MACROLIDES: pharmacokinetics and pharmacodynamics

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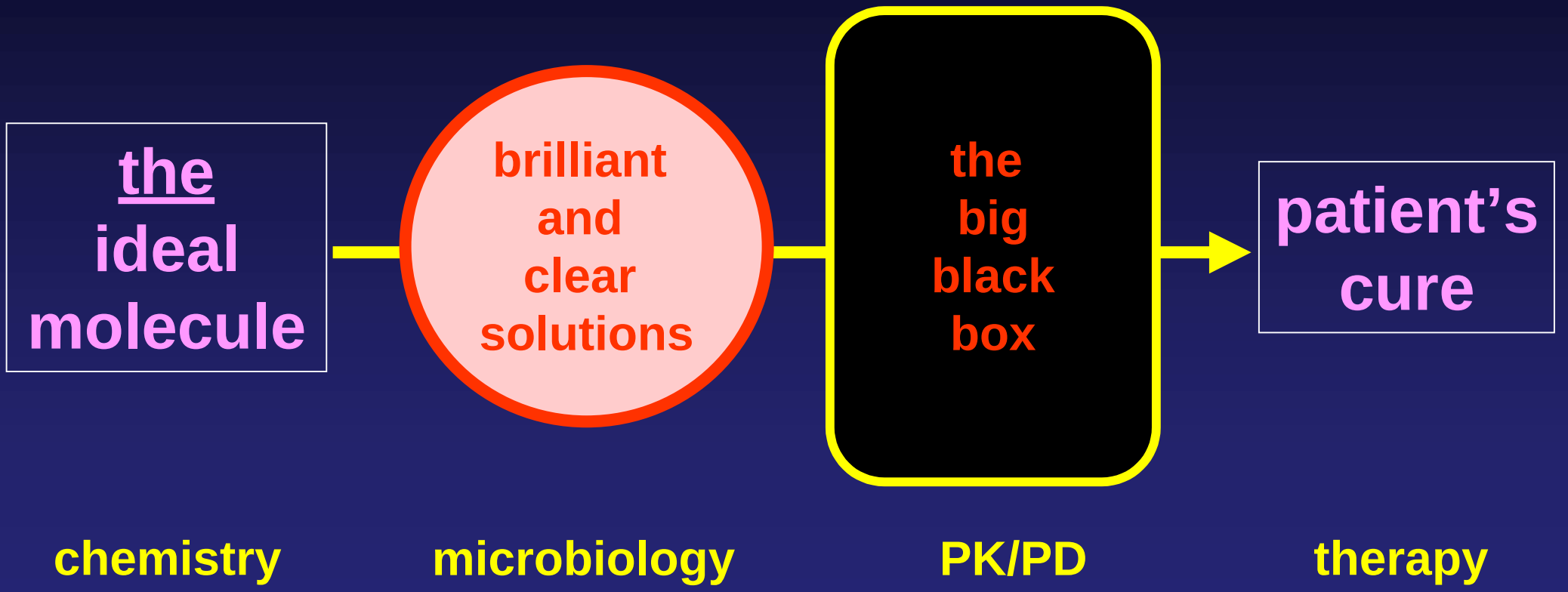
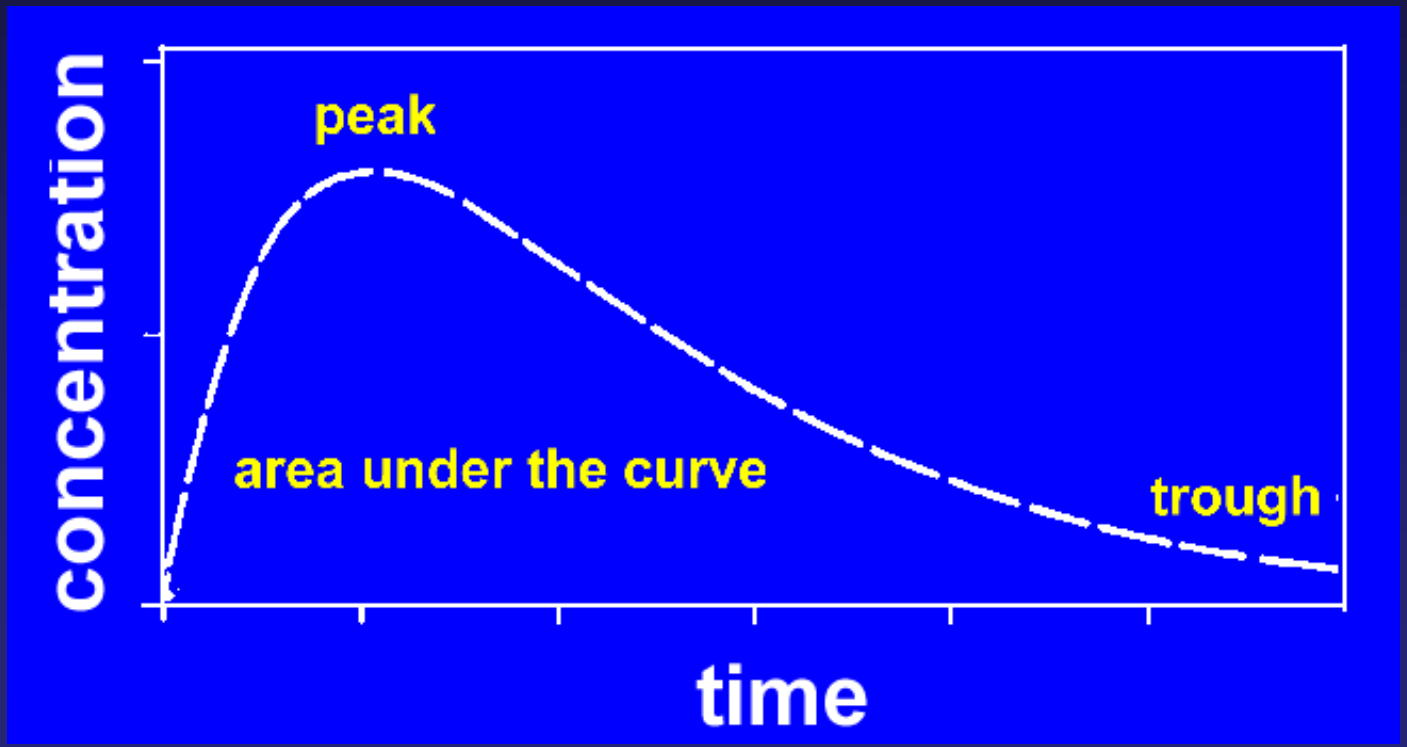
Pharmacokinetics / pharmacodynamics as a step towards therapy...



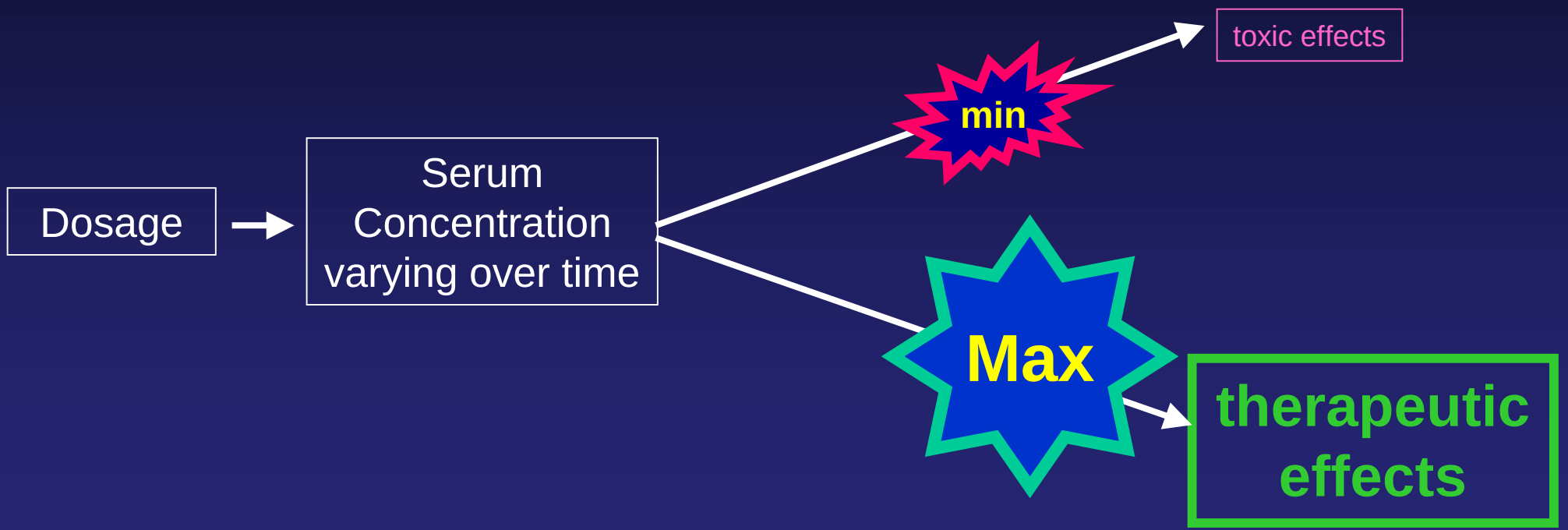
PK/PD parameters: a first sight

Serum Concentration varying with time

- Peak
- Trough
- Area under the curve

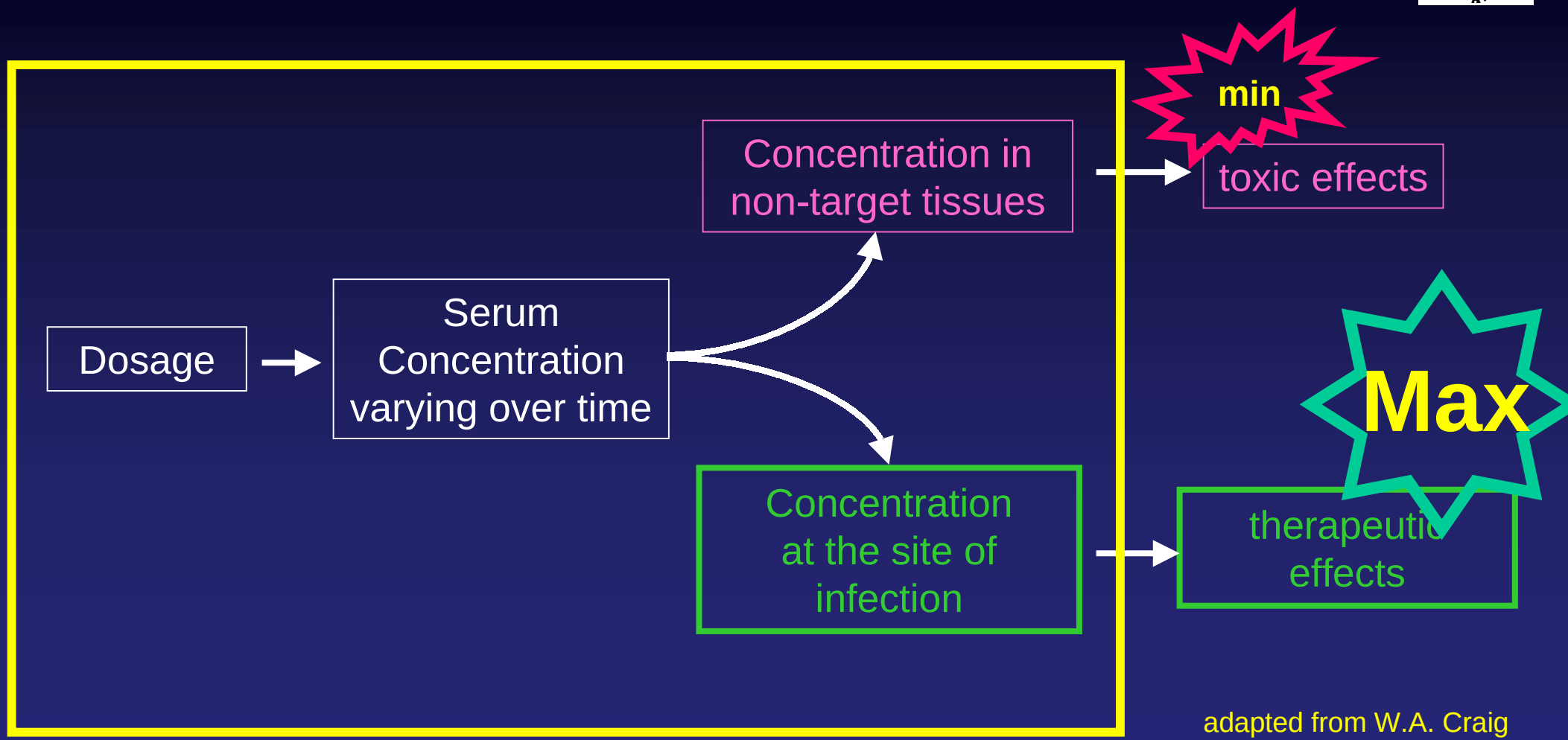


What does the clinician (and the patient) want ?



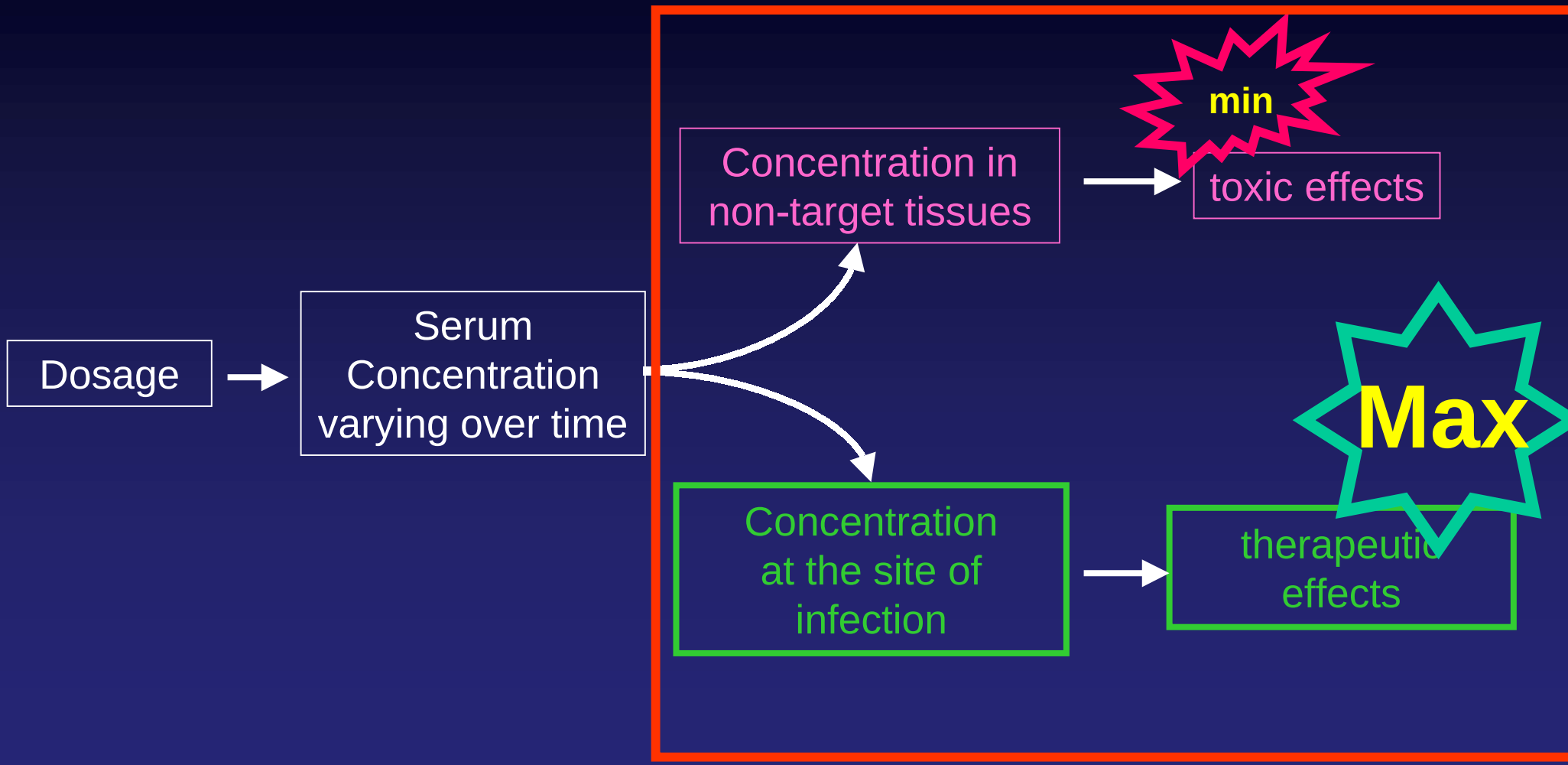
freely adapted from W.A. Craig

Pharmacokinetics ...



adapted from W.A. Craig

Pharmacodynamics ...



adapted from W.A. Craig

Pharmacokinetic/ Pharmacodynamics in Drug Development and Evaluation of Efficacy (1/2)

The combination of

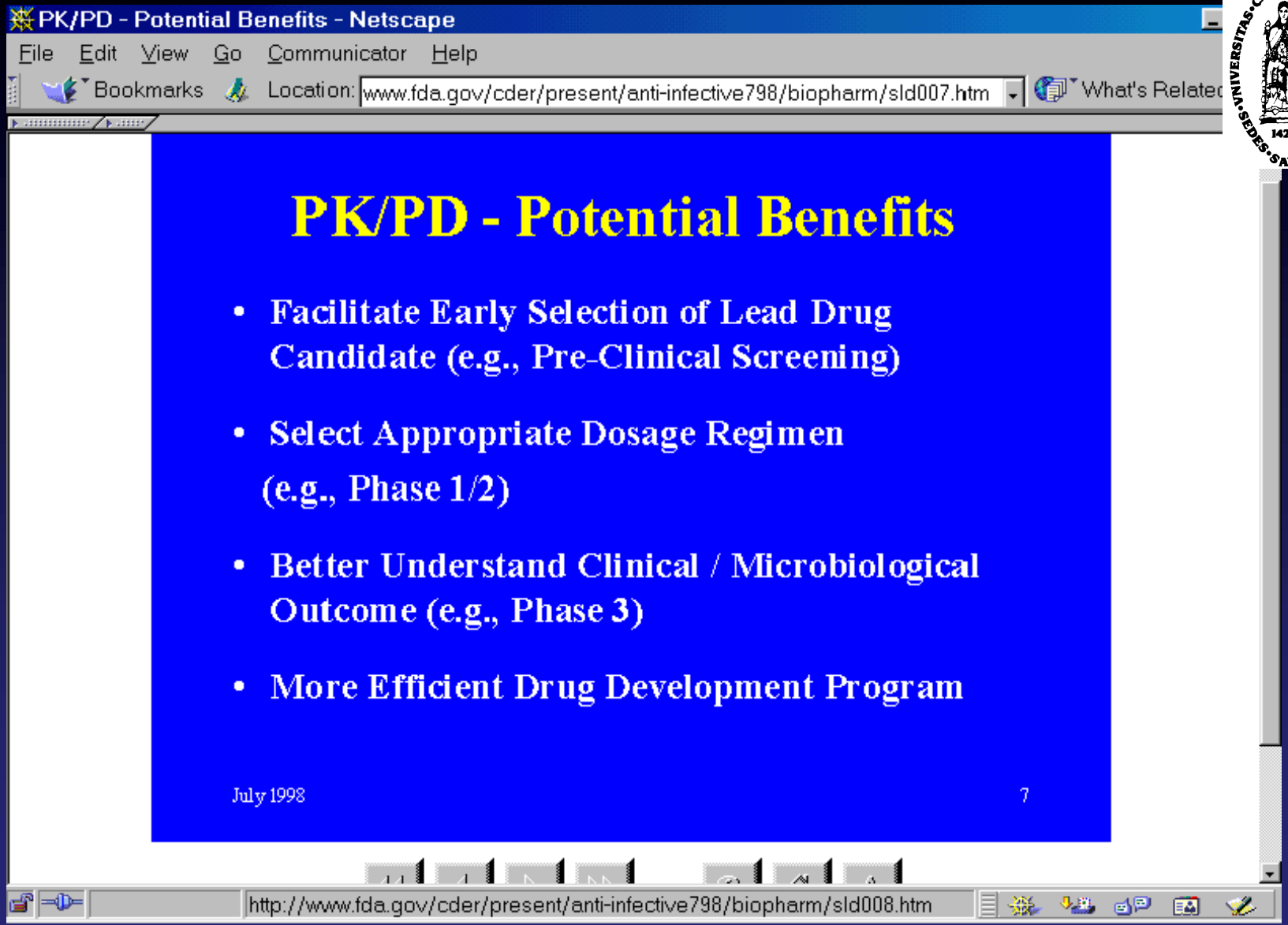
- in vitro modelling,
- proper design of animal model experiments,
- pharmacokinetic information on patients in clinical trials

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

PK/PD in drug develop-ment

A view from FDA



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

Pharmacokinetic/ Pharmacodynamics in Drug Development and Evaluation of Efficacy (2/2)

By providing such information to clinicians, drug therapy can achieve the goal of maximal therapeutic effect while engendering the lowest probability of encountering a drug exposure-related adverse event.

ISAP / FDA workshop, March 1st, 1999

http://www.isap.org/Rockville-1999.htm

Pharmacokinetic/ Pharmacodynamics and antibiotic resistance...

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

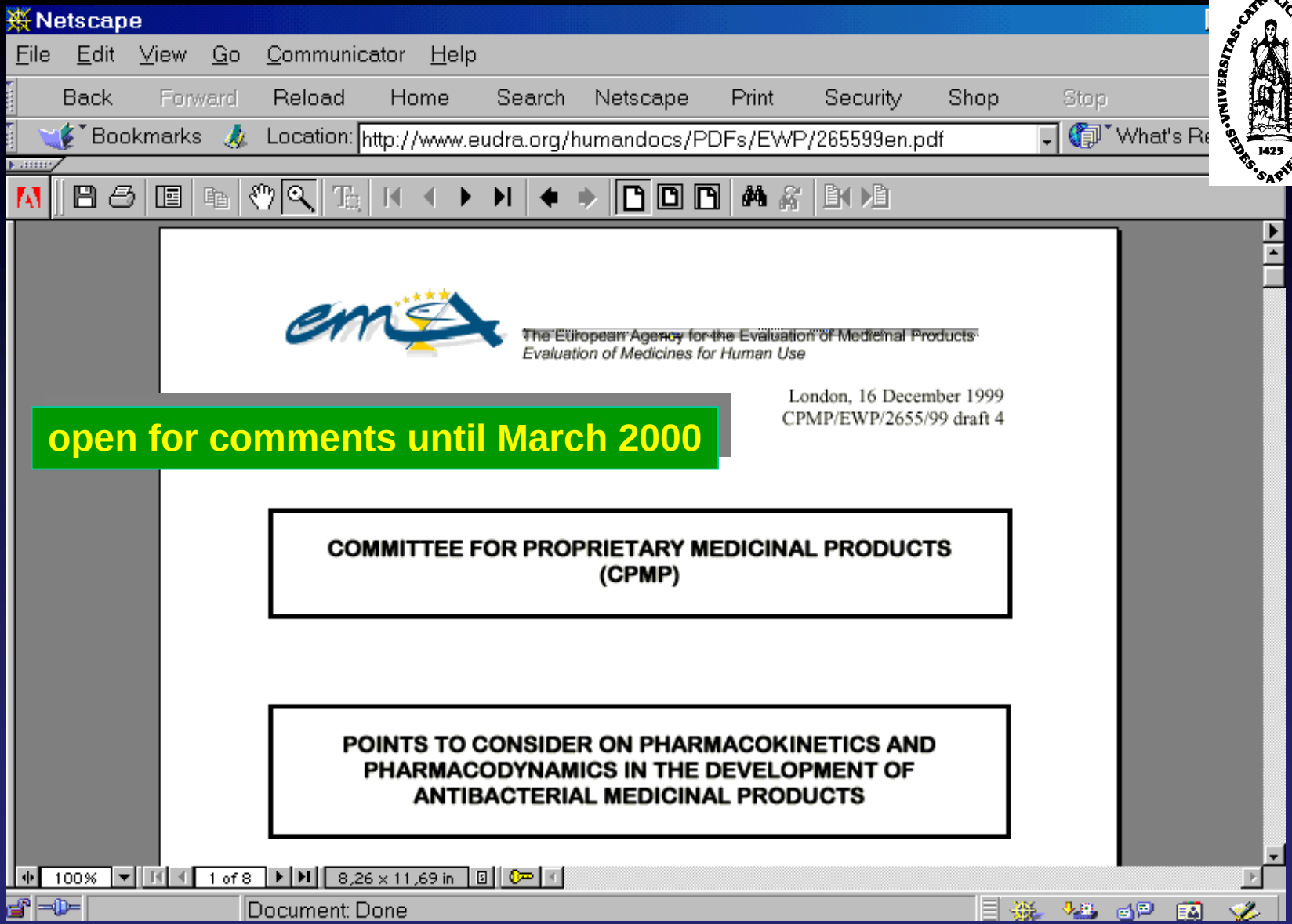
A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy.

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

Pharmacokinetic/ Pharmacodynamics in Drug Development and Evaluation

Who should take these points in consideration ?

1. **Industry: surely !**
   (for sake of efficacy both short and long term)
   but what do they do with that ?

2. **Clinicians: more and more (to optimize therapy)**
   but they often feel alone or insufficiently informed

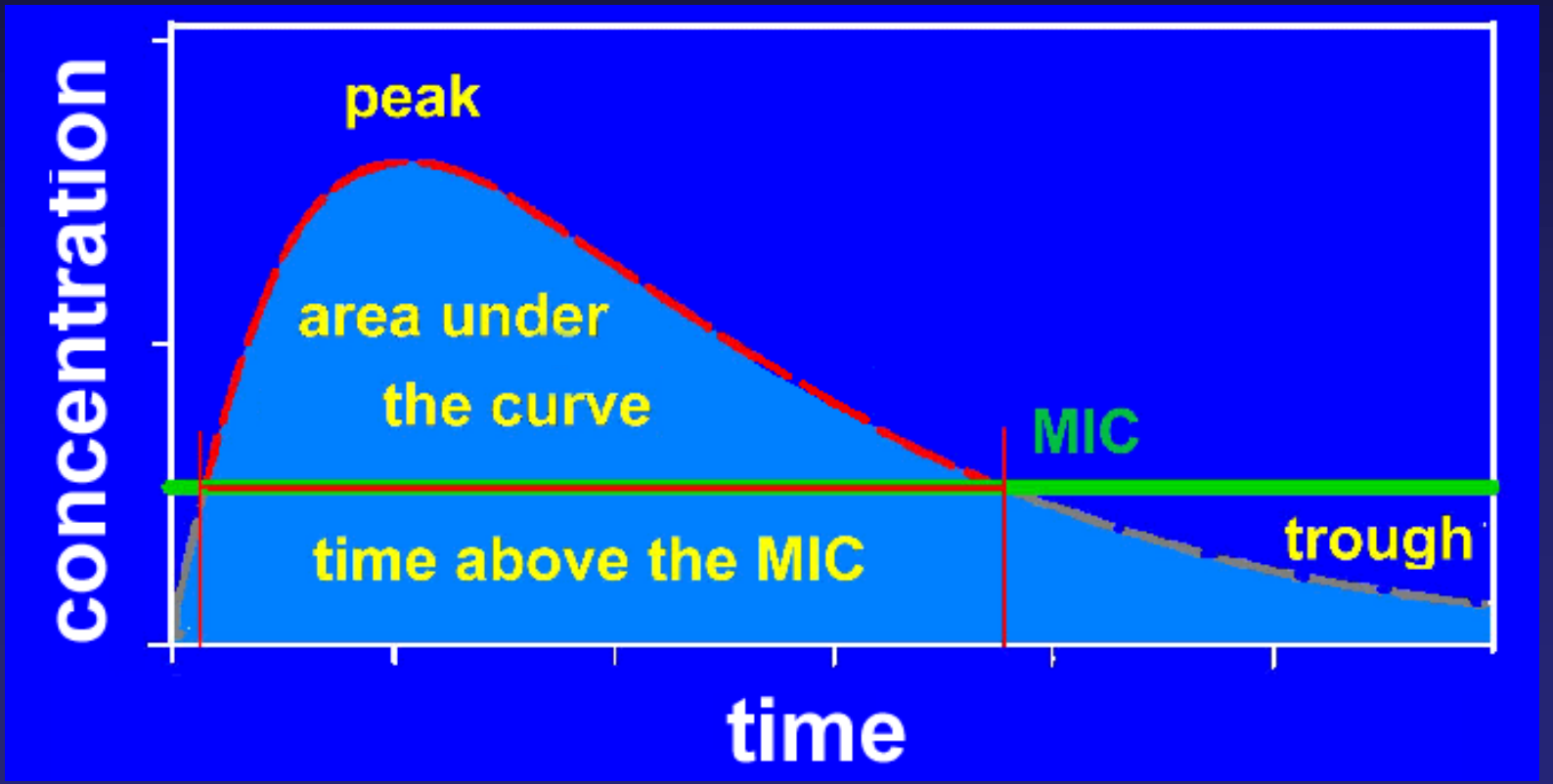
3. **Regulatory bodies (to better appraise new drugs)**
   but they wish to be certain that this is the correct way !

Pharmacokinetic / Pharmacodynamic parameters: a 2d sight

Peak / trough
AUC / Time

>

Minimal inhibitory concentration



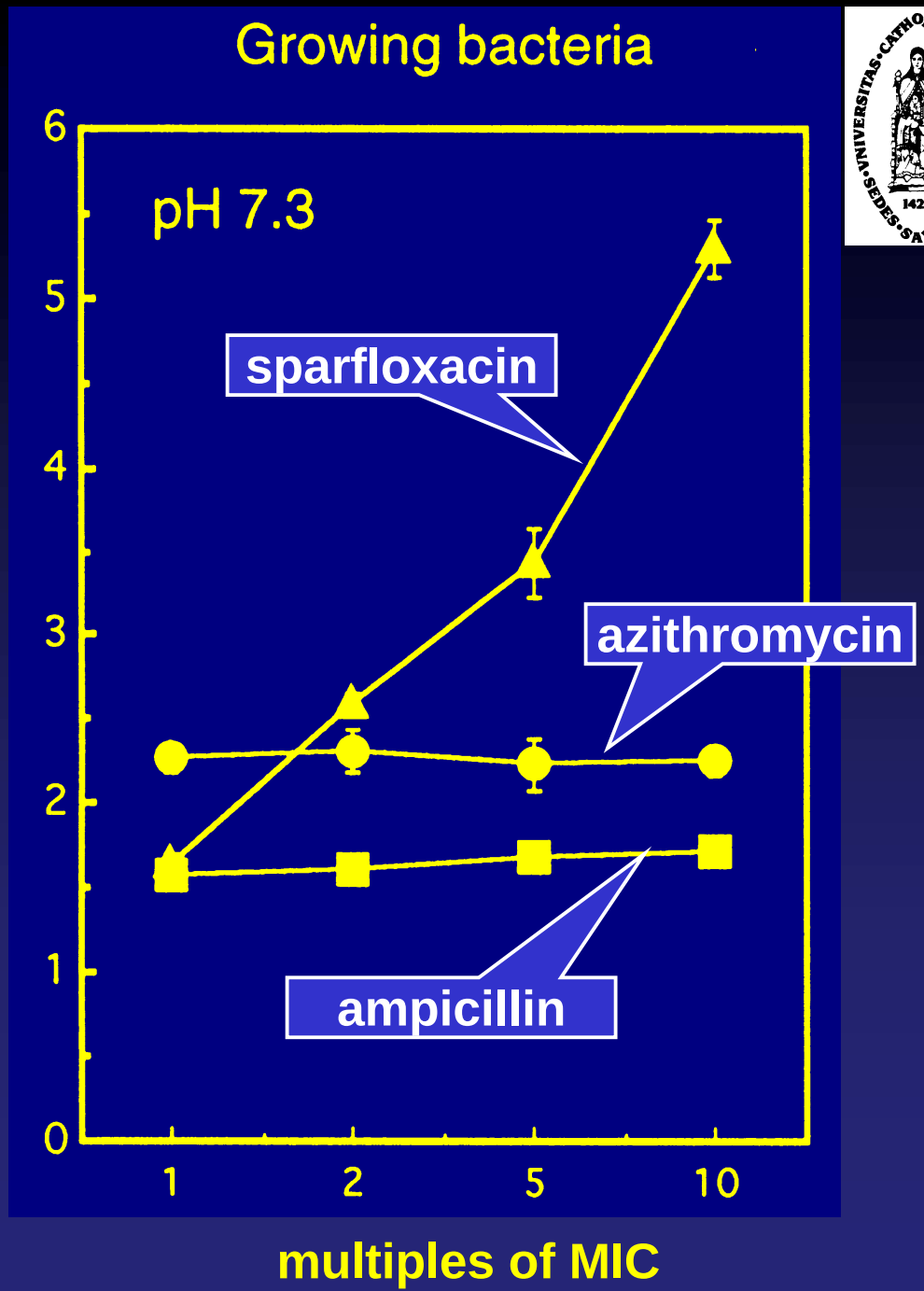
PK/PD: role of concentration

Marked effect important concentration dependency	Weak effect little or no concentration dependency
aminoglycosides	β-lactams (all)
fluoroquinolones	glycopeptides
metronidazole	macrolides
daptomycin	clindamycine
ketolides	tétracyclines
amphotericin	

Optimize the concentration

PK/PD: role of concentration

an example with *Listeria monocytogenes*



Ouadrhiri et al., Antimicrob. Agents Chemother., 1999

PK/PD: role of time

Kill quickly	Kill more slowly
aminoglycosides	β-lactams (all)
fluoroquinolones	glycopeptides
	macrolides
	oxazolidinones
	clindamycine
	tetracyclines
	flucytosine

→ Optimize the time

PK/PD: prolonged effects

- **Post antibiotic effect (PAE)**
  delay in regrowth upon antibiotic removal

- **Sub-MIC activity (SME)**
  tests the distribution of antibiotic susceptibility in the bacterial population

- **Post antibiotic leucocyte enhanced effect (PLAE)**
  pre-treatment makes bacteria more susceptible to phagocytosis and killing

PK/PD: role of prolonged effects

Marked influence	Weak of no influence
aminoglycosides	β-lactams (all)
fluoroquinolones	macrolides
azithromycin	clindamycine
glycopeptides	
tertracyclines	
streptogramins	
fluconazole	

Optimize the amount of drug

Neutropenic Murine Thigh and Lung Infection Models

- Cyclophosphamide 150 and 100 mg/kg at 4 and 1 day before infection
- Thigh infection produced by injection of 0.1 ml of 10^7 CFU/ml 2 hrs before treatment
- Lung infection produced by 45 min aerosol of 10^9 CFU/ml 14 hrs before treatment
- 10^{7-8} CFU/g in thigh or lung at start of therapy

W.A. Craig et al.

PK/PD Parameters Correlating with Efficacy in Murine Thigh and Lung Infections

Time Above MIC	AUC (Peak)
Penicillins	Aminoglycosides
Cephalosporins	Fluoroquinolones
Carbapenems	Metronidazole
Monobactams	Daptomycin
Tribactams	Ketolides
Macrolides	Azithromycin
Clindamycin	Streptogramins
Oxazolidinones	Glycopeptides
Glycylcyclines	Tetracyclines

W.A. Craig et al.

How do you get a given 24h-AUC ?
1. importance of the dose (a)

the 24h-AUC is the integral of the serum concentration over the 24h interval…

→ proport. to the <u>total daily dose</u> and the bioavailability

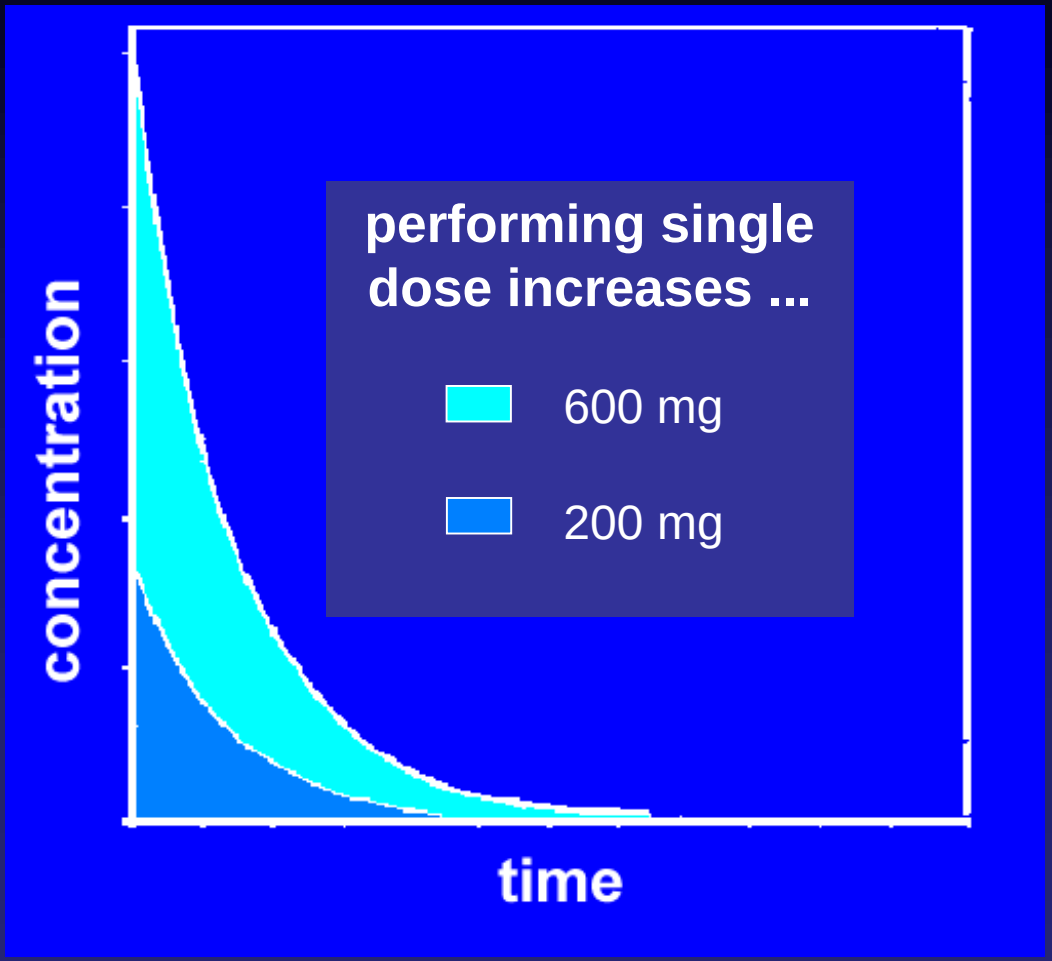
adjust the total daily dose by ...

How do you get a given 24h-AUC ?
1. administer the right dose...

the 24h-AUC is the integral of the serum concentration over the 24h interval…

→ proport. to the <u>total daily dose</u> and the bioavailability

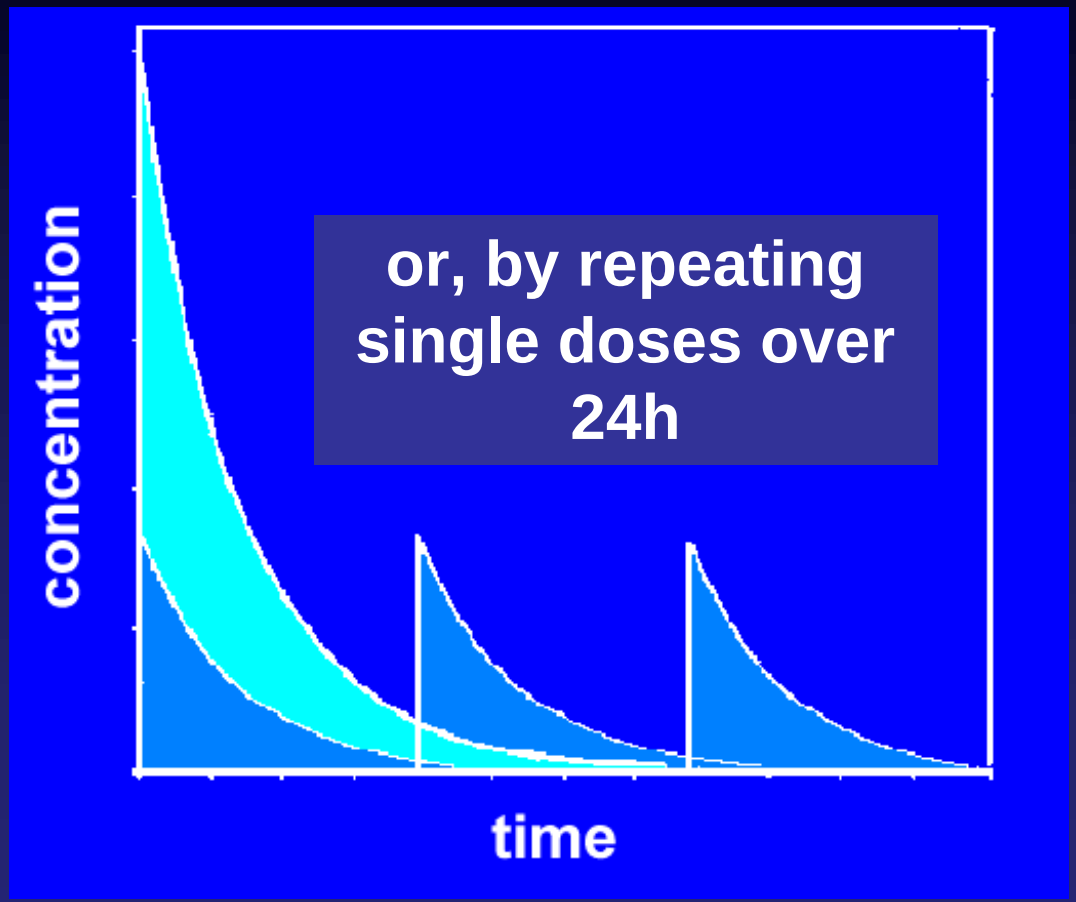
Thus...



adjust the total daily dose by ...

How do you get a given 24h-AUC ?
2. give a dose frequently

the 24h-AUC is the integral of the serum concentration over the 24h interval…



➡ proport. to the <u>total daily dose</u> and the bioavailability

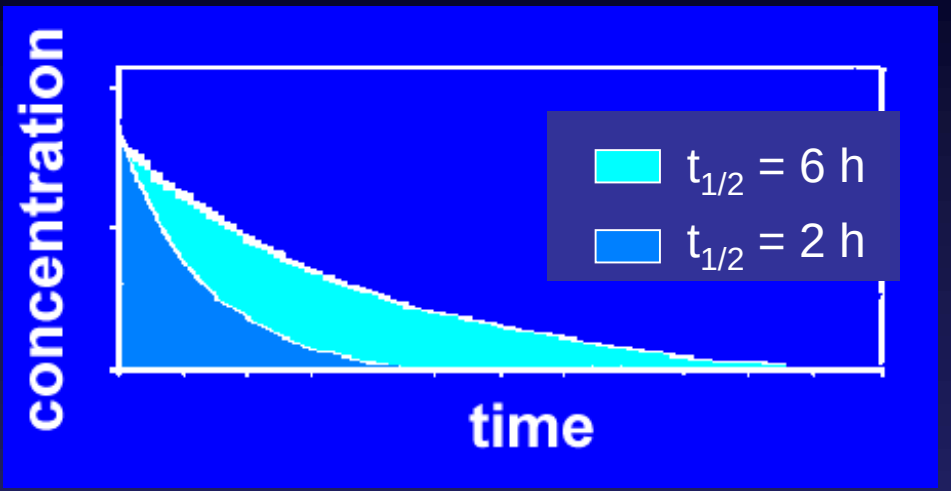
Thus…

adjust the total daily dose ...

How do you get a given 24h-AUC ?
3. get a low clearance

the 24h-AUC is

inversely proport.
to the clearance



24h-AUC =

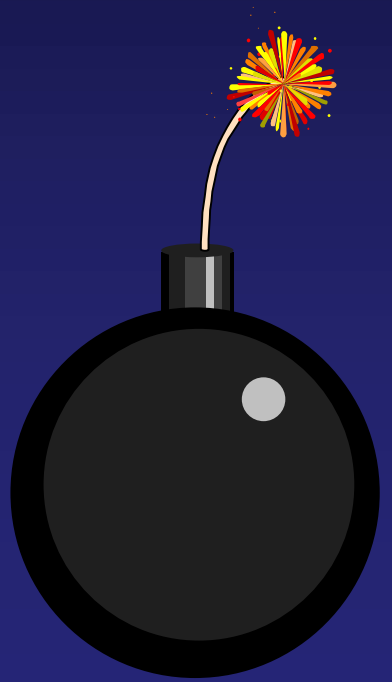
(24h-Dose x B_{av}) / Cl

Use a drug with a long half-life

Thus...

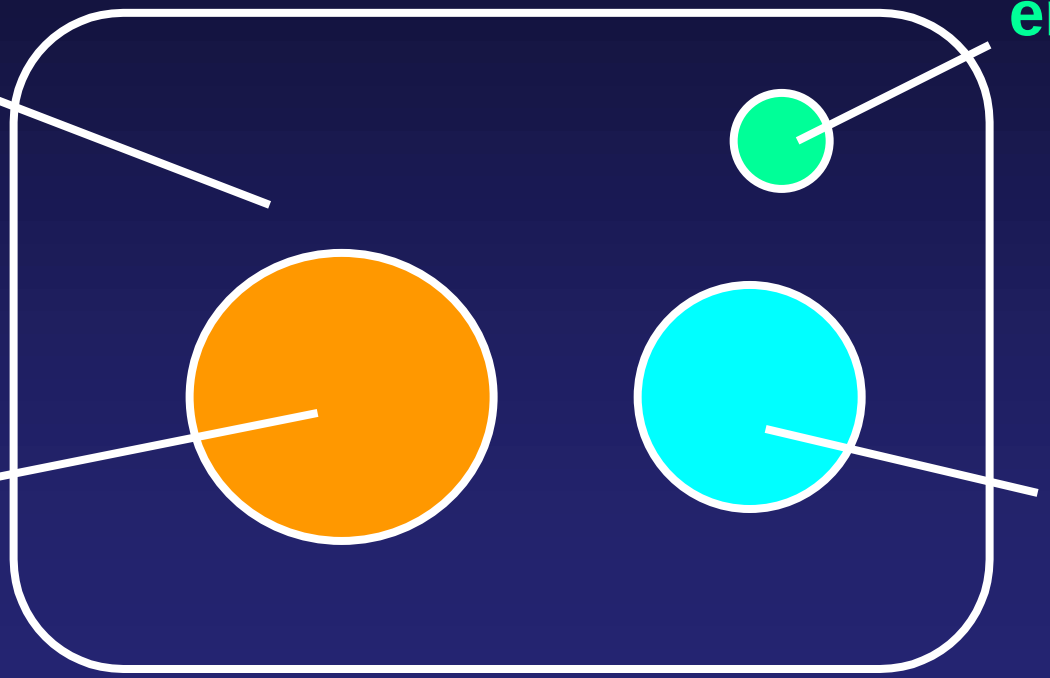
But isn’t anything more ?

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



How to predict efficacy in the intracellular milieu ?

Where are bacteria ?



cytosol

Listeria hly+,
Shigella

endosomes

phagolysosomes

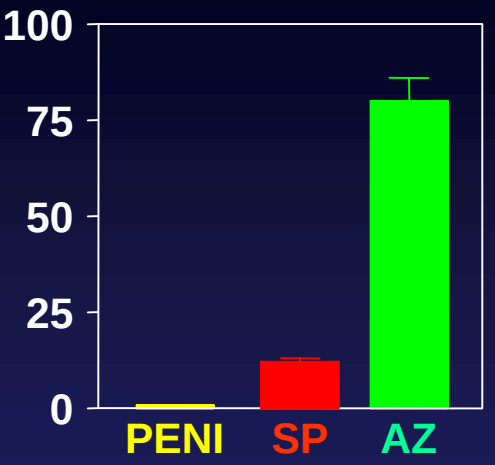
S. aureus
Salmonella,
M. leprae, ...

phagosomes

Legionella
Chlamydia, ...

Pharmacokinetic modulation of intracellular activity: drug trapping

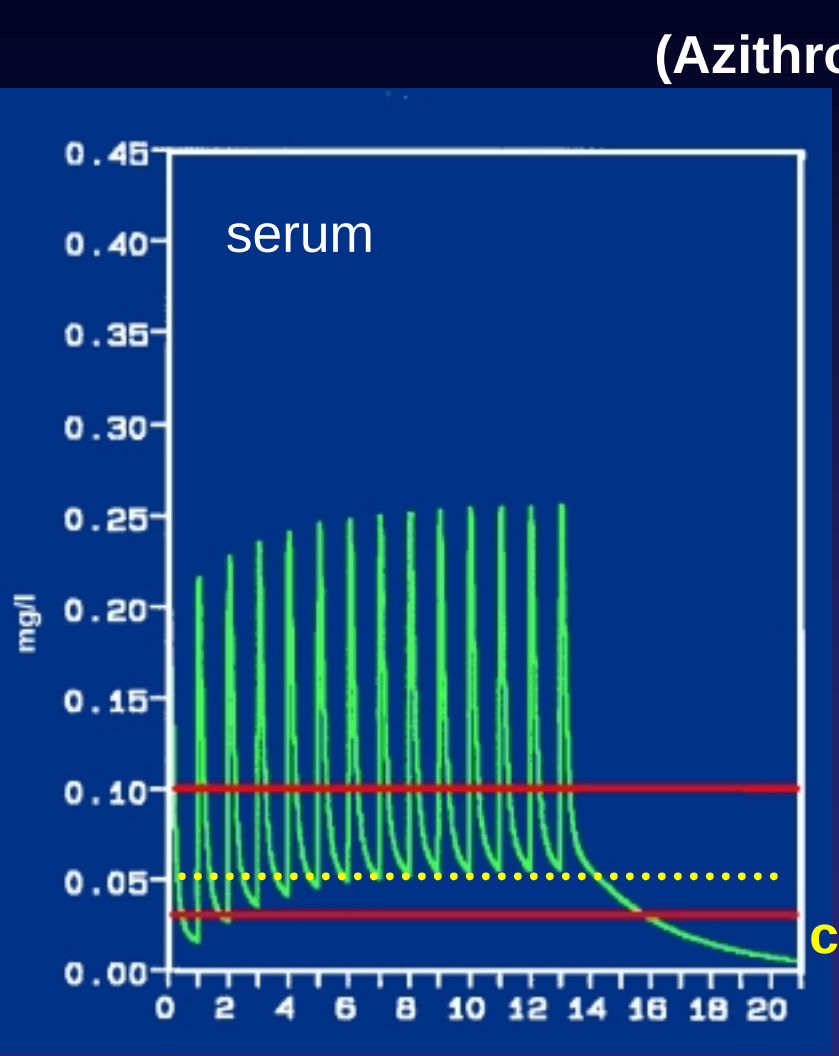
+ cellular accumulation:



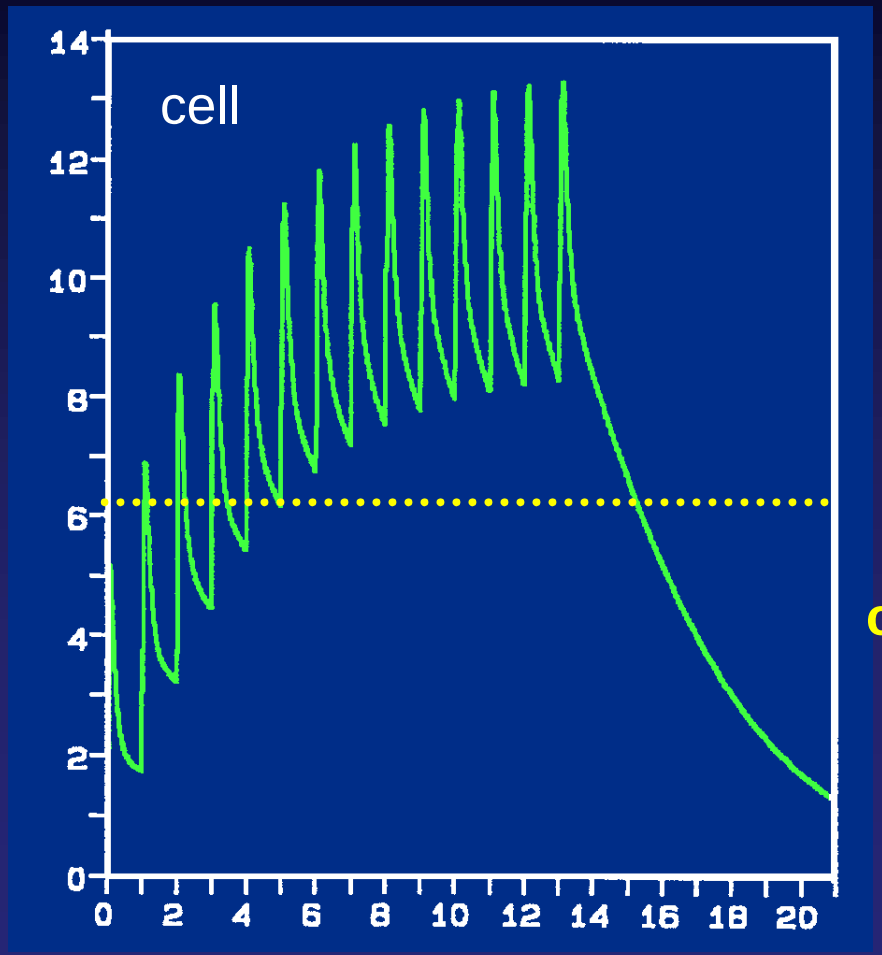
How to predict efficacy in the intracellular milieu ?

Both serum and cellular concentration fluctuate !

(Azithromycin; 500 mg qd)



Serum min. concentr. ~ 0.05



Intra-cellular min. concentr. > 6 !

Van Bambeke et al, JAC, 1998, 42:761-767

And we may have a very bright future...

www.md.ucl.ac.be/facm

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Y. Ouadrhiri
S. Carryn
H. Chanteux
H. Servais

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G.L. Drusano
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