European Federation of Pharmaceutical Industries and Associations

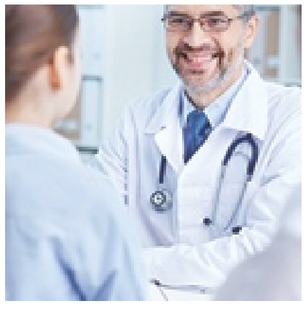
Topic 3a: PD Targets in Nonclinical Models:

How Much Bacterial Killing?

Michael Dudley, *on behalf of the EFPIA team*





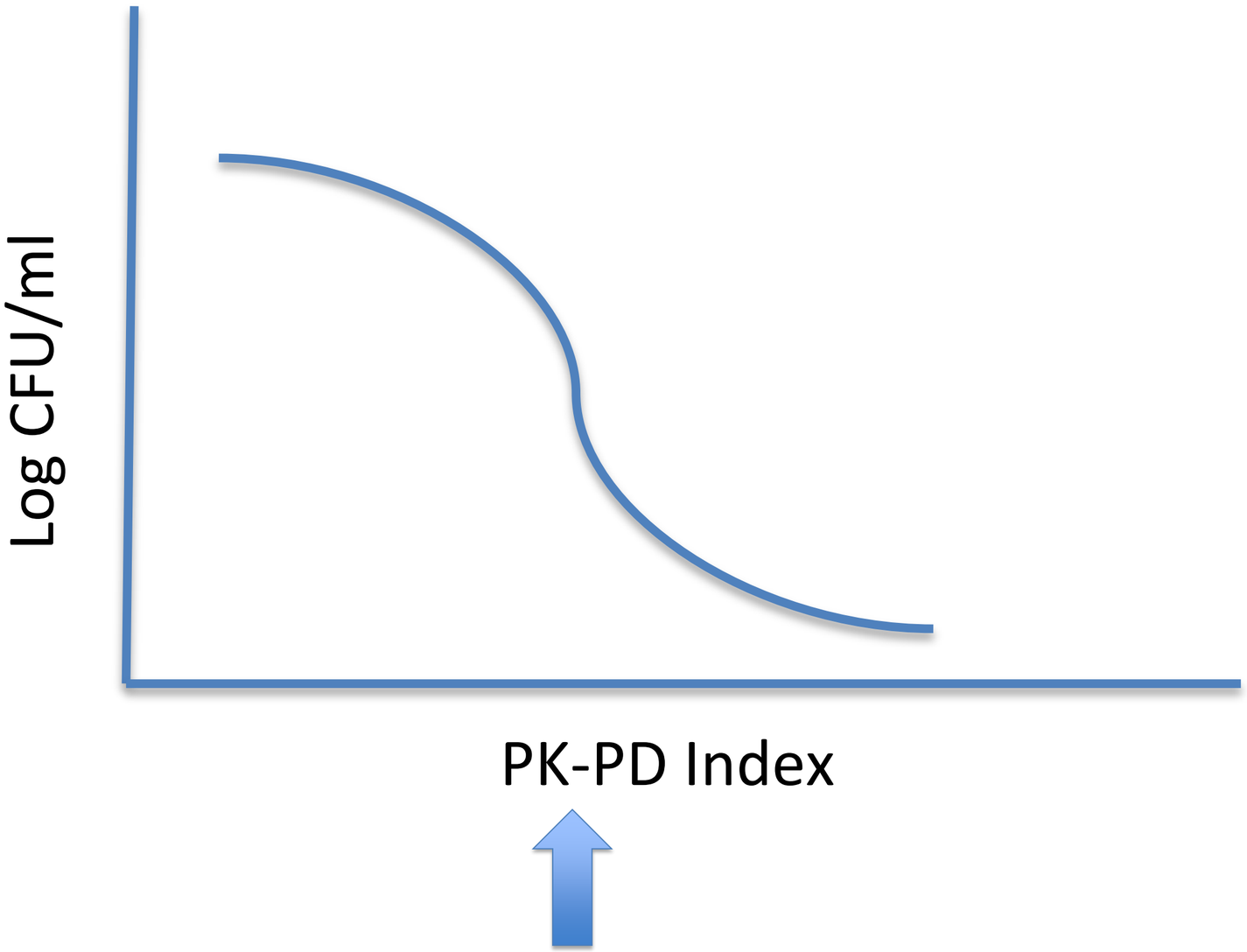
EMA PK-PD Workshop

12-13 Nov 2015

Topics 3a and 3b:
Deconvoluting PD, PDT, and PTA

Topic 3a:
- *How Much Killing (PD)?*

This presentation!



Topic 3b:
- *How much PK-PD exposure (PDT:PK-PD Target) ?*
- *How often should we expect to get it given a dose, PK, and MIC in a patient population (PTA- Probability of Target Attainment) ?*

Exec Summary: PD Targets in Nonclinical Models : *How Much is Enough??*

- Most would agree that ***more*** bacterial killing ***is better!***
- But, let's not be too prescriptive about the magnitude…
  - **Bacterial killing is linked to conditions** of the experimental model, mode of action of drug, inoculum size, and other factors
  - Experimental models and properties observed in preclinical models may or may not **translate to clinical setting**
    - e.g., immunosuppression in animal models (helps bugs grow- see earlier presentation)
- ***<u>Global EFPIA Comment/Recommendation</u>:***
  - Don't rely on **just one** non-clinical model of infection
  - Data linking **<u>specific</u> drops in bacterial counts** in nonclinical models with clinical data still are few, and **are done retrospectively** only following completion of clinical trials
  - **Justification of targets** based on **totality of data** for a given drug/pathogen combination is data driven, and is the **burden of the sponsor**

Target: Stasis, 1 or 2 log drop

Section 4.2.3: PK-PD Relationships

- "…report magnitude of PDTs for stasis, 1-log, and 2-log reductions…"
- "...taking into account ***not all agents will achieve 2-log reductions, or at least, not for all pathogens…***"

- ***EFPIA Recommendation:***

- *We **agree!**-- this is a very important point.*
- *(Indeed, let us not even think about using base "e" as a standard!)*
- *Sponsor needs to justify selection of endpoint in nonclinical studies and linkage to the appropriate exposure:MIC metric*
- *Suggest adding "not for all pathogens **or in all models**" to the end of the text on lines 312-315.*

Considerations of Target: Stasis, 1 or 2 log drop?

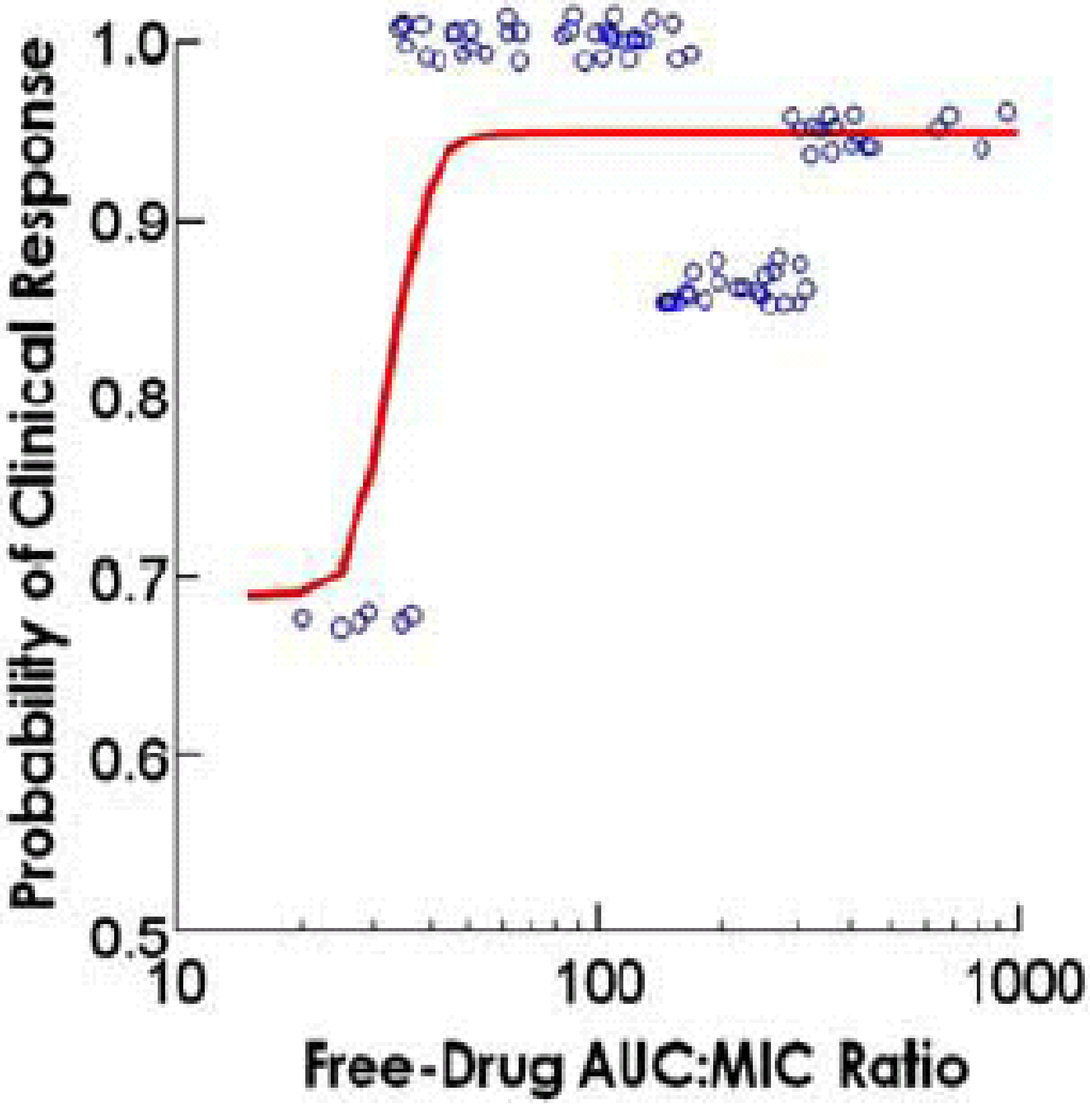
- *The case for more killing…*
  - "Deeper" killing of a large inocula also allows one to probe other important issues for dose selection/exposure-response
    - Impact of host factors on reduction in starting inoculum, release of LPS, etc.
  - Deeper killing and testing of high bacterial inocula may be important to insuring resistant bacterial populations are represented and can be counter-selected by optimized dosage regimens
    - Selection of **resistant mutants/sub-populations** that are more readily selected by deeper kill
    - Recall "inverted U" exposure-response relationships, demonstrated for several classes of drugs for resistance selection
- Consideration of safety with higher drug exposures
  - Totality of nonclinical and ultimately clinical data
  - Breakpoints will define what can be treated at safe doses/exposures

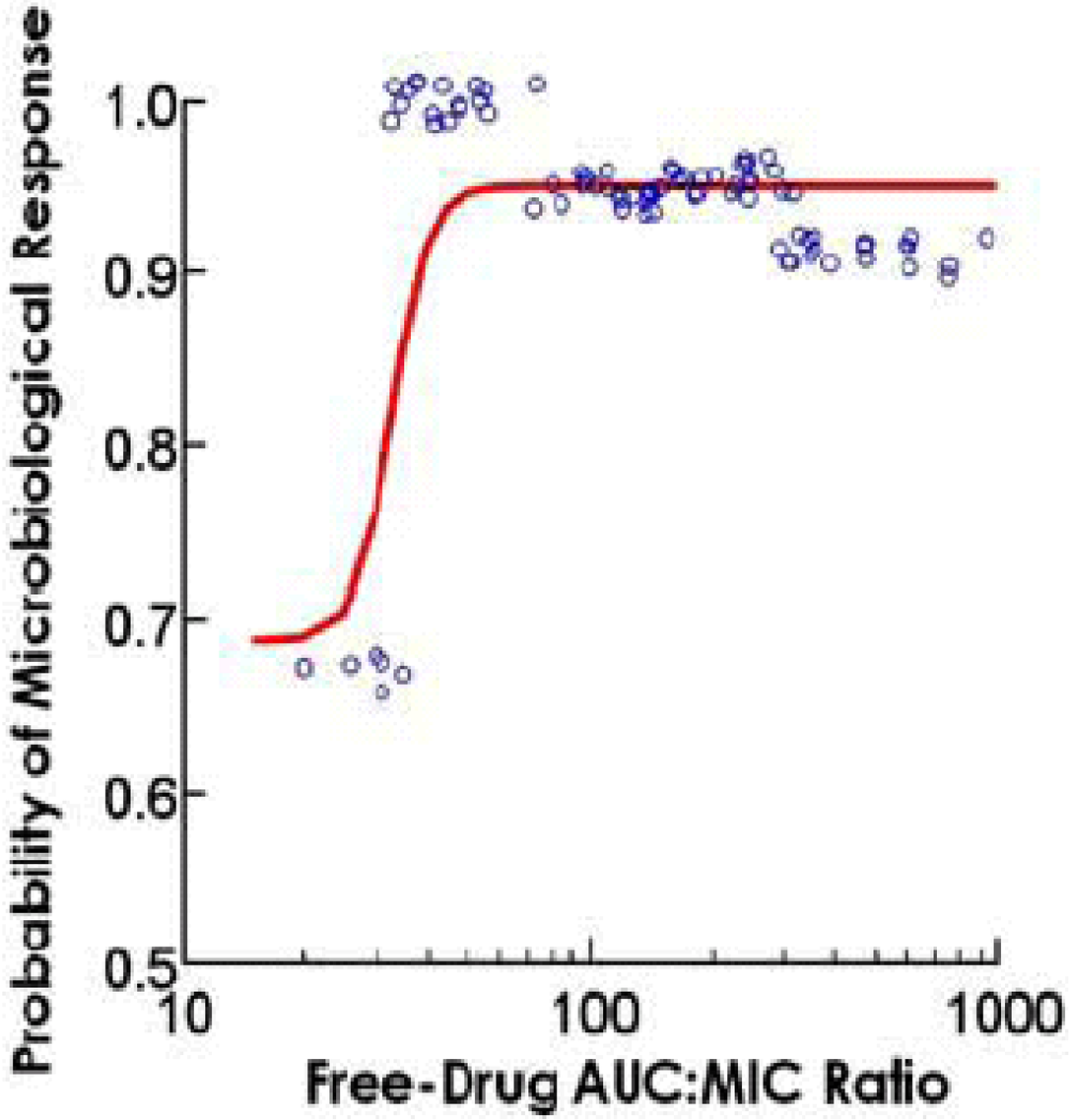
Specific Levels of Bacterial Killing in Non-clinical Models Have Only Been Linked to Patient Trials Only for a Few Drugs

- Most of the data showing such a linkage of PK-PD are
  - for fluoroquinolones and penicillins…
  - for gram-positive infections,
  - and were derived *retrospectively* following clinical trials
- Resistance selection in nonclinical models predicted failure in clinical trials
  - e.g., low doses of ciprofloxacin showed selection of ciprofloxacin-resistant mutants of *Pseudomonas aeruginosa* in hollow fiber models, and clinical failure with low doses of ciprofloxacin in nosocomial pneumonia due to resistance *(Am J Med 1987 82 (suppl A):363-8. Arch Inter Med 1989;149:2269-73)*
- We are indebted to the late Dr. William Craig for his tireless work in animal models of infection, and linking to observations in humans.

FLUOROQUINOLONES

Human PK-PD in Pneumococcal Pneumonia





Bhavnani SM, Forrest A, Hammel JP, Drusano GL, Rubino CM, Ambrose PG. Diagnostic Microbio Infect Dis. 2008;62:99-101.

Linking PK-PD of Fluoroquinolones vs. *S. pneumoniae* in Animals and Clinical Data-

*What you do when you have all the data **retrospectively!***

Source	Endpoint	Free Drug AUC_{24}/MIC
Animal Non-neutropenic	Stasis	12 ± 2
	50% Survival	18 ± 1
	1 Log Kill	19 ± 4
	2 Log Kill	31 ± 6
	90% Survival	35 ± 2
Human	90% Clinical Cure	34
	90% Microbiological Cure	29

(From WA Craig, CLSI Workshop, 2011)

Benchmarking Nonclinical Data with Observed Clinical Efficacy For Established Drug Classes: PDTs for New Agents of Same Class

ESTABLISHED DRUG

NEW DRUG, Same Class

"Effective" Drug Dosage Regimen in Humans

Target PK-PD Index from human data (24h AUC:MIC=100)

New Drug Target PK-PD Index

Human PK, Dosage Regimens, PTA

Clinical Testing; etc

"the human world"

"the nonclinical world"

PK-PD Index in Animal Model (24h AUC:MIC=100)

PD: "x- log drop in animal model"

New Drug Target PK-PD Index in Animal Model

New Drug: "x- log drop in animal model"

Section 4.4.2: Probability of Target Attainment and Log-Drops in Nonclinical Models (1 of 2)

- EFPIA recognizes that other organizations have opined on the level of bacterial killing and PDTs (e.g., CLSI for breakpoint setting).
  - These recommendations may only apply in specific uses (e.g., breakpoint setting), but not others (e.g., early clinical trial planning).
- Lines 422-9 provide recommendations for log drops in nonclinical models and apply them for various infections based on infection site, and other non-quantifiable clinical criteria, e.g.:
  - *"…high organism burden..."*
  - *"…low spontaneous resolution rates…"*
  - *"…lower organism burden…"*
  - *"…skin and skin-structure and intra-abdominal infections…"*

Section 4.4.2: PK-PD Target (PDT) Selection:

EFPIA Comment (2 of 2)

<u>EFPIA Recommendation regarding Lines 419-35:</u>

- We do not believe that such specific recommendations for log-drops and specific infections or “burden levels” are supported by adequate data for all drugs such that specific thresholds should be provided.
- Suggest *<u>replacement</u>* of text in 419-35 with the following points for consideration:
  - Sponsor should justify the selection of the target based on the totality of the data, which includes consideration of:
    - Mode of action and drug class
    - Resistance development
    - Endpoint and timing (e.g., rapidity of clinical and microbiological response)
    - Linkage (where possible) to other members of a drug class, e.g.,
      - New fluoroquinolone
      - Existing beta-lactam with a beta-lactamase inhibitor (restoring activity to that of a fully susceptible/beta-lactamase negative strain)

Suggested new text: *Lines 419-35 (1 of 2)*

Based on the **current body of evidence***, it is not possible to broadly specify levels of bacterial killing in in vitro and animal models of infection that relate to efficacy at specific sites of infections or indications in patients. A drug's mechanisms of action and resistance, inoculum size, and duration of therapy in the model are among several factors that preclude generalized recommendations.

However, **there may be instances** where one can use previously derived clinical and nonclinical data for existing approved antimicrobial agents as "benchmarks" for determining the PDTs of agents from the same class, or for drug combinations where one component restores the potency of a previously well characterized antimicrobial (e.g., approved beta-lactam when combined with a beta-lactamase inhibitor). In these cases, the extent of bacterial killing and PDTs in nonclinical models with humanized exposures of an **existing approved agent may provide a "benchmark" target for the new agent from the same class.**

Continued on next slide…

: Note-bolded phrases** are for clarity here, and not actually suggested for use in the final guidance*

Suggested new text: *Lines 419-35 (2 of 2)*

… continued from prior slide

The sponsor should provide justification of PDTs selected for use in analyses of PTA by considering **clinical endpoints, disease severity, burden level of the pathogen, and drug specific properties**. Furthermore, the sponsor can consider additional aims in the justification of the magnitude of the PDT, such as minimizing the risk of selecting for resistance (10,18, 28), rapidity of response to treatment, or specific patient populations (e.g., profoundly neutropenic).

: Note-bolded phrases** are for clarity here, and not actually suggested for use in the final guidance*

Summary

- E-R relationships in non-clinical models **can produce different levels of reduction in bacterial counts** depending on drug and model factors
- Many considerations preclude designation of specific target levels of bacterial reduction and linkage to clinical outcomes in human infection. **Thus, the final guidance should NOT prescribe specific thresholds in nonclinical models for specific infection sites or uses in humans**
- Prior experience from both nonclinical and clinical studies can **benchmark existing classes** and can be used **to develop a PK-PD bridge** to new agents from these existing drug classes
- **Sponsor has burden of developing justification** for specific levels of bacterial killing based on the totality of both nonclinical and clinical data

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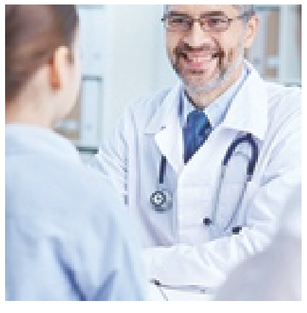
Thank you!





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