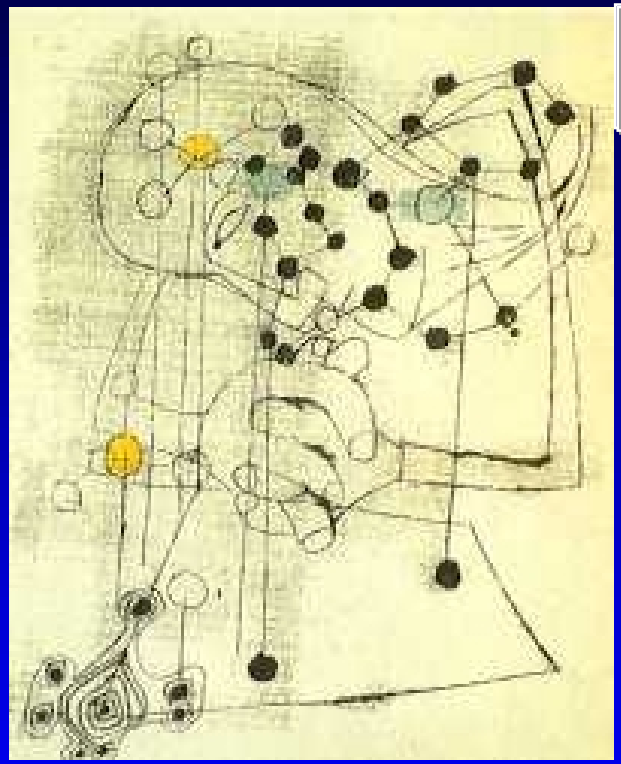


Use information to construct local guidelines based on local epidemiology and sound PK/PD concepts

Better approaches in antibiotic usage...

Was it a nice tale ?

Better approaches in antibiotic usage…



"Scientist" by Ben Shahn
New Jersey State Museum,
Trenton, N.J.

www.md.ucl.ac.be/facm

F. Van Bambeke
Y. Ouadrhiri
S. Carryn
H. Chanteux
H. Servais

Not so magic, and perhaps sooner and easier than you tought...

W.A. Craig
G.L. Drusano
J.J. Schentag
A. McGowan
X. Zao
V. Firsov
S. Zinner
A. Dalhoff
...

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