# Adopting EUCAST breakpoints in countries currently on CLSI breakpoints …

## and some personal thinking…

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19th European Congress of Clinical Microbiology
and Infectious Diseases (ECCMID)
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# Why do we need breakpoints ?

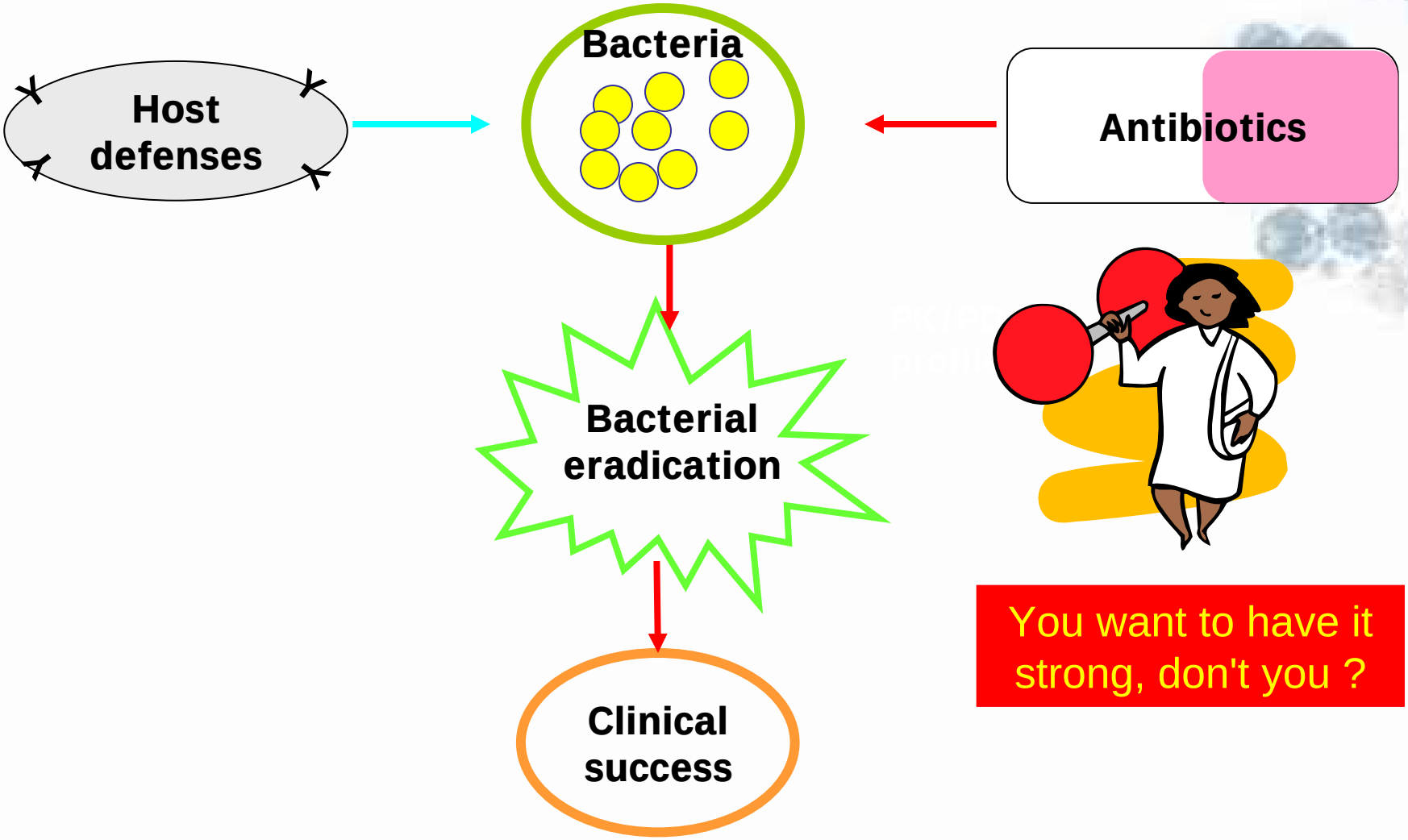
To be honest, I always wondered …

# Why do we need breakpoints ?

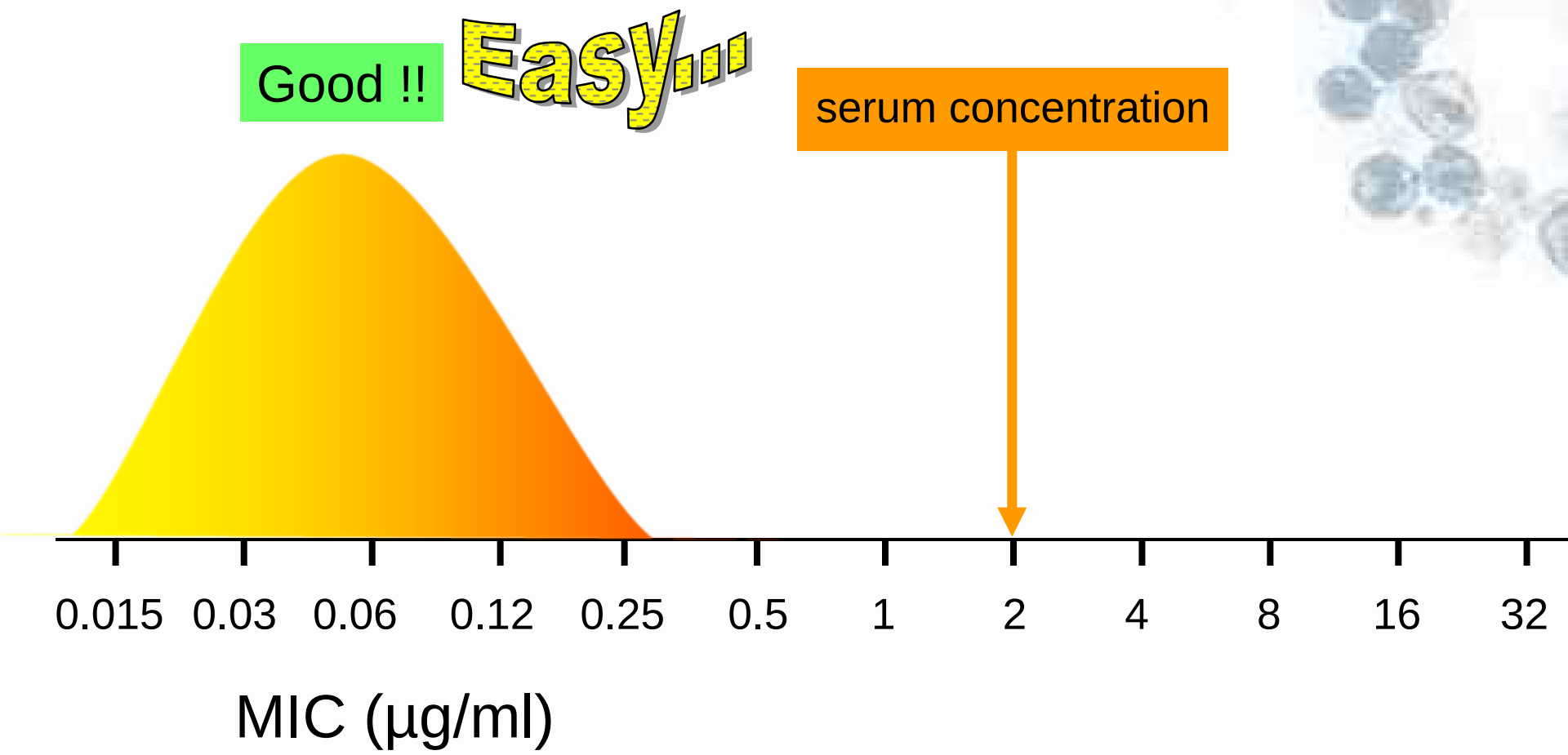
but perhaps…

1. Doctors like to know if the bug is "**good**" or "**bad**" …
2. Regulators like to tell people "**DO**" or "**Don't**"
3. Lawyers like you to be **guilty** or **innocent** …
4. Microbiologists wish to give them all **simple answers…**

# What do clinician want when treating an infection ?

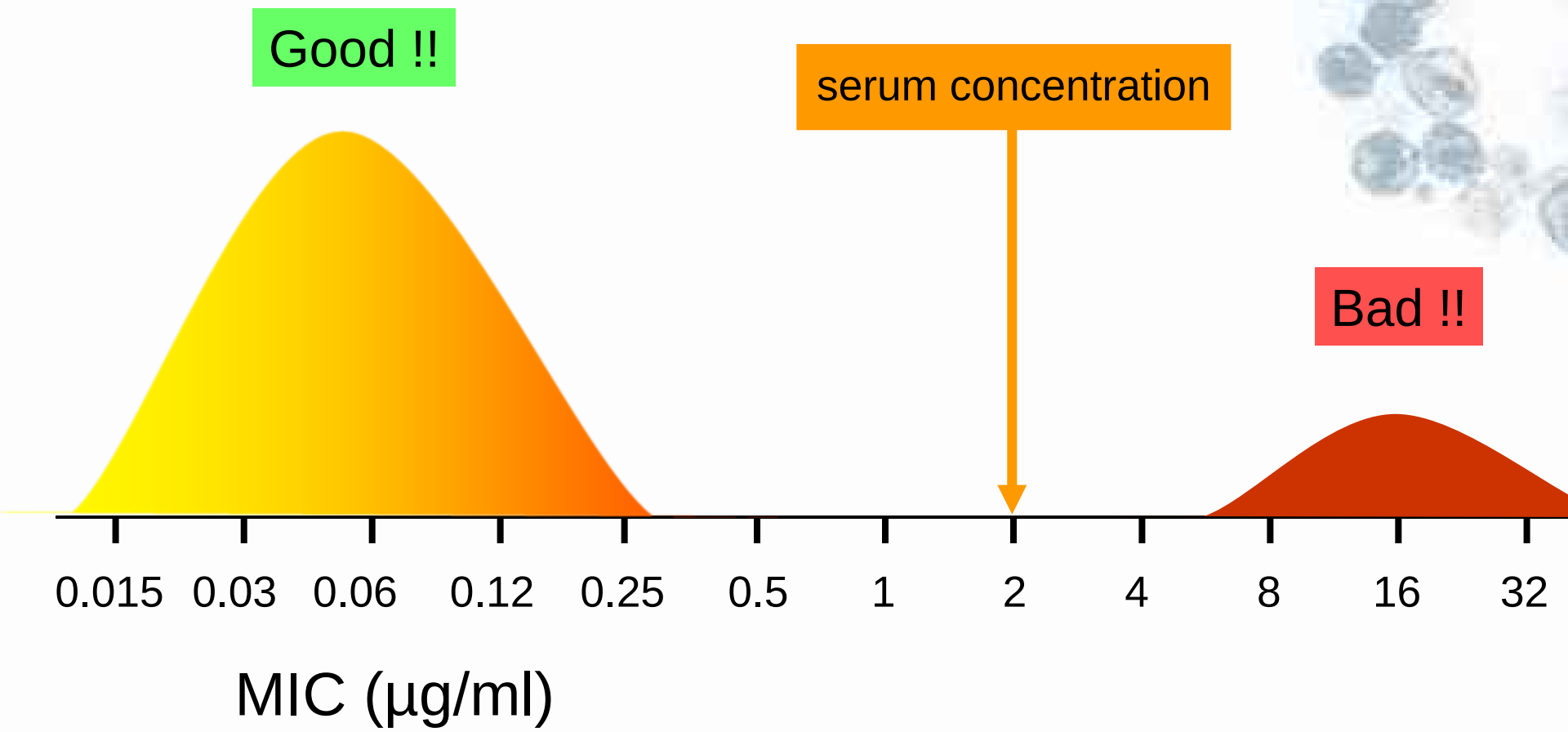


# But, what is strong ?



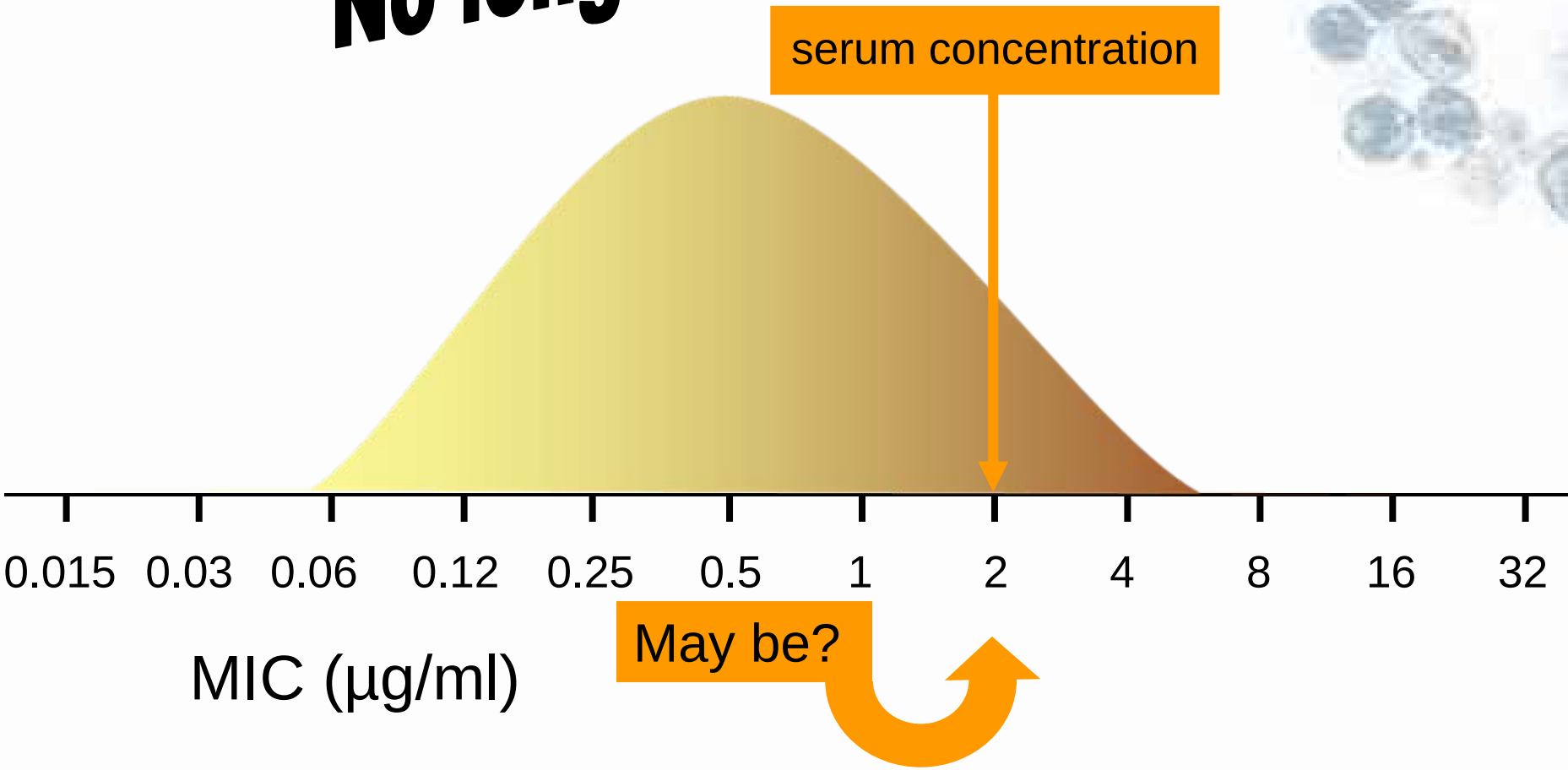
# But, what is strong ?

Still Easy...

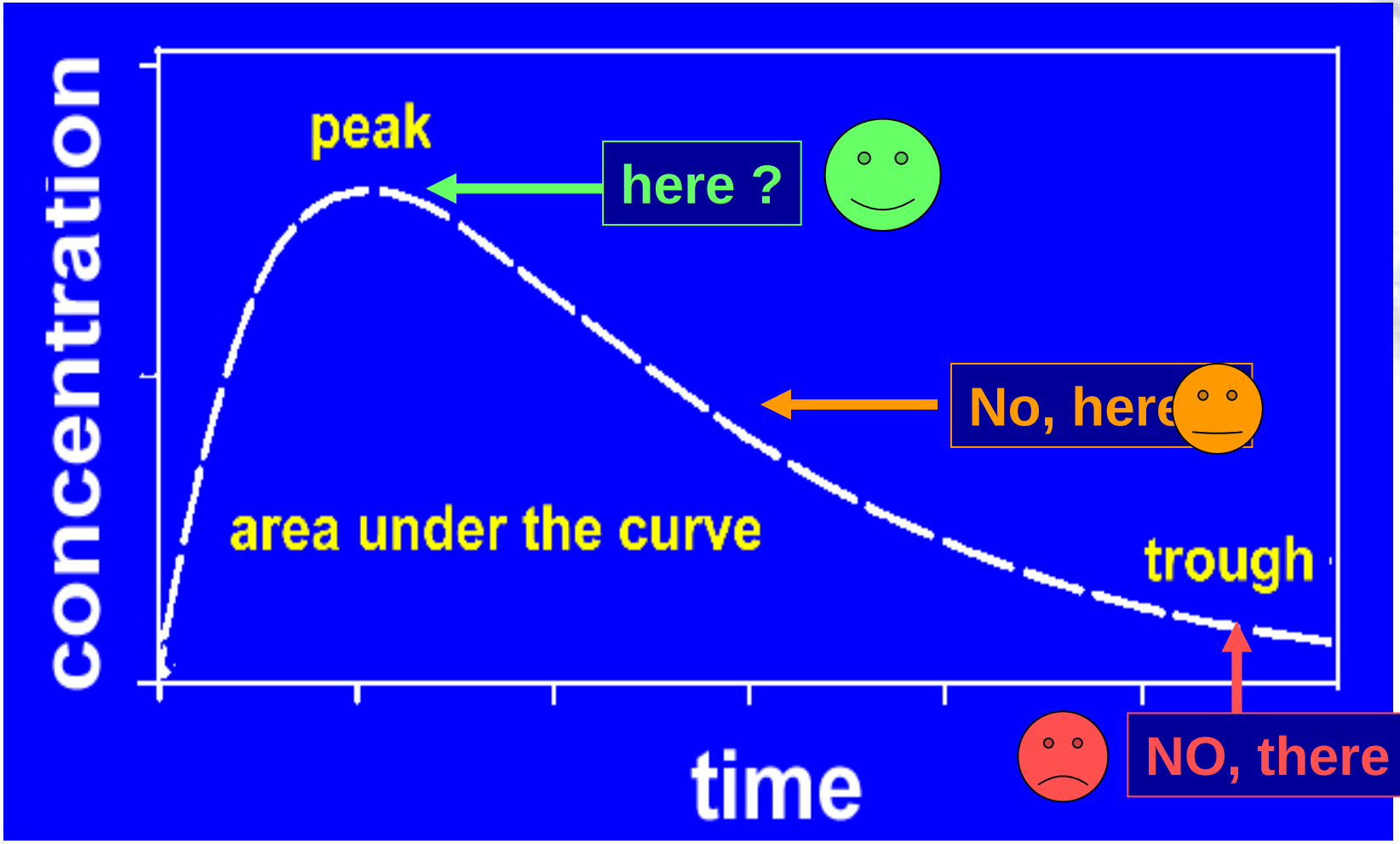


# But, what is strong ?

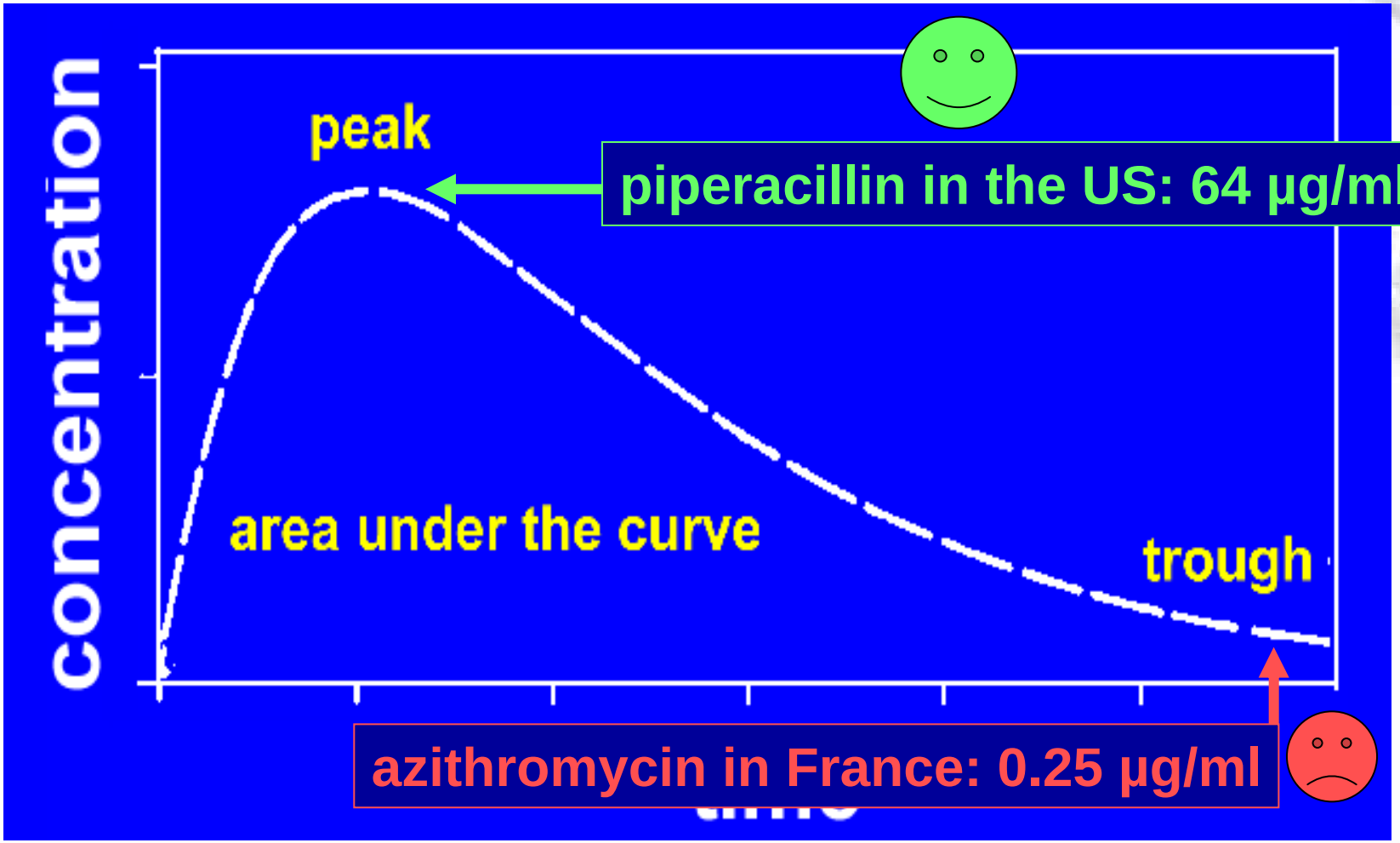
**No longer so easy...**



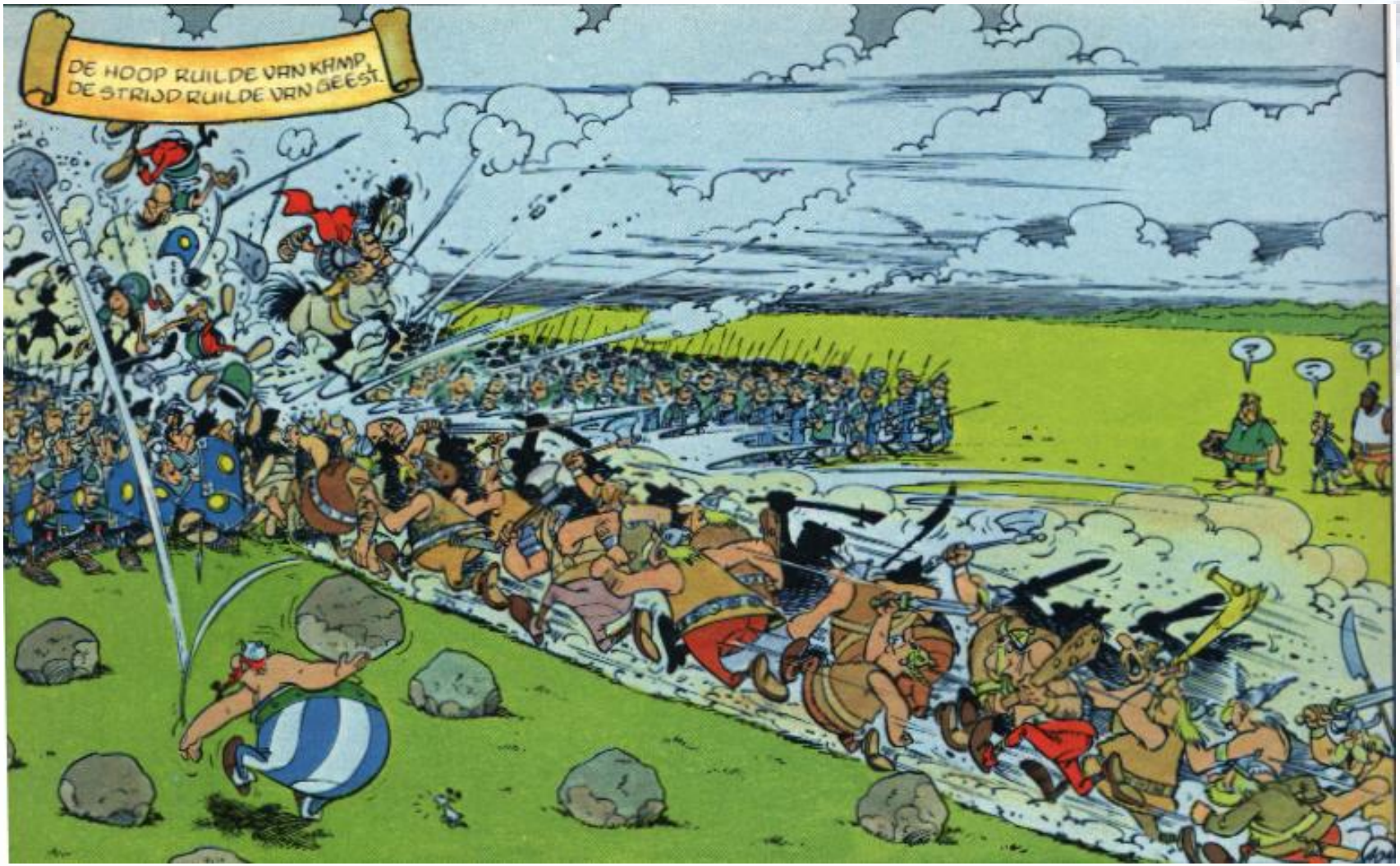
# Where should the breakpoint be ?



# Where should the breakpoint be ?



# And there were fierce battles …




From Mouton, 8th ISAP symposium, Nijmegen, 2001

# What was THE problem ?

- Europe had 6 national breakpoint- setting authorities … and, therefore (?), possibly up to 6 different breakpoints for each antibiotic – bug combination …
- The situation was not better in many other parts of the world …

# A simple example …

| **cefotaxime vs. *E.coli*** | | **S≤ / R** |
|---|---|---|
| BSAC | United Kingdom | 2 / ≥4 |
| CA-SFM | France | 4 / >32 |
| CRG | The Netherlands | 4 / >16 |
| DIN | Germany | 2 / ≥16 |
| NWGA | Norway | 1 / ≥32 |
| SRGA | Sweden | 0.5 / ≥2 |

**Yet, these breakpoints were used everyday by clinical microbiology laboratories to advise clinicians about which antibiotic(s) they could sucessfully use against the bacteria they were supposed to fight …**

# So, what should other countries do ?

Countries without national breakpoint authorities did not really know which one to follow for guidance…

# So, what should other countries do ?

*Do you really need this antibiotic ?*



**2 / >4**

**2 / >16**

**4 / >32**

# So, what if you are small ?
## but [hopefully]) smart …

The
"filet américain"
attitude *

* Broodjes filet américain 100% rundvlees

# A simple decision …

Now, the clinician can treat all patients

| | | |
|---|---|---|
| NCCLS | U.S.A. | 8 / ≥64 |

**Was this not smart decision ?**

# The pros and cons of using CLSI breakpoints

Pros

- Readily available for most antibiotics
- Based on evaluation of molecules by an independent committee acting very scientifically and clinically…
- Backed by an extensive set of guidelines and recommendations for testing…
- Used widely and considered as 'gold standard' in most publications and surveillance networks…
- Subject to periodic revisions to remain in line with the evolution of science, including PK/PD and increase of resistance

# The pros and cons of using CLSI breakpoints

Cons

- You need to pay for …
- Limited access of non-US persons to the decision process …
- Decisions based on proposals made by Industry…
- Guidelines and recommendations for testing not necessarily applicable specifically where you are…
- Antibiotics not registered for used in the US may not be included and/or fully studied
- Revision process not always as effective as it could be…
- For certain antibiotics, CLSI breakpoints have been notoriously too high

# An example of (probably) too high breakpoints

| Drug | Typical daily dosage[a] | Typical PK values: $C_{max}$ in mg/L total/free (dose) | Typical PK values: $AUC_{24\ h}$ (mg × h/L) total/free | Proposed PK/PD upper limit: Efficacy[b] | Proposed PK/PD upper limit: Prevention of resistance[c] | Breakpoints (mg/L)[d]: NCCLS (S/I/R) |
|---|---|---|---|---|---|---|
| Norfloxacin | 800 mg | 1.4/1.1 (400 mg PO) | 14/11 | 0.1–0.4 | 0.1 | ≤4/8/>16[j] |
| Ciprofloxacin | 1000 mg | 2.5/1.75 (500 mg PO) | 24/18 | 0.2–0.8 | 0.2 | ≤1/2/>4[k] |
| Ofloxacin | 400 mg | 4/3 (400 mg PO) | 40/30 | 0.3–0.9 | 0.4 | ≤2/4/8[l] |
| Levofloxacin | 500 mg | 4/2.8 (500 mg PO) | 40/28 | 0.3–0.9 | 0.3 | ≤2/4/8[l] |
| Moxifloxacin | 400 mg | 3.1/1.8 (400 mg PO) | 35/21 | 0.2–0.7 | 0.2 | ≤1/2/4[m] |

NCCLS, National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute) (http://www.ncc

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

# An unanticipated problem …
## (if you are a non-US microbiologist)

CLINICAL AND LABORATORY STANDARDS INSTITUTE®
(Formerly NCCLS)

# An unanticipated problem …

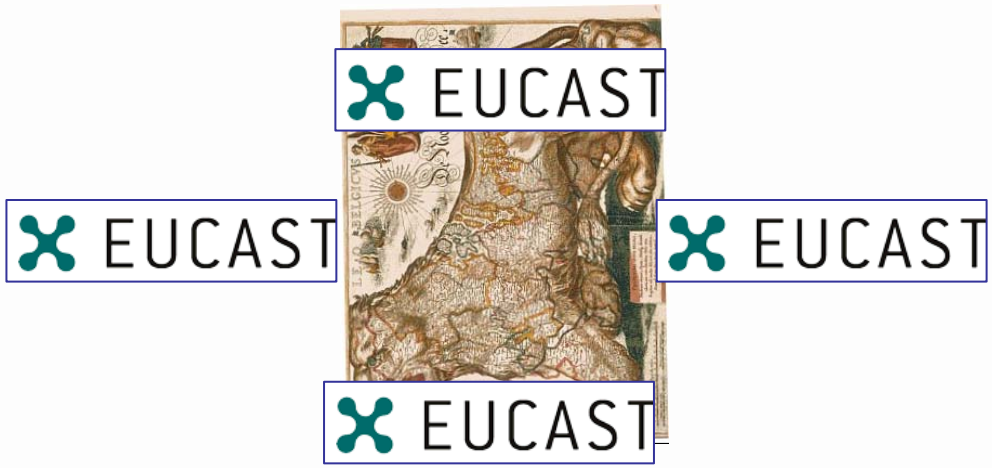
- Since 2006, FDA has reasserted its legal rights to define official breakpoints
- CLSI may determine and publish breakpoints no sooner than 24 months after FDA decision
  (and only if the company requests this [?])
- In the meantime, only FDA breakpoints will be legal in the US, and will be essentially geared to the protection of the **US** Public for drugs registered in the US.
- Non-US organizations have no direct possibility to impact on the FDA-decision process ...

**communicated at the General meeting of EUCAST during the 17th ECCMID & 25th ICC (Munich, Germany) by the CLSI representative**

# Two important change in Europe

1. Each national committee in EU (UK, FR, NL, DE, SV, NO) has pledged that the EUCAST breakpoints will be part of their respective systems January the year after the decision was made. This means that any decision taken in 2008 should be into their systems in January 2009, and so on …

   In parallel, (i) the manufacturers of devices (BM and BD) have both said that it is realistic that their machines will have EUCAST breakpoints in 2009; (ii) interpretative criteria for disk-based assay will be released by EUCAST in 2009



# Two important change in Europe

2. EMEA and EUCAST have set up an agreement that makes EUCAST responsible for defining breakpoints for new molecules proposed for registration in Europe.

   EUCAST breakpoints will be accepted by EMEA and put into the "Summary of Product Characteristics", which is part of legal documents accompanying the marketing authorization in EU.

# Doripenème: concentrations critiques

Concentrations critiques

Les concentrations minimales inhibitrices (CMI) critiques établies par l'European Committee on Antimicrobial Susceptibility Testing (EUCAST) sont les suivantes :

| | |
|---|---|
| Non liée à l'espèce | S ≤1 mg/L et R >4 mg/L |
| Staphylocoques | déduite de la sensibilité à la méticilline |
| *Enterobacteriaceae* | S ≤1 mg/L et R >4 mg/L |
| *Acinetobacter* spp. | S ≤1 mg/L et R >4 mg/L |
| *Pseudomonas* spp. | S ≤1 mg/L et R >4 mg/L |
| *Streptococcus* spp. autres que *S. pneumoniae* | S ≤1 mg/L et R >1 mg/L |
| *S. pneumoniae* | S ≤ 1 mg/L et R >1 mg/L |
| Entérocoques | « cible non appropriée » |
| *Haemophilus* spp. | S ≤ 1 mg/L et R >1 mg/L |
| *N. gonorrhoeae* | DI (données insuffisantes) |
| Anaérobies | S ≤ 1 mg/L et R >1mg/L |

DORIBAX® Résumé des caractéristques du produit (EMEA)

# Why could (should ?) non-EU countries follow EUCAST breakpoints ?

Pros

- The procedure is rational and transparent
- All proposals are subject to open discussions through the web site and/or by direct contact
- All breakpoints and the supporting material ("rational documents") is available free on the web site for inspection and analysis *
- Adaptation to local conditions can, therefore, be made seamlessly if needed (changes in dosages, PK, resistance patterns…)

Cons

- There is no specific procedure for requesting and implementing changes based on national realities outside of EU **
- Material must be submitted by the organization requesting a breakpoint.

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* would be correct if I had made my homework as Gunnar instructed me and Derek reminded me …

** except via country representatives (see www.eucast.org), ISC (me) or FESCI (Dr D. Livermore)

# But, at the end, this may be better

| Drug | Typical daily dosage[a] | Typical PK values: $C_{max}$ in mg/L total/free (dose) | Typical PK values: $AUC_{24\,h}$ (mg × h/L) total/free | Proposed PK/PD upper limit: Efficacy[b] | Proposed PK/PD upper limit: Prevention of resistance[c] | Breakpoints (mg/L)[d]: EUCAST (S/R) | Breakpoints (mg/L)[d]: NCCLS (S/I/R) |
|---|---|---|---|---|---|---|---|
| Norfloxacin | 800 mg | 1.4/1.1 (400 mg PO) | 14/11 | 0.1–0.4 | 0.1 | ≤0.5/>1[e] | ≤4/8/>16[j] |
| Ciprofloxacin | 1000 mg | 2.5/1.75 (500 mg PO) | 24/18 | 0.2–0.8 | 0.2 | ≤0.5/>1[f] (≤0.125/>2)[g] | ≤1/2/>4[k] |
| Ofloxacin | 400 mg | 4/3 (400 mg PO) | 40/30 | 0.3–0.9 | 0.4 | ≤0.5/>1[f] (≤0.125/>4)[g] | ≤2/4/8[l] |
| Levofloxacin | 500 mg | 4/2.8 (500 mg PO) | 40/28 | 0.3–0.9 | 0.3 | ≤1/>2[f] (≤2/>2)[h] | ≤2/4/8[l] |
| Moxifloxacin | 400 mg | 3.1/1.8 (400 mg PO) | 35/21 | 0.2–0.7 | 0.2 | ≤0.5/>1)[e] (≤0.5/>0.5)[i] | ≤1/2/4[m] |

EUCAST, European Committee on Antimicrobial Susceptibility Testing (http://www.eucast.org) [241].
NCCLS, National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute) (http://www.ncc

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

# So, if you like, you may join the club…

# Backup slides

# EUCAST procedure for setting breakpoints

The next slides describe the EUCAST procedure for harmonising European breakpoints and reach rational values.

# 1. Data on dosing, formulations, clinical indications and target organisms are reviewed and differences which might influence breakpoints are highlighted

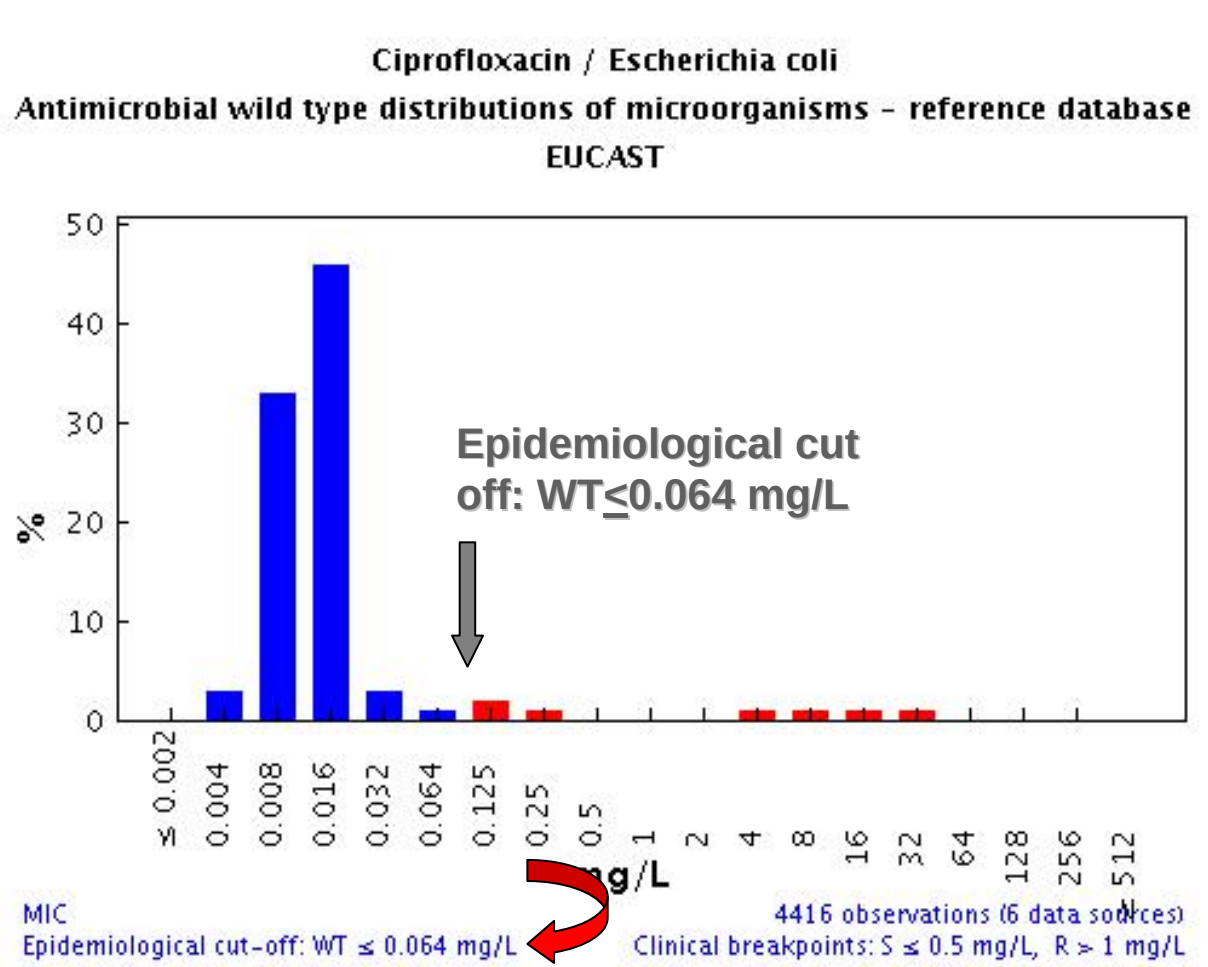
| Dosage | National breakpoint committees | | | | | | |
|---|---|---|---|---|---|---|---|
| **Most common dose** | 500 x 2 oral<br>400 x 2 iv | 500 x 2 oral<br>200 x 2 iv | 250 x 2 oral<br>200 x iv | 500 x 2 oral<br>200 x 2 iv | 200-400 x 2 oral<br>400 x 2 iv | 500 x 2 oral<br>400 x 2 iv | |
| **Maximum dose schedule** | 750 x 2 oral<br>400 x 3 iv | 750 x 2 oral<br>400 x 3 iv | 750 x 2 oral<br>400 x 3 iv | 750 x 2 oral<br>400 x 2 iv | data pending | 750 x 2 oral<br>400 x 3 iv | |
| **Available formulations** | oral, iv | oral, iv | oral, iv | oral, iv | oral, iv | oral, iv | |

## Clinical data

There is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by *Salmonellae* with low-level fluoroquinolone resistance (MIC>0.064 mg/L) EUCAST has suggested that the epidemiological cut off value (S≤0.064/R>0.064 mg/L) be used in Salmonellae systemic infections. These strains are best found using a nalidixic acid 30 µg screen disc in routine susceptibility testing.

There is agreement in EUCAST that ciprofloxacin activity against Enterococci and Streptococci, including S.pneumoniae, is insufficient to categorize wild type bacteria “susceptible”.

## 2. Multiple MIC-distributions are collected, the wild type MIC distribution is defined and tentative epidemiological cut-off values determined (WT ≤X mg/L)



# 3. Existing national clinical breakpoints are compared

**Ciprofloxacin** was used in this example:

| Breakpoints prior to harmonisation (mg/L) S≤ R> | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **BSAC** | **CA-SFM** | **CRG** | **DIN** | **NWGA** | **SRGA** | **NCCLS** |
| **General breakpoints** | **ND** | **1/2** | **1/2** | **1/2** | **0.125/2** | **1/2** | |
| **Species related breakpoints** | | **not yet** | | **no** | | | |
| Enterobacteriaceae | **1/1** | | | | **0.12/2** | **0.12/1** | **1/2** |
| *Pseudomonas* spp. | **1/4** | | | | **ND** | **1/1** | **1/2** |
| *Acinetobacter* spp. | | | | | | **1/1** | **1/2** |
| Staphylococci | **1/1** | | | | **0.12/2** | **0.06/2** | **1/2** |
| Streptococci | **1/1** | **excluded** | | | **0.12/2** | **0.12/2** | **excl** |
| *S. pneumoniae* | **2/2 (I)*** | **excluded** | | | **0.12/2 (I)*** | **0.12/2 (I)*** | **excl** |
| Enterococci | **excluded** | **excluded** | | | **0.12/2** | **0.12/2** | **1/2** |
| *Haemophilus/Moraxella* spp. | **1/1** | | | | **0.12/0.5** | **0.12/0.25** | **1/-** |
| Corynebacteria | | | | | | **excl** | |
| *N. Meningitidis* | **1/1** | | | | **0.06/0.12** | **0.03/0.25** | |
| *N. Gonorrhoeae* | **0.06/-** | | **0.06/1** | | **0.06/0.12** | **0.06/0.25** | **0.06/0.5** |
| *P. Multocida* | **ND** | | | | **ND** | **0.12/0.25** | |
| Anaerobes | **excluded** | | | | **ND** | **excluded** | |
| *Campylobacter* spp. | **1/1** | | | | | | |
| *Helicobacter pylori* | **2/2** | **no** | **no** | | **no** | **no** | |

## 4. Pharmacokinetic data are collected and evaluated

Pharmacokinetic data are collected from various sources, particularly data from patients. If the data allow it and if necessary, population pharmacokinetic models are developed.

These are necessary for PK/PD analyses, including Monte Carlo simulations

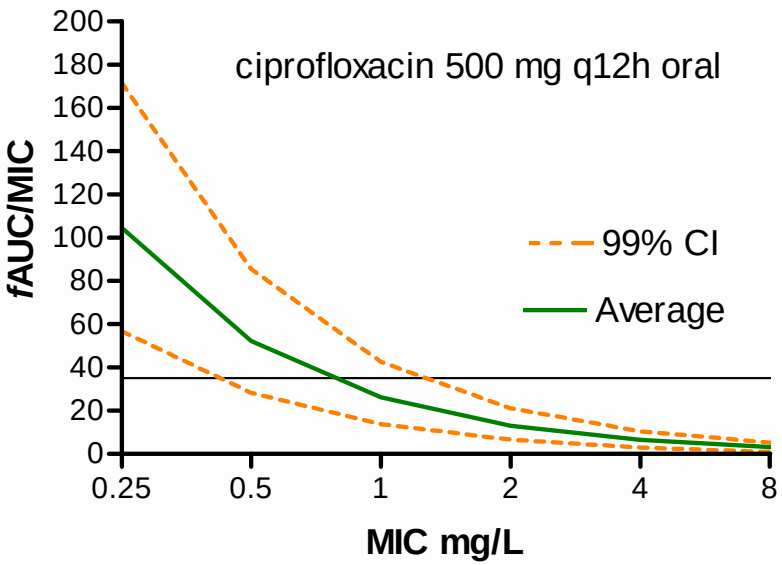
## 5. Pharmacodynamic data are evaluated

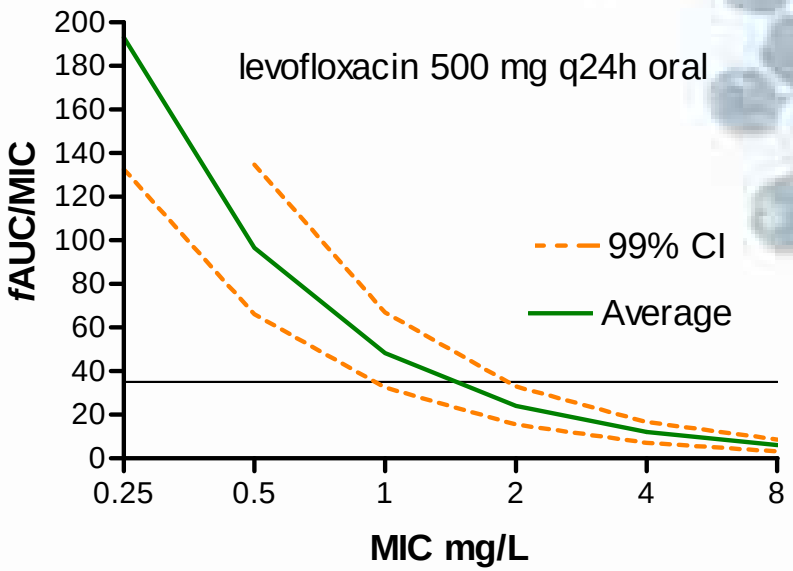
The PK/PD index value of the pertinent PK/PD parameter (time above MIC, AUC/MIC, $C_{max}$/MIC…) resulting in optimal outcome is determined from:

- in vitro data
- animal studies
- clinical trials
- The efficacy of the drugs is assessed quantitatively.

Relationships between concentration time profiles and emergence of resistance are evaluated

# Monte Carlo simulations are performed and a PK/PD breakpoint calculated based on conventional dosing regimens




S = 0.5 mg/L

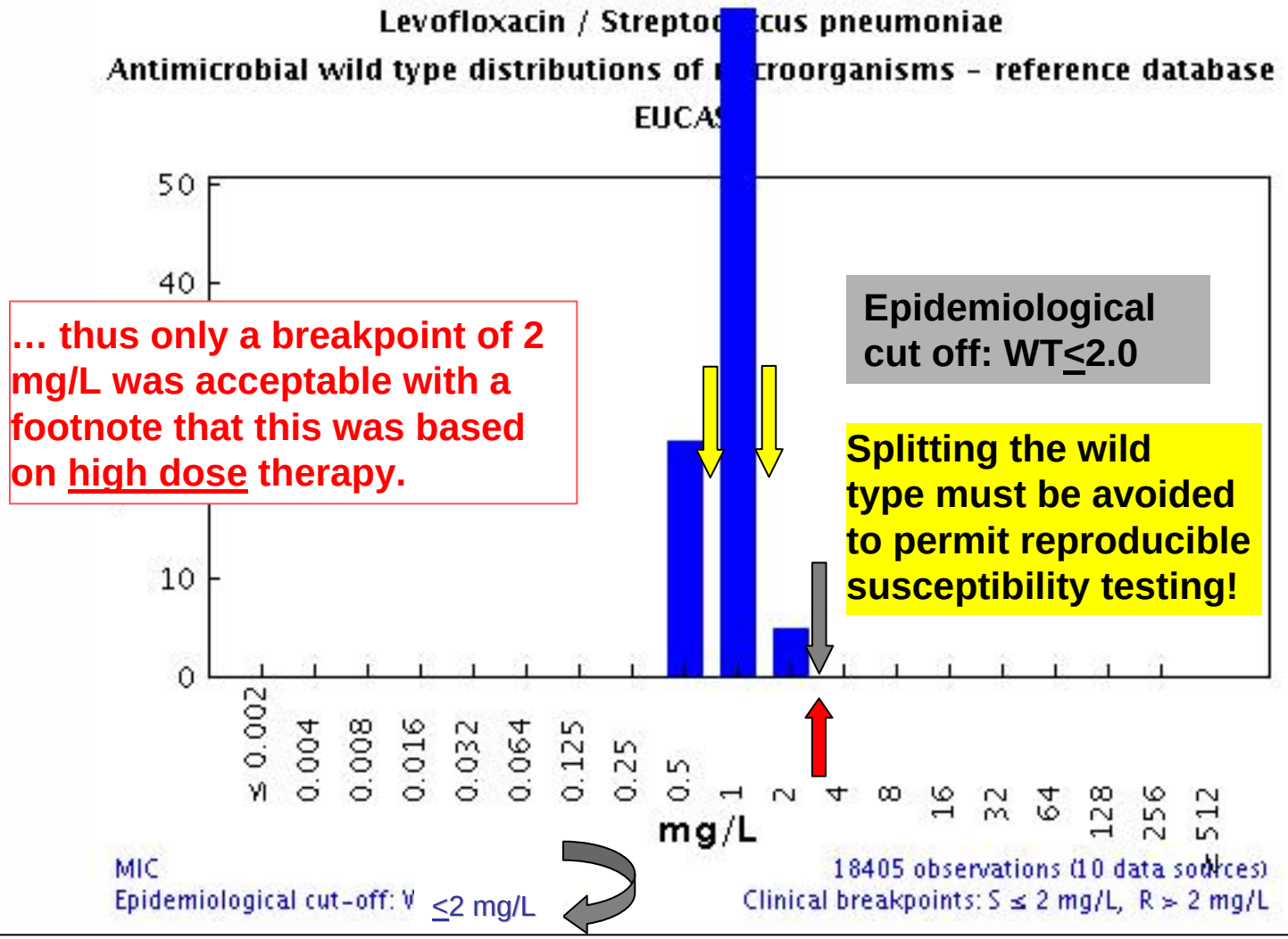
Pk/Pd

S = 1 mg/L

## 5. Clinical data relating outcome to MIC-values, wildtype and resistance mechanisms are assessed in relation to the tentative breakpoint

”Minimum requirement for S-category” is that the highest MIC value of the wild type MIC-distribution is consistent with the MIC derived from the PK/PD index needed for optimal efficacy based on free drug”.

# 6. Pk/Pd breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain tentative breakpoints - example levofloxacin



**7. Tentative breakpoints by the EUCAST Steering Committee are referred to the national breakpoint committees for comments.**
**When steering committee and national committees agree the tentative breakpoints are subjected to the EUCAST consultation process:**

**8. Consultation process on tentative breakpoints:**

**- EUCAST general committee**

**- Expert committees (*Neisseria*, Anaerobes, others)**

**- pharmaceutical industry, AST device manufacturers**

**- others via EUCAST website**

**9 . Rationale document prepared and published on website**

# Aminoglycosides - EUCAST clinical MIC breakpoints 23 november 2004

| Aminoglycosides[1] | Species-related breakpoints (S≤/R>) | | | | | | | | | | | Non-species related breakpoints[5] S≤/R> |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Enterobacteriaceae* | *Pseudomonas*[2] | *Acinetobacter*[2] | *Staphylococcus* | *Enterococcus*[3] | *Streptococcus A,B,C,G* | *S.pneumoniae* | *H.influenzae M.catarrhalis* | *N.gonorrhoeae* | *N.meningitidis* | *Gram-negative anaerobes* | |
| Amikacin | 8/16 | 8/16 | 8/16 | 8/16[4] | -- | -- | -- | IE | -- | -- | -- | 8/16 |
| Gentamicin | 2/4 | 4/4 | 4/4 | 1/1 | -- | -- | -- | IE | -- | -- | -- | 2/4 |
| Netilmicin | 2/4 | 4/4 | 4/4 | 1/1 | -- | -- | -- | IE | -- | -- | -- | 2/4 |
| Tobramycin | 2/4 | 4/4 | 4/4 | 1/1 | -- | -- | -- | IE | -- | -- | -- | 2/4 |

1. The aminoglycoside breakpoints are based on modern once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents. For unlisted aminoglycosides refer to breakpoints determined by national breakpoint committees.
2. The S/I breakpoint has been increased from 2 to 4 mg/L for agents other than amikacin to avoid dividing the wild type MIC distribution. Thus there is no intermediate category for *Pseudomonas* species and *Acinetobacter* species.
3. *Enterococcus* spp - aminoglycoside monotherapy is ineffective against enterococci. There is synergism between aminoglycosides and betalactams in enterococci without acquired resistance mechanisms. There is no synergistic effect in enterococci with high level aminoglycoside resistance, i.e with gentamicin MIC>128 mg/L.
4. Resistance to amikacin and kanamycin is most reliably determined using kanamycin as test substance.
5. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).

**--** = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
**IE** = There is insufficient evidence that the species in question is a good target for therapy with the drug.

*Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30 and updated 22 November 2004*

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*EUCAST 2003 (The European Committee on Antimicrobial Susceptibility Testing)*
*Updated 2004-11-23, G Kahlmeter*

# Oxazolidinones - EUCAST clinical MIC breakpoints 30 april 2004

| Oxazolidinone | Species-related breakpoints (S≤/R>) | | | | | | | | | | | Non-species related breakpoints[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Enterobacteriaceae* | *Pseudomonas* | *Acinetobacter* | *Staphylococcus*[1] | *Enterococcus*[1] | *Streptococcus A,B,C,G* | *S.pneumoniae* | *H.influenzae M.catarrhalis* | *N.gonorrhoeae* | *N.meningitidis* | *Gram-negative anaerobes* | |
| Linezolid | -- | -- | -- | 4/4 | 4/4 | 2/4 | 2/4 | -- | -- | -- | -- | 2/4 |

1. The S/I-breakpoint has been increased from 2.0 to 4.0 mg/L to avoid dividing wild type MIC-distributions. Hence there is no intermediate category.

2. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
**IE** = There is insufficient evidence that the species in question is a good target for therapy with the drug.

*Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30.*

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*EUCAST 2003 (The European Committee on Antimicrobial Susceptibility Testing)*
*Updated 2004-11-23, G Kahlmeter*

EUCAST clinical MIC breakpoints - cephalosporins - Mozilla Firefox

File Edit View Go Bookmarks Tools Help

http://www.srga.org/eucastwt/MICTAB/MICcephalosporins.html

| Cephalosporins<br>Click on antibiotic name to see wild type MIC distributions. | | Species-related breakpoints (S≤/R>) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *Enterobacteriaceae*[2] | *Pseudomonas*[3] | *Acinetobacter* | *Staphylococcus*[4] | *Enterococcus* | *Streptococcus A,B,C,G* | *S.pneumoniae* | *H.influen M.catarrh* |
| Cefazolin | RD | -- | -- | -- | note[4] | -- | -- | -- | -- |
| Cefepime | RD | 1/8 | 8/8 | -- | note[4] | -- | 0.5/*0.5*[6] | 1/2 | 0.25/0.2 |
| Cefotaxime | RD | 1/2 | -- | -- | note[4] | -- | 0.5/*0.5*[6] | 0.5/*2*[6] | 0.12/*0.1* |
| Ceftazidime | RD | 1/8 | 8/8 | -- | -- | -- | -- | -- | -- |
| Ceftriaxone | RD | 1/2 | -- | -- | note[4] | -- | 0.5/*0.5*[6] | 0.5/*2*[6] | 0.12/*0.1* |
| Cefuroxime | RD | 8/*8*[5] | -- | -- | note[4] | -- | 0.5/*0.5*[6] | 0.5/1 | 1/2 |

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).
2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.
3. For cefepime and ceftazidime the susceptible breakpoint for *Pseudomonas aeruginosa* has been increased to avoid dividing the MIC wild type distribution. The breakpoint relates to high dosage of both drugs, i.e. 2 g x 3.
4. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility (except ceftazidime which should not be used for staphylococcal infections).
5. The non-species related S/I breakpoint of 4 mg/L divides the wild type MIC distributions of relevant Enterobacteriacae. To avoid this, the S/I-breakpoint has been increased to 8 mg/L. The breakpoint pertains to a dosage of 1.5 g x 3 and to *E.coli* and *Klebsiella spp* only.
6. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

**--** = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
**IE** = There is insufficient evidence that the species in question is a good target for therapy with the drug.
**RD** = rationale document listing data used by EUCAST for determining breakpoints.

Done Now: Partly Cloudy, 7° C Mon: 12° C Tue: 10° C

# EMEA – ISAP SOP

European Medicines Agency
*Standard Operating Procedure*

| Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST | | Document no.: SOP/H/3043 |
|---|---|---|
| Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST | | Effective Date: 14 February 2005 |
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| Signature: On file | Signature: On file | Signature: On file |
| Date: 10 Feb 05 | Date: 10 Feb 05 | Date: 10 Feb 05 |

**1. Purpose**

To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European breakpoints.

# Will good breakpoints solve everything ?

- Breakpoints should only be used as a guidance for a the general usage of an existing drug (is it still worth to use it ?) or for the positioning of a new drug (has it any chance of being successful ?)

- MIC distributions (local and national) must be obtained regularly to check for decreased susceptibilities (epidemiology) and reassessment of posologies and/or therapeutic choices (hospital…)

- Difficult-to-treat patients must be evaluated individually (and MIC obtained …)