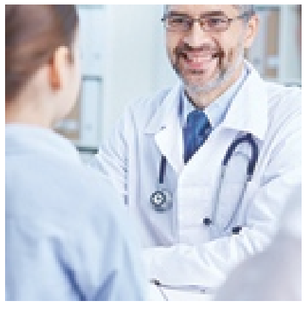
European Federation of Pharmaceutical Industries and Associations

Replacing and interpreting clinical data

John H. Rex, MD, *on behalf of the EFPIA team*





EMA PK-PD Workshop

12-13 Nov 2015

Context: Section 4.7 of the draft

Excerpts from Section 4.7 (Regulatory Implications)

- Well conducted simulations based on relevant POPPK models may serve to replace the need for clinical dose-finding but they cannot wholly replace the need for clinical efficacy data
- PK-PD analyses are expected to provide much of the evidence to support the adequacy of the dose regimen for target MDR pathogens in limited clinical development programs
- Other uses could include
  - Investigation of unexpected findings
  - Identification of need for & prediction of dose modifications in patient subsets
  - Identification of dose regimens in new formulations with different PK
  - Interpretation of clinical relevance of DDI results
  - Identification of regimens that reduce risk of resistance
  - Implementation of adaptive trial designs
  - Validation of biomarkers
  - Estimation of no-treatment effect and (hence) derivation of NI margins

EFPIA comment: We agree with all these ideas

Other Topics

- Remainder of this talk will survey 5 ideas
  - Pooling of data
  - Pediatrics
  - Interpretive breakpoints
  - Communication about dosing at higher MICs
  - List 1/List 2 for PK data
- Beneath it all: A patient-centric viewpoint
  - Bacterial resistance is progressing steadily
    - Our pipeline is razor thin
    - PK-PD can enable earlier access to drugs
  - We'll never have all the data we'd like
    - Physicians have to treat *now* … despite gaps in the data
    - PK-PD can be used to enable a best guess when the edges of our knowledge are reached

Pooling of data (1 of 3)

- PK-PD can support more than one kind of pooling
- Usual meaning: Pooling efficacy across sites
  - Reaching a reasonable number of cases when the focus is on a single pathogen may require pooling of efficacy data on treatment of infections at different body sites
  - PK-PD is clearly relevant as a source of much of the evidence for programs where only limited clinical data are possible
- Another meaning: Reduce program (trial) size even when a larger program is possible
  - Recognizing the trade-offs (especially that limited use labeling will result), a developer could rationally pursue a smaller trial(s) even if larger trials are possible
- Examples help…

Pooling of data (2 of 3)

- Program idea #1
  - Small studies in 2+ indications (wide margins)
  - Comprehensive PK-PD support
  - Result: Approval in both with caveat of “only for patients with limited treatment options”
- Program idea #2
  - Complete a fully powered study in indication A
  - Seek also limited approval in indication B via PK-PD (perhaps also with a small amount of clinical data in indication B
  - Subsequently, complete (fully powered?) study in indication B or a study for a specific pathogen
  - Result: Stepwise, early access where there is a high unmet need, then full approval for both indications (or the specific pathogen)
- Program idea #3
  - Fully powered study in indication A
  - Smaller study in indication B (wide margins)
  - Bridging of the indications by PK-PD
  - Result: Standard approval for both indications

Pooling of data (3 of 3)

- The goal: A confident extrapolation
- ***EFPIA recommendation:***
  - **Add "support for pooling of data across body sites" as a use of PK-PD**
  - **Reference EMA concept paper on extrapolation**
  - **Reference ideas from Adaptive Pathways**
    - **"… balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits & harms…" (Eichler 2015 Clin Pharm Ther)**
  - **Expanded notes could discuss importance of ideas such as**
    - **Analyses using data in which relative human/animal model exposures in plasma and target tissues are considered and**
    - **Study of (a variety of) relevant pathogens in infection models at those sites**

Pediatrics (1 of 1)

- Obtaining clinical efficacy data in children is hard & slow
  - It's even harder in settings where only limited clinical data can be produced in adults
- In practice, pediatric development is now being reduced to identifying age-related doses based on PK
  - May need to consider differences in pathogens but, …
  - … the mechanism of action is otherwise independent of age!
  - The safety database will be small, but the rule of 3 says that adding just a few more cases doesn't really add insight. Rather than delaying knowledge on dosing in children, post-approval pharmacovigilance should round out the safety database.
- Core point: It's a balance between maximizing knowledge and speeding access
- ***EFPIA recommendation:*** **Explicitly recognize expectation that pediatric development is for data needed to recommend doses producing adequate PK**

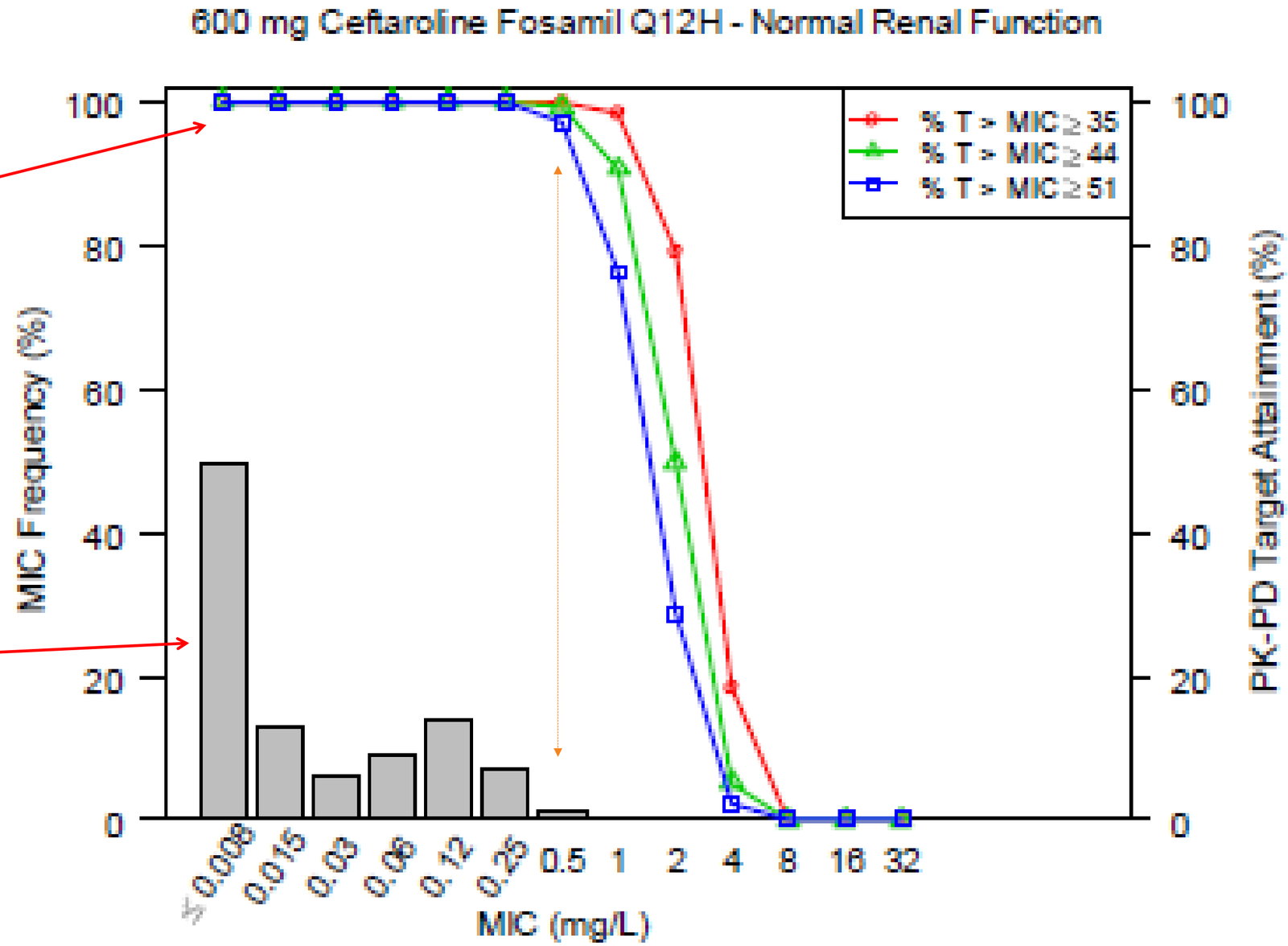
Interpretive breakpoints (1 of several)

- Although it is useful to review outcomes by MIC, it is not usually possible to determine appropriate breakpoints from clinical data:
  - Comparative designs will have to exclude highly resistant (comparator-resistant) infections
  - Dose regimen(s) will usually ensure coverage of isolates with MICs spanning the wild-type range
  - Pathogens with high MICs to the new agent may be rare at the time of development
  - Range of sites studied may limit species studied
- This has very practical consequences…

Ceftaroline in CA(B)P: *S. pneumoniae**

PK-PD shows > 97% target attainment up to an MIC = 0.5 mg/L

- Lines: % target attainment for %T > MIC of 35, 44, and 51%
- In grey: MIC population distribution (surveillance data) for *S. pneumoniae*



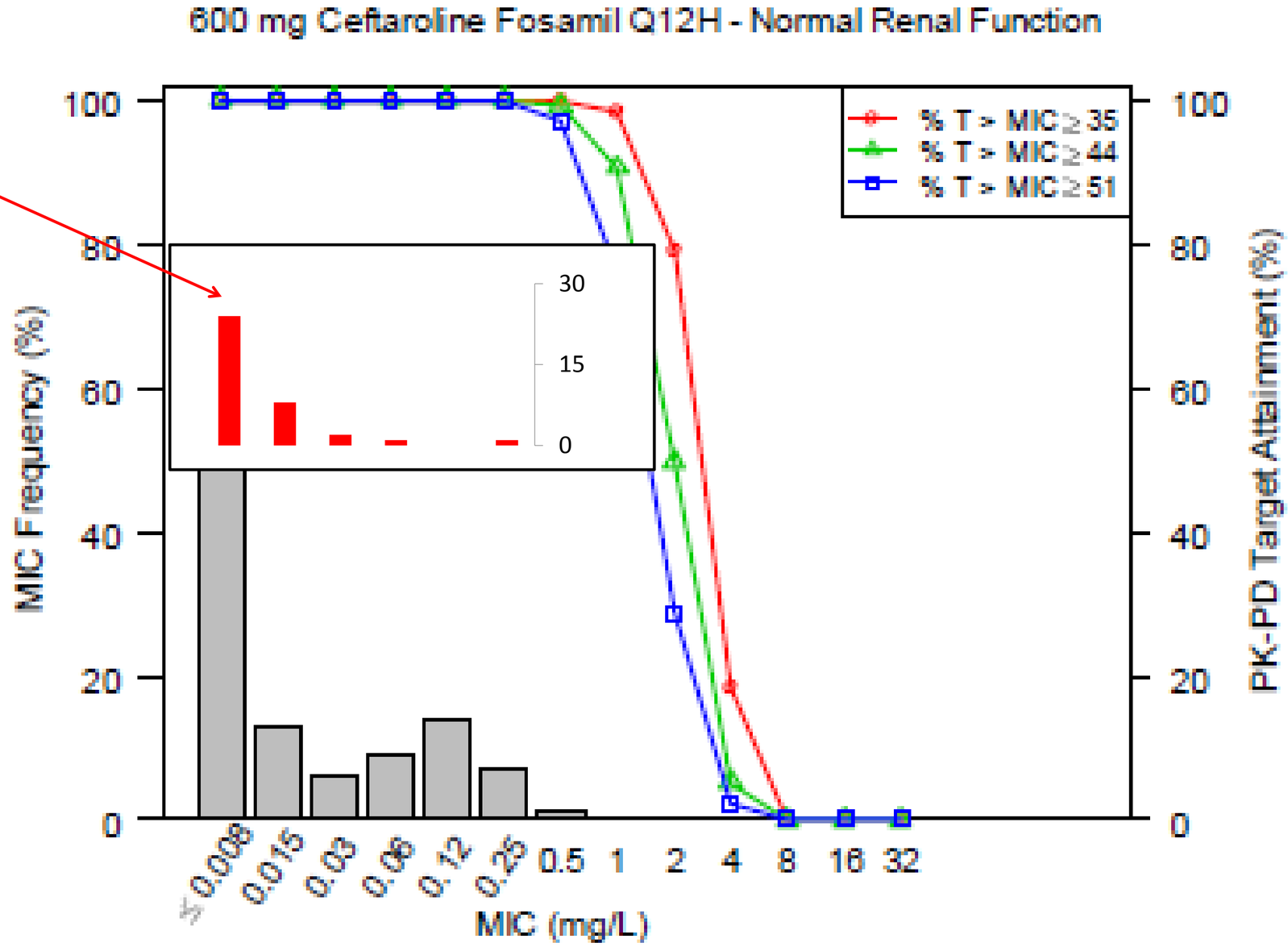
Source: Section 9.2.3 and figure 9.2.3-1 from 4 May 2012 data package presented to CLSI on ceftaroline

*Audience alert: I am going to talk about ceftaroline, an AZ-Allergan drug, in some detail on the next few slides. I'm using it as the example because it's easy for me to get the respective companies to permit me to do this! Other drugs may well have similar stories, but I don't have access to those data.

Ceftaroline in CAP: *S. pneumoniae*

Trial isolates mirrored wild-type MIC distribution

- Inset graph: MICs of trial isolates
  - 24 @ ≤ 0.008
  - 8 @ 0.015
  - 2 @ 0.03
  - 1 @ 0.06 & 0.25
- Clinical Failures
  - 4 @ 0.008
  - 2 @ 0.015
- Others: Success

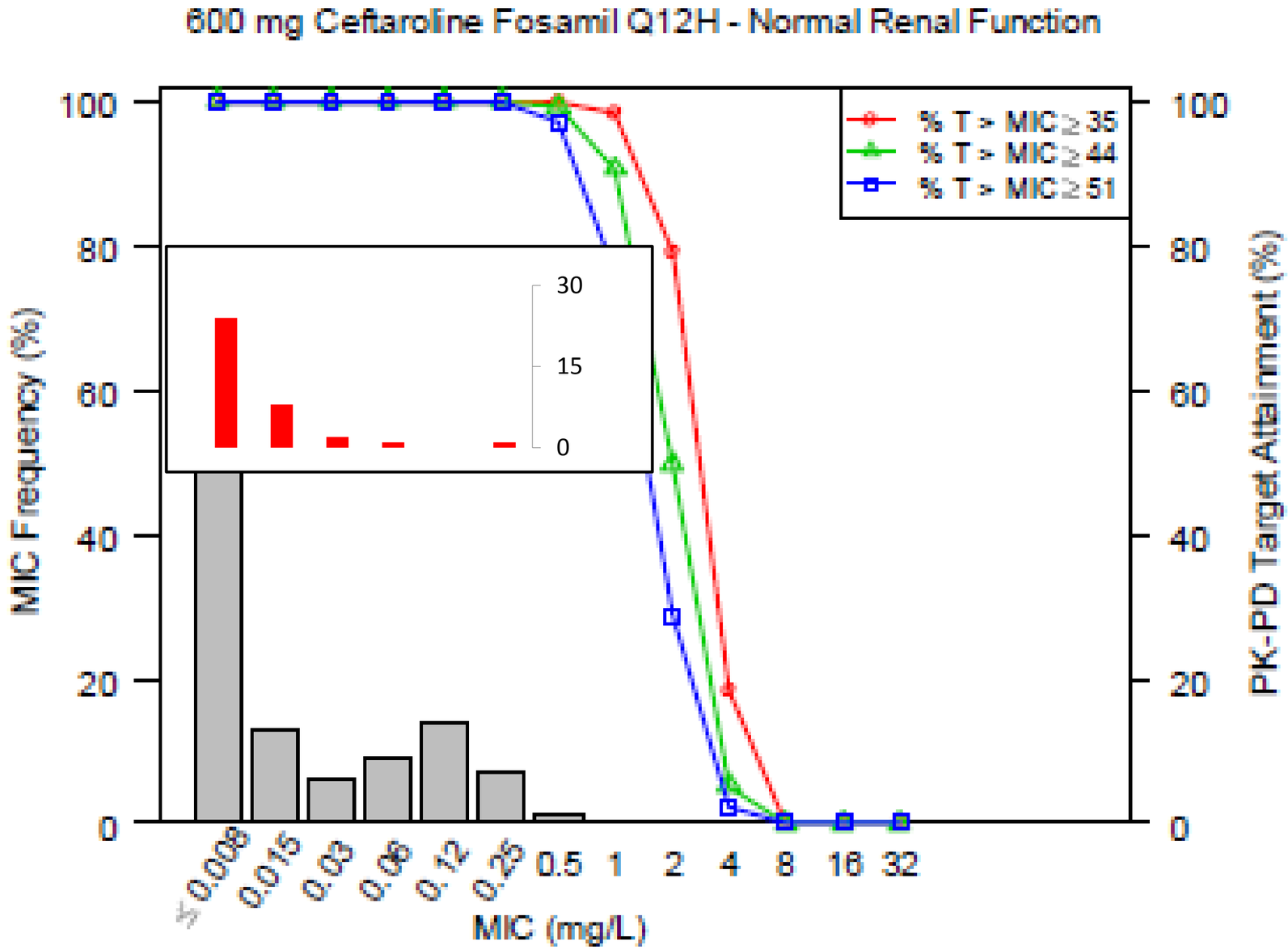


Source: Figure 9.2.3-1 and Table 9.2.2-1 from 4 May 2012 data package presented to CLSI on ceftaroline

Ceftaroline in CAP: *S. pneumoniae*

What do you do?

- Only 4 isolates at MIC ≥ 0.03 mg/L
- Setting S cut-off at ≤ 0.015 mg/L would cause 34% of current isolates to be reported as non-susceptible

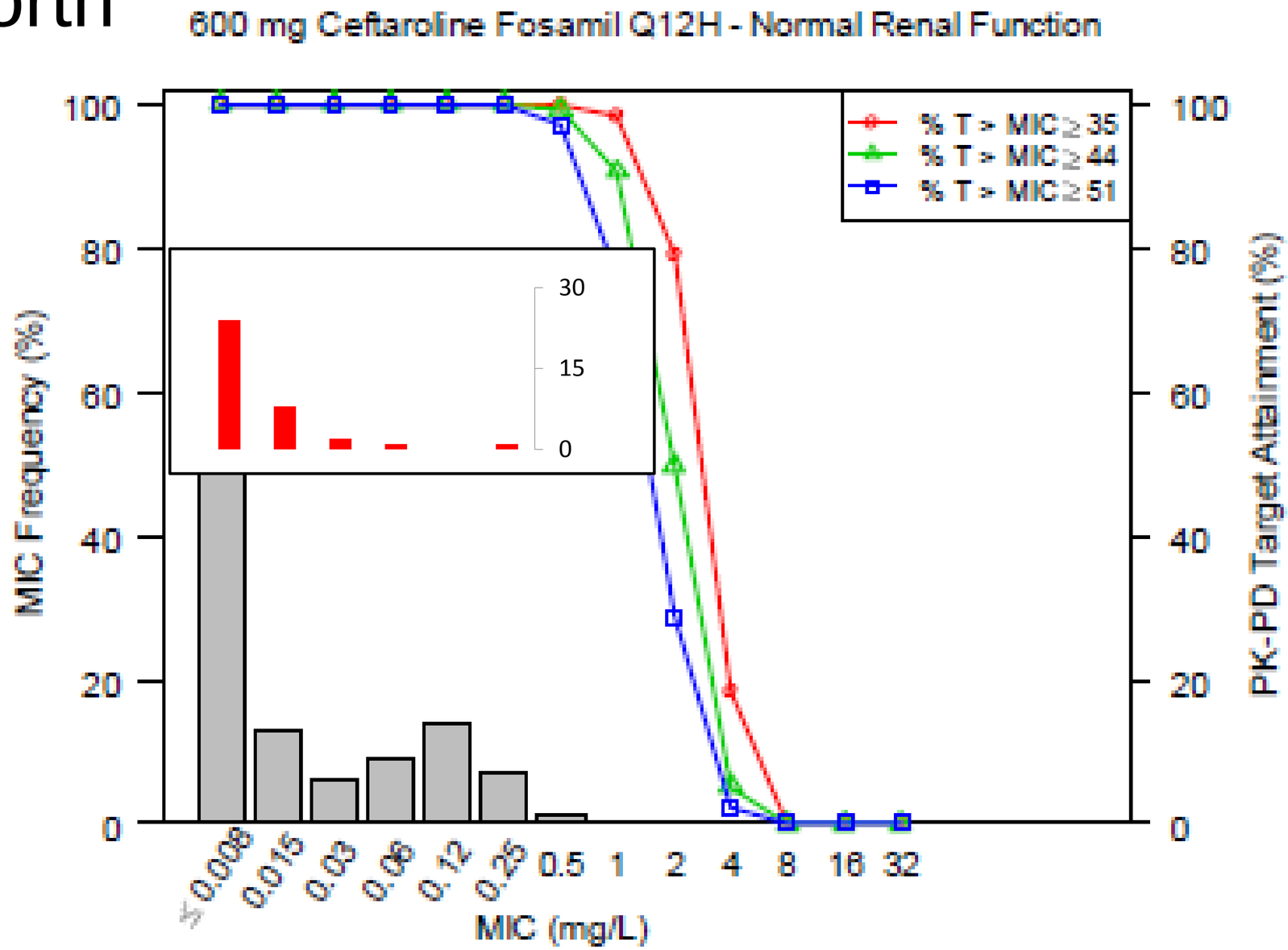


Source: Figure 9.2.3-1, Table 9.2.2-1, and Table 9.2.4-1 from 4 May 2012 data package presented to CLSI on ceftaroline

Ceftaroline in CAP: *S. pneumoniae*

The debate

- Lots of back and forth across a range of possibilities
- Ultimately, it came down to 0.25 vs. 0.5 mg/L
- Both breakpoints are now in use in different regions

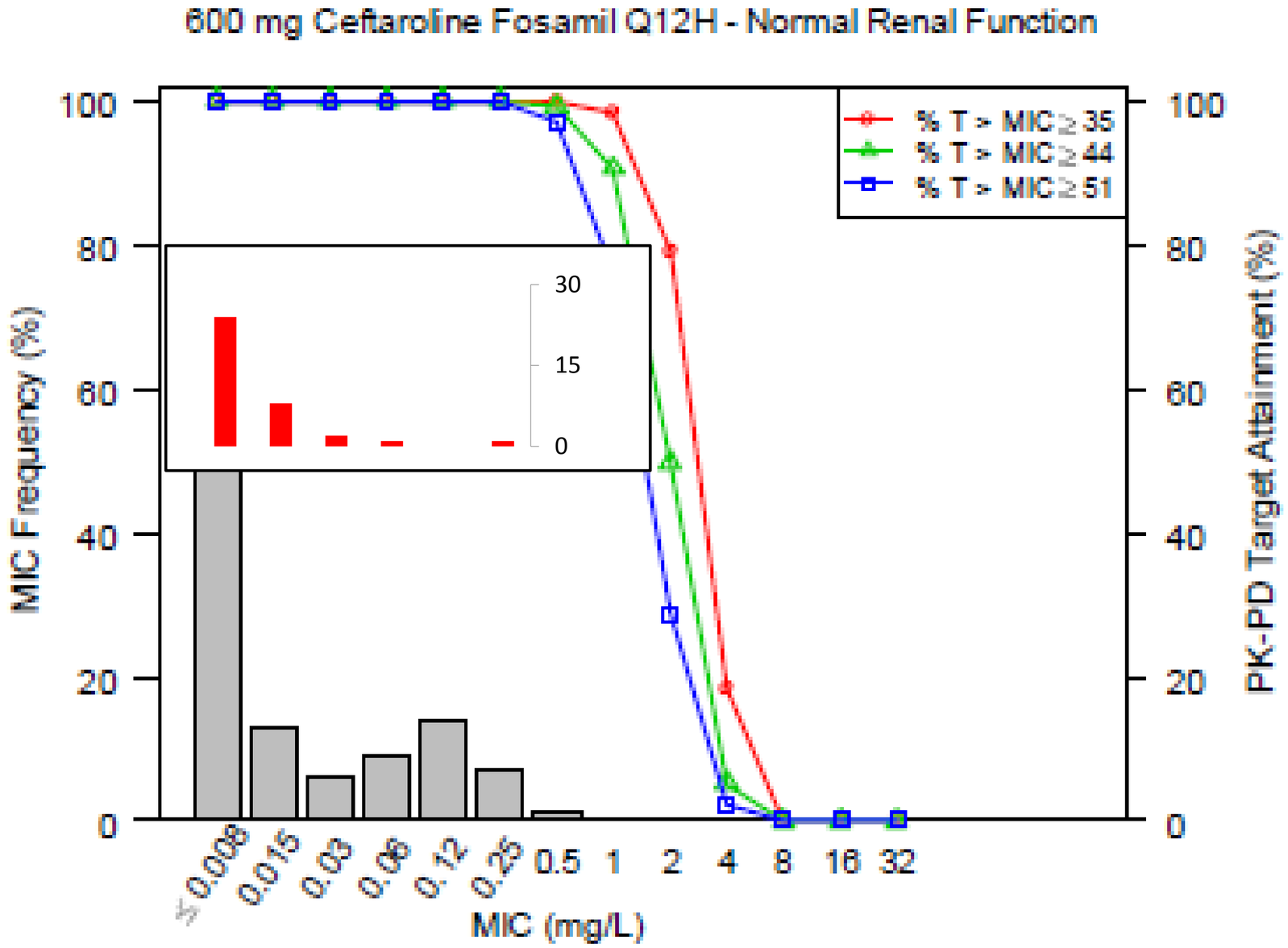


Source: Figure 9.2.3-1 and Table 7.1.3.3.1-1 from 4 May 2012 data package presented to CLSI on ceftaroline. July 2013 US PI (Teflaro), ZINFORO EMEA SMPC (as accessed online 27 Sep 2013), and CLSI meeting minutes.

Ceftaroline in CAP: *S. pneumoniae*

Is this correct?

- So the question for today is…
- Does one case where the MIC is 0.25 mg/L really create or define the correct upper boundary?



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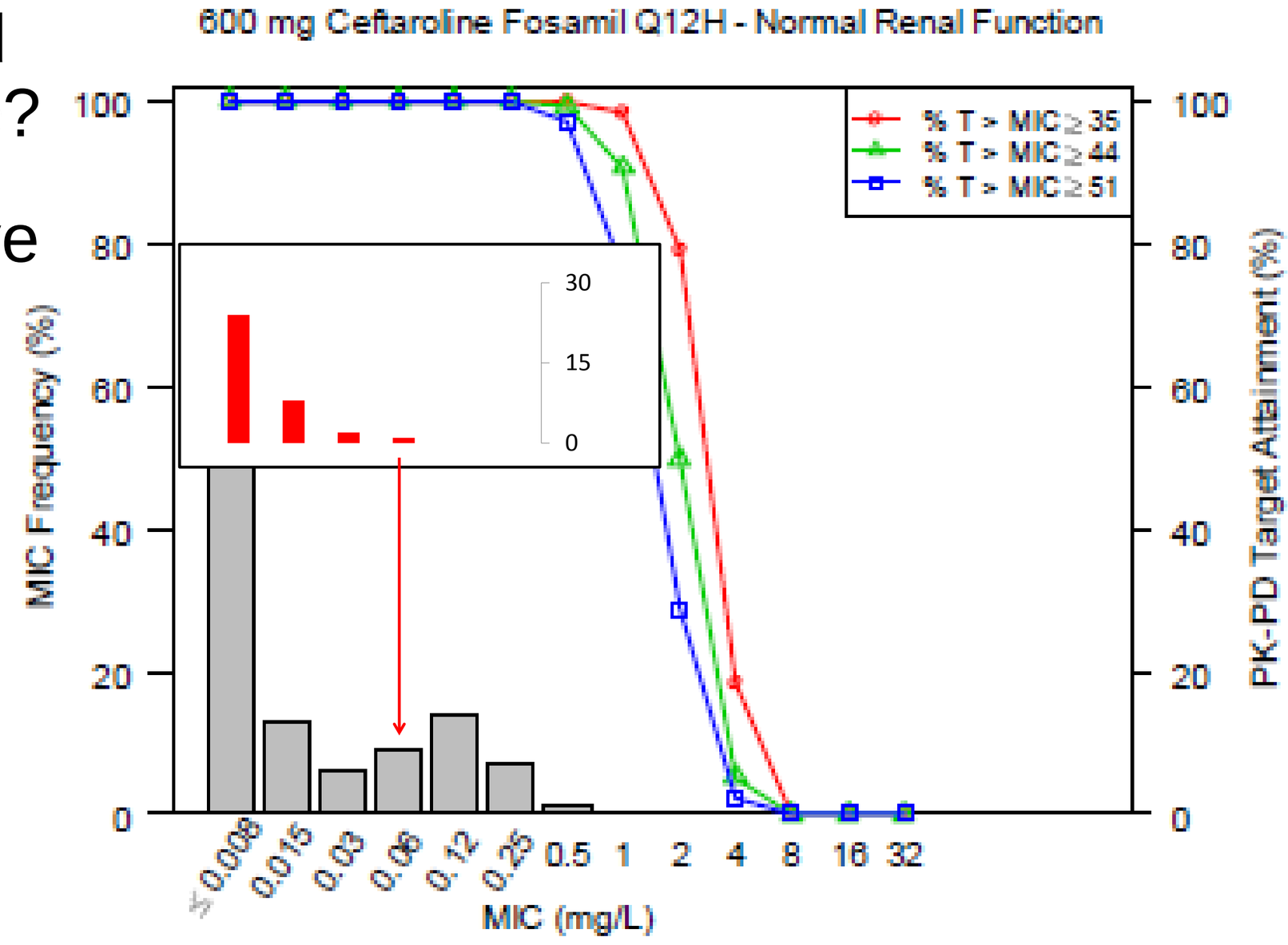
Ceftaroline in CAP: *S. pneumoniae*

Pre-clinical data give more latitude for exploration

- And if we erase that one case? Or retest it and have the MIC change?
- We think the extensive preclinical data are much stronger than any single case anecdote
- We would hope to *often* see this problem with novel agents



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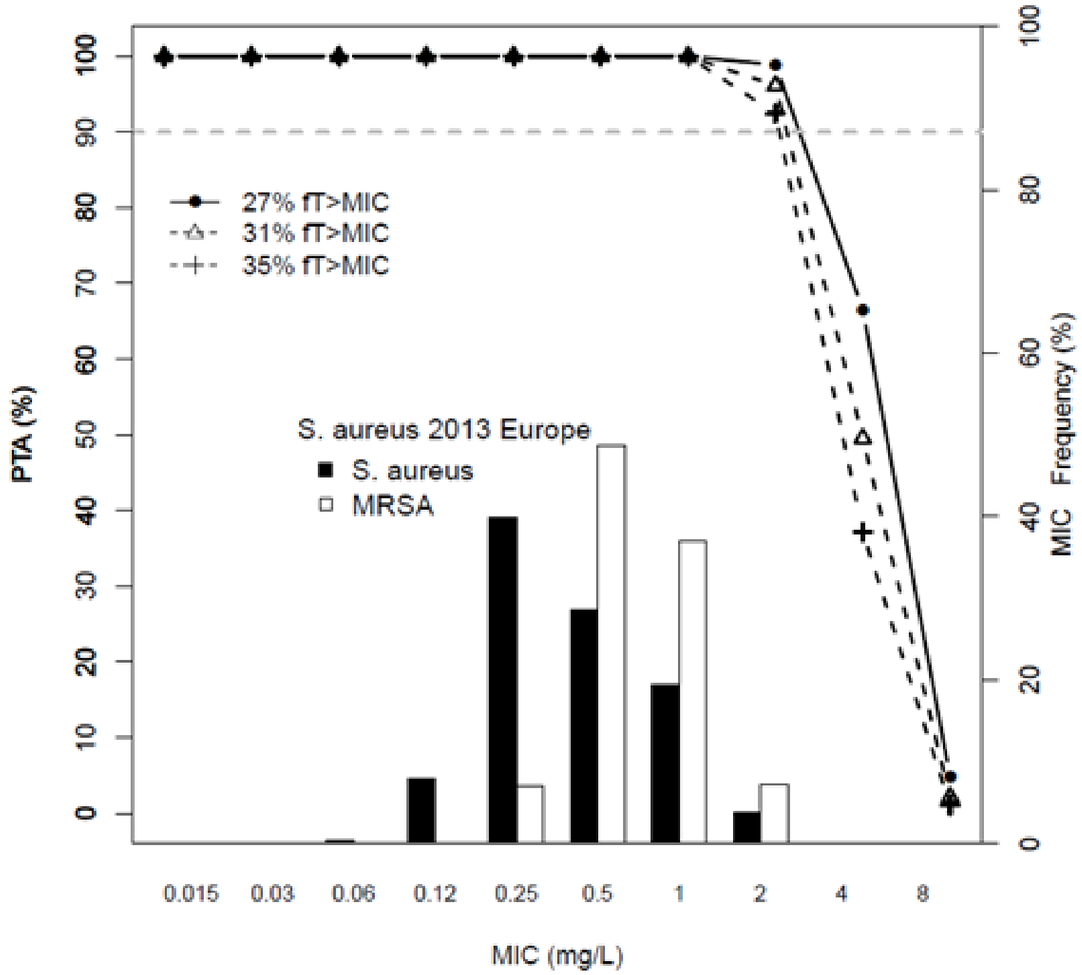
So, what if you decide you really want to go get those higher MIC isolates?

Ceftaroline again, this time for MRSA in ABSSSI

- PTA > 95% up to MIC of 2 mg/L
- Isolates with MICs of 2 mg/L are seen (inset)
- But, a trial designed to capture such isolates failed to enroll *any* with an MIC of 2!



- **Core causes:** Prior antibiotics & hospital acquisition are key risks for high MICs. Prior therapy is an exclusion. ABSSSI starting in hospital is caught before growing to size (≥ 75 cm^2, size of a dinner plate!) needed for modern trials.

Interpretive breakpoints (last of several)

EFPIA recommendation:

- **Guidance should recognize that high MIC isolates are an area where only limited clinical data can be generated**
- **Guidance to note that breakpoints will often need to be set at concentrations for which clinical data are absent:**
  - This is the pattern of an agent with limited pre-existing resistance. We would hope this is a common situation and be pleased when we see it!
  - Limiting breakpoints to the highest observed MICs is inappropriate
  - Preclinical experiments generate stronger data than clinical trials
- **Just as for dose selection, PK-PD should be expected to provide most of the evidence for selection of the interpretive breakpoint**
- **Failing to pursue this will lead to developers studying the least possible dose of their agent – there is no incentive to studying maximal doses as the breakpoints won't be set to take advantage of this work**

Communication about dosing at higher MICs (1 of 3)

- Standard interpretive categories are S, I, & R
- The problem with I…
  - Does it mean Indeterminate? Intermediate? Inconclusive?
  - **For the knowledgeable,**[1] I means Intermediate and is a cue to use a higher dose
  - Unfortunately, I communicates an ambiguous message to many (if not most) physicians
  - MS (moderately susceptible) and MR (moderately resistant) are also flawed: They don't tell you what to do
- A PK-PD-linked alternative label exists: S-DD
  - S-DD = Susceptibility is dose (or dosage) dependent
  - Communicates what we know – a higher dose is needed
  - Has been used for antifungal susceptibility testing for years
  - Is being used now by CLSI in the United States

[1]See for example, the excellent discussion in a proposal by EUCAST to eliminate the Intermediate category as a buffer zone (http://www.eucast.org/documents/discussion_documents/)

Communication about dosing at higher MICs (2 of 3)

From CLSI's M-100 summary document[1]:

- The "susceptible-dose dependent" category (S-DD) implies that susceptibility is dependent on the drug dose that is used.
- In order to achieve levels that are likely to be clinically effective against isolates with MICs or disk zone diameters in this category, it is necessary to use a dose higher than the dose that was used to establish the susceptible category.

[1]See also discussion in Labreche MJ et al., Clin Infect Dis 61:1446-52, 2015

Communication: I vs. S-DD (3 of 3)

S-DD may help with stewardship

- Applies only if range of dosing options exists
- When isolates have MICs in the S-DD range:
  - Using the higher dosage is supported by PK-PD
  - Although the proper meaning of “I” is known to those trained in ID, it is not widely understood by others (and ID-trained staff are not found in all facilities)
  - Good communication will allow physicians to employ agents that might otherwise not be considered
- ***EFPIA recommendation:*** **Use S-DD in settings where appropriate. The category I would be used if S-DD not justified.**

Microbiology: “List 1 & List 2” (1 of 2)

In the section 5.1 of a typical SmPC, we find…

- **“List 1”**[1]
  - Efficacy has been demonstrated by indication in clinical studies against the pathogens listed below. *List goes here…*
- **“List 2”**
  - Clinical efficacy has not been established against the following pathogens although in vitro studies suggest that they would be susceptible to drug XXX in the absence of acquired mechanisms of resistance: *List goes here…*

[1]The titles “List 1” and “List 2“ don’t actually appear in the approved labeling – they are just added here for clarity

Can we adapt the “List 1” & “List 2” idea for PK data in the SmPC? (2 of 2)

- Can we take do a List 1 & List 2 for PK data?
  - The data are a crude aid to be sure, but it may be critical to know (for example) that CSF concentrations are 10% of plasma … or 85%, as the case may be
  - Why? It may be necessary to use a drug in settings for which efficacy data have not (or will never be) developed
  - Practitioners often must make a guess. For that guess, they want access to the best available data (even if limited)
    - Providing PK by site provides the best available data (even if flawed). The alternative is that the practitioner goes to library-land, finds whatever s/he finds, and uses that.
- ***EFPIA recommendation:*** **To the extent the data are available, provide a table of tissue penetration by body site in the SmPC. Sites without indications can be listed separately.**

Summary

- Many thanks to EMA for this forward-looking document and for this workshop
- Points from this review
  - PK-PD can support extrapolation that permits both pooling across body sites and reduction in the overall size of trial programs
  - PK-PD is the bridge for selection of pediatric dosing regimens
  - Interpretive breakpoint setting requires use of PK-PD rather than demonstrations of clinical efficacy across all MICs. High MIC isolates are a setting where only limited clinical data are possible
  - An S-DD category may improve communication
  - The SmPC should provide data on PK by body site
- Overall, we must learn to use PK-PD despite its limits
  - Clinical trials also have limitations – staying ahead of the epidemic requires us to use both tools
  - Patients will present with infections for which limited data are available. We need to find ways maximize access to those limited data while communicating our uncertainty about them

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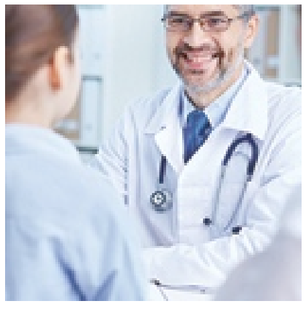
Thank you!





EFPIA Brussels Office
Leopold Plaza Building * Rue du Trône 108
B-1050 Brussels * Belgium
Tel: + 32 (0)2 626 25 55
www.efpia.eu * info@efpia.eu