Pharmacokinetics and Pharmacodynamics as a Decision Support Tool for Setting BPs: A Workshop on Basic Concepts and Use

January 8, 2011 3:30-6:30pm

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- Antibiotic PK-PD, Clinical Efficacy, and Breakpoints: An overview of how they are used in breakpoint decisions (***Mike Dudley)***
- Pharmacokinetic data for BP analysis ***(George Drusano)***
- Pharmacodynamic Data from Mice and Men: Use and Calibration of Animal Models for BP Analysis ***(William Craig)***
- Simulations and PK-PD Data for BP Assessment and Decisions ***(Sujata Bhavnani)***
- Putting it all together: an example ***(Paul Ambrose)***
- Q&A/Discussion

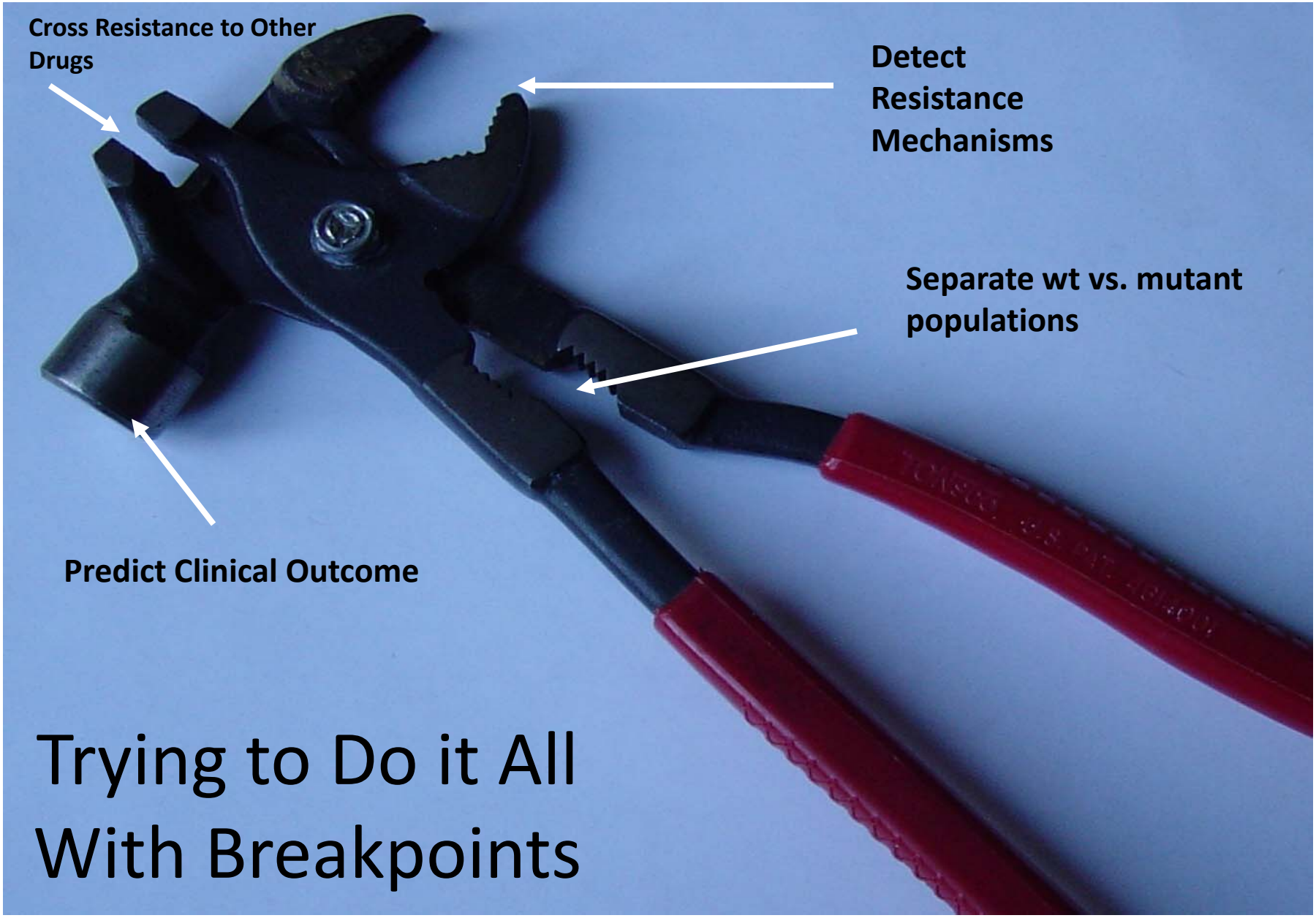
Antibiotic PK-PD, Clinical Efficacy, and Breakpoints:

Overview of Considerations and Use in Breakpoint Decisions

Michael N. Dudley, PharmD, FCCP, FIDSA
Senior Vice President, Research & Development and
Chief Scientific Officer

San Diego, CA
www.mpexpharma.com
mdudley@mpexpharma.com

What Do We Want a Susceptibility Breakpoint to Do?



Trying to Do it All With Breakpoints

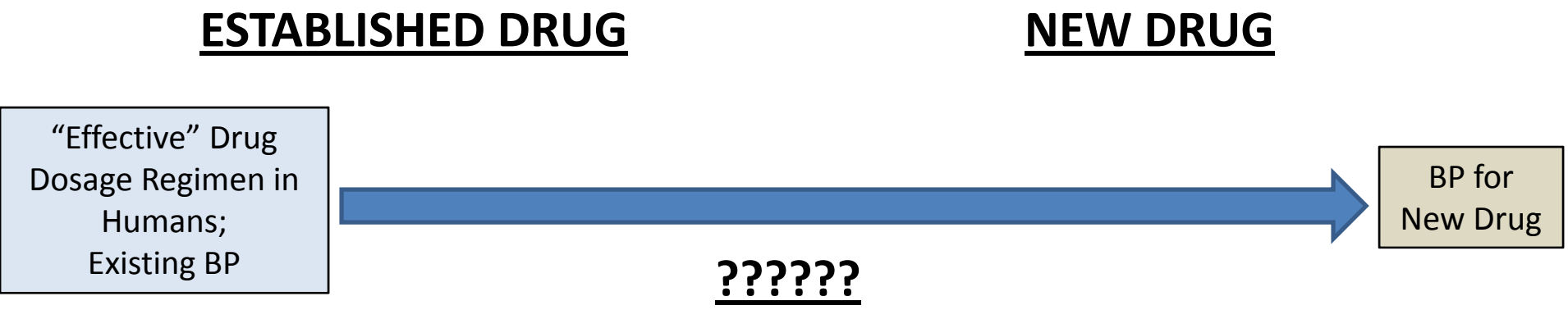
What Do We Want a "Clinical" Breakpoint to Do?

Identify patient isolates by MIC

for which there is a high probability of clinical response

to a properly dosed antimicrobial agent.

Old and New Members of Drug Class and the "Level the Playing Field"



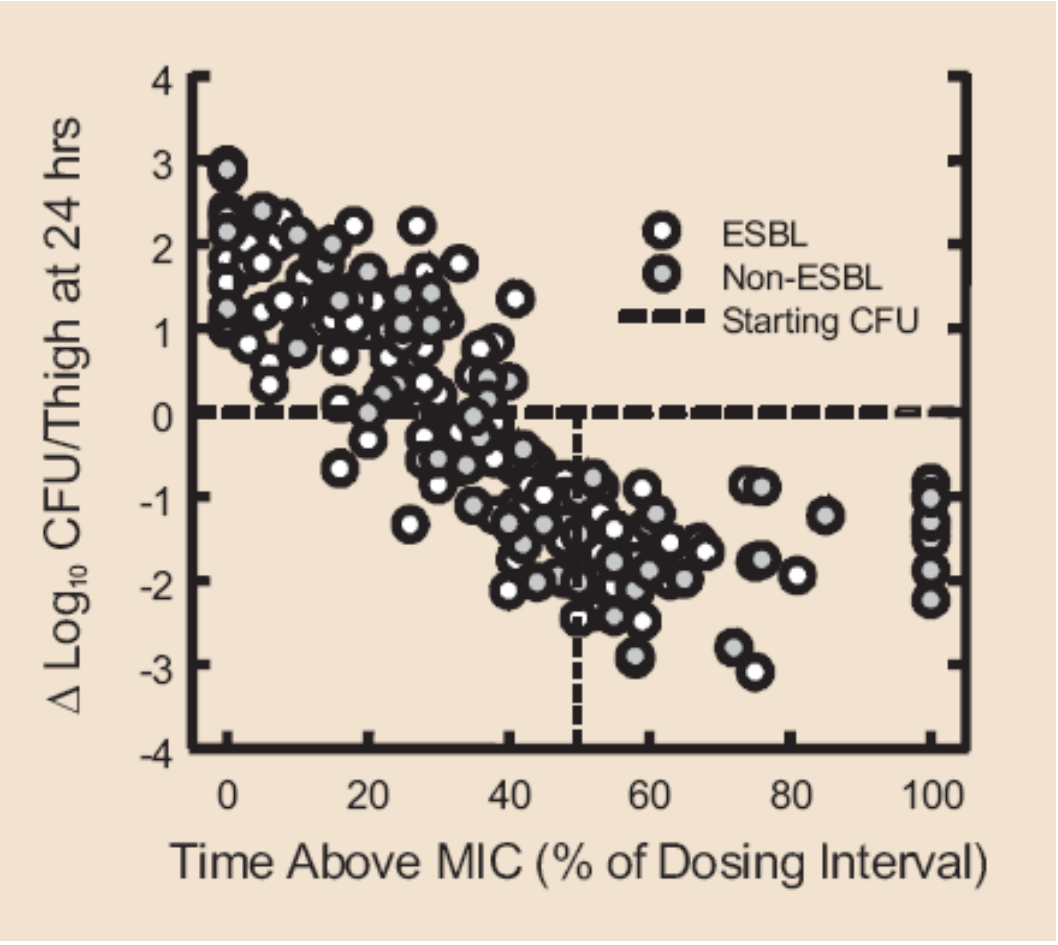
- The level playing field CANNOT ignore important differences in drug pharmacology
- Need to consider important differences in pharmacokinetics and dosage regimen

What are the Assumptions When Using PK-PD as a Support Tool?

- There is a relationship between antimicrobial drug concentration, and effect (bacterial killing)
  - *We know this from MICs, timed-kill curves, dose response experiments*

- PK-PD indices for a drug are known
  - Reasonable (or quantifiable) variability in target index among strains
- In raising the MIC, all resistance mechanisms are created equal
  - *Example: ESBLs are no different than other beta-lactamases*

Cephalosporin Exposure-Response In Vivo
ESBL Versus Non-ESBL Producing Strains



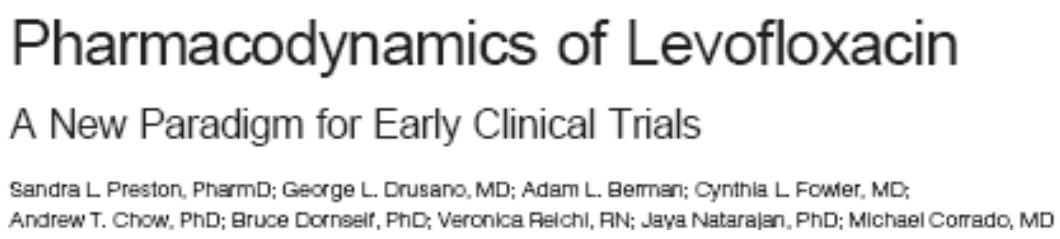
Key message: When adequate concentrations of drug are provided, ESBL and non-ESBL producing strains share the same exposure-response curve.

There is no hidden, "mystery" behind ESBL-producing strains (i.e., "it's all about the MIC")

Ambrose PG, Bhavnani SM, Jones RN, Craig WA, Dudley MN. Use of PK-PD and Monte Carlo Simulation as Decision Support for the Re-Evaluation of NCCLS Cephem Susceptibility Breakpoints for Enterobacteriaceae [abstract A-138]. 44th ICAAC; Washington; 2004 Oct 30-Nov 2. Washington.

Why is Achieving this Goal so Difficult?

- We have imperfect (poor) datasets from registration trials of new antibiotics



Pharmacodynamics of Levofloxacin

A New Paradigm for Early Clinical Trials

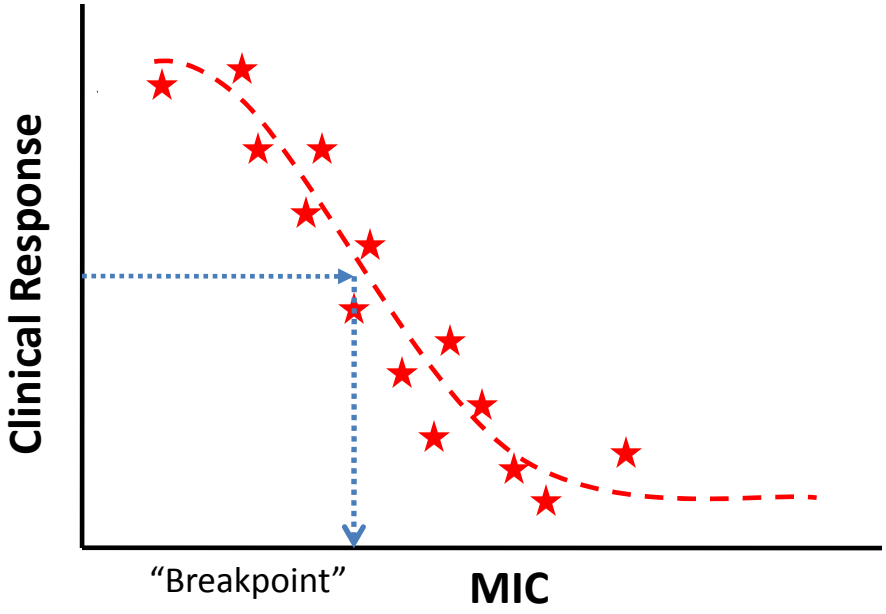
Sandra L. Preston, PharmD; George L. Drusano, MD; Adam L. Berman; Cynthia L. Fowler, MD; Andrew T. Chow, PhD; Bruce Dornseif, PhD; Veronica Reichl, RN; Jaya Natarajan, PhD; Michael Corrado, MD

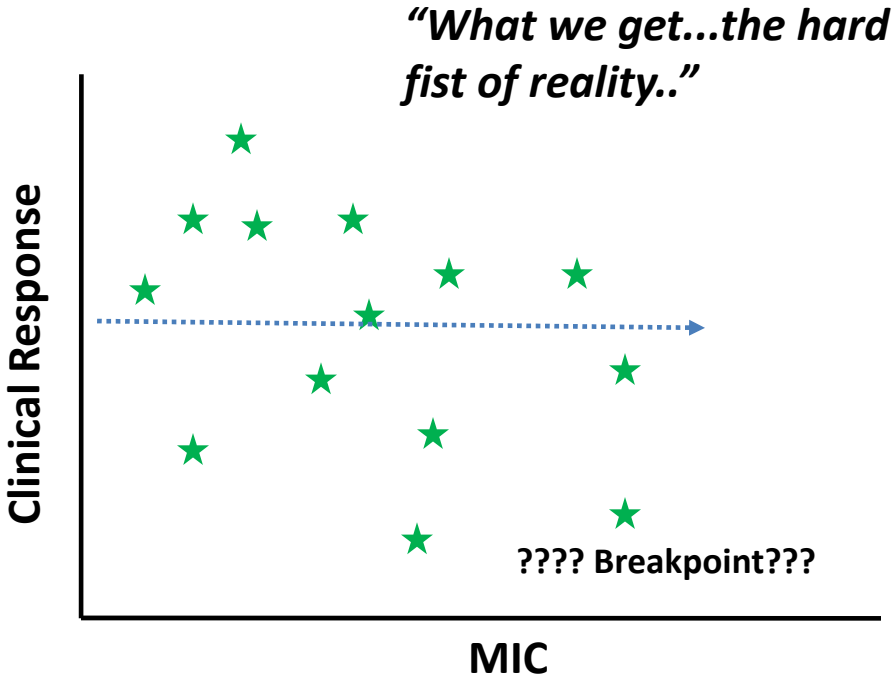
  - Despite Drusano's 1998 landmark study in JAMA with levofloxacin where PK , MIC, and response was measured in patients in a prospectively conducted clinical trial, most clinical trials don't provide sufficient information to set breakpoints
- No chance for good data with old drugs.....

What is the Perfect Dataset for "Clinical Breakpoints"?

- Assume NO inter-patient PK variability
  - For a given dose, all patients have the same Cmax, AUC, half-life
    - Dose is a good control of exposure
- Trial design
  - All patients treated with the same dose
  - MICs performed at baseline
  - Clinical and microbiological outcomes assessed
  - Clinical, Micro response rate by MIC

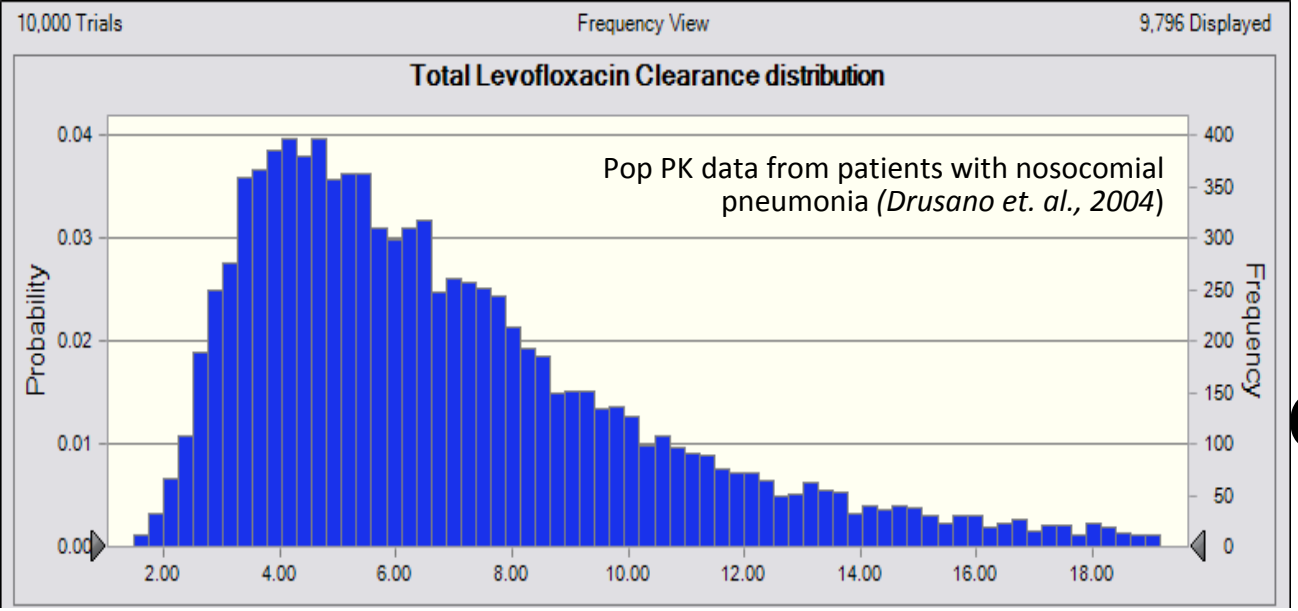
Why Won't Clinical Data Tell Us What We Want to Know?



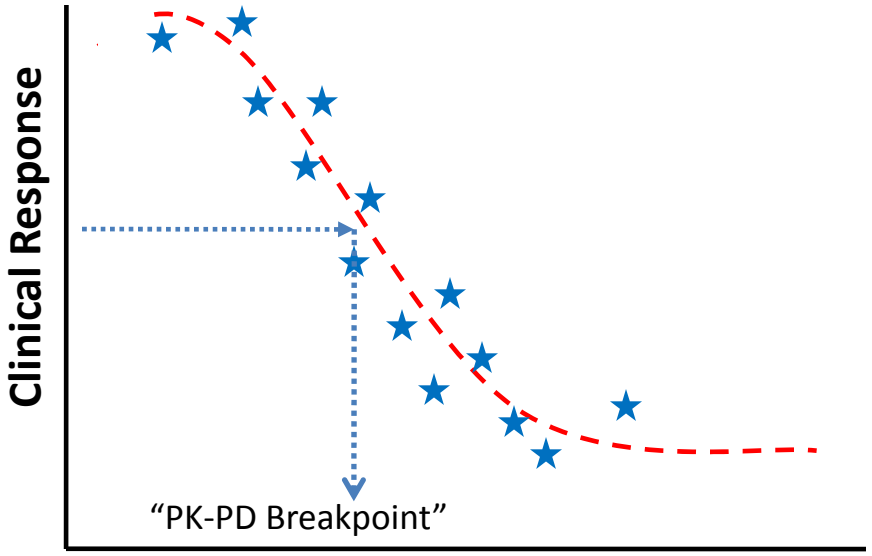


- Ideas?

PK Variability Obscures Our Ability to "See" Clinical Response by MIC



Individual Patient Levofloxacin Serum Clearance



- Assuming everybody has the same PK will inevitably fail to reveal a clinical breakpoint.
- While the analysis at the left identifies the critical level of exposure, we still need to account for PK variability in choosing the MIC breakpoint for a dosage regimen (see later)

Clinical PK-PD vs. Clinical Data
A False Dichotomy

- PK-PD is a tool that helps us get to the information in the clinical data we all want to see

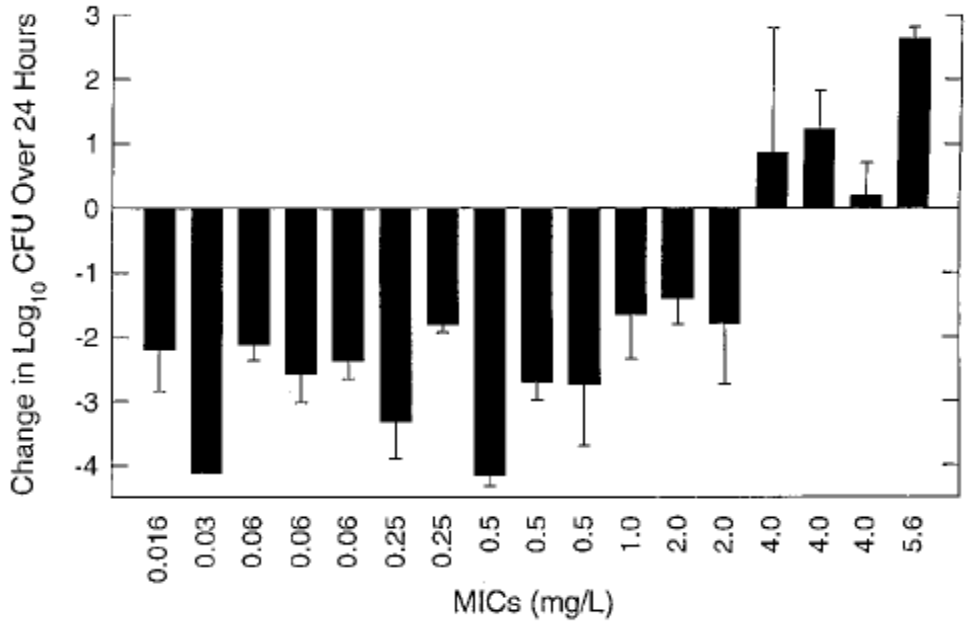
- Clinical trials *sometimes* are appropriately designed and have sufficient data to identify these relationships
  - When unavailable, we have to "cobble" the story together
  - *Examples:*
    - Normal volunteer vs. patient pharmacokinetics (often case with old drugs)
    - Many papers do not describe clinical outcome by MIC or by dose!!
      - Please!- In writing or editing papers, make sure authors include information on MICs (not just outcome by susceptible or resistant--which breakpoints!!??)
      - Please! Include dosing information in analysis of response by MIC!

What About Preclinical Data?

- Impressions from the gallery
  - "Breakpoints are all based on mouse data..."
  - "Is it 1-log or 2-log drop that is important?"
- Importance Elements of Animal Data
  - Tests the MIC vs. resistance mechanism on in vivo response
  - "Humanized PK" can identify suboptimal result based on PK

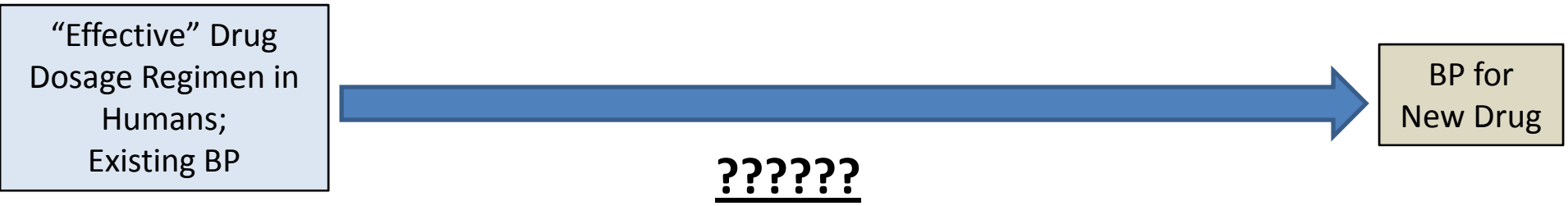
Amoxicillin and pneumococci

Andes & Craig, AAC 1998



Animal PK-PD Can Help "Bridge" Between Old and New Members of Drug Class and "Level the Playing Field"

ESTABLISHED DRUG **NEW DRUG**



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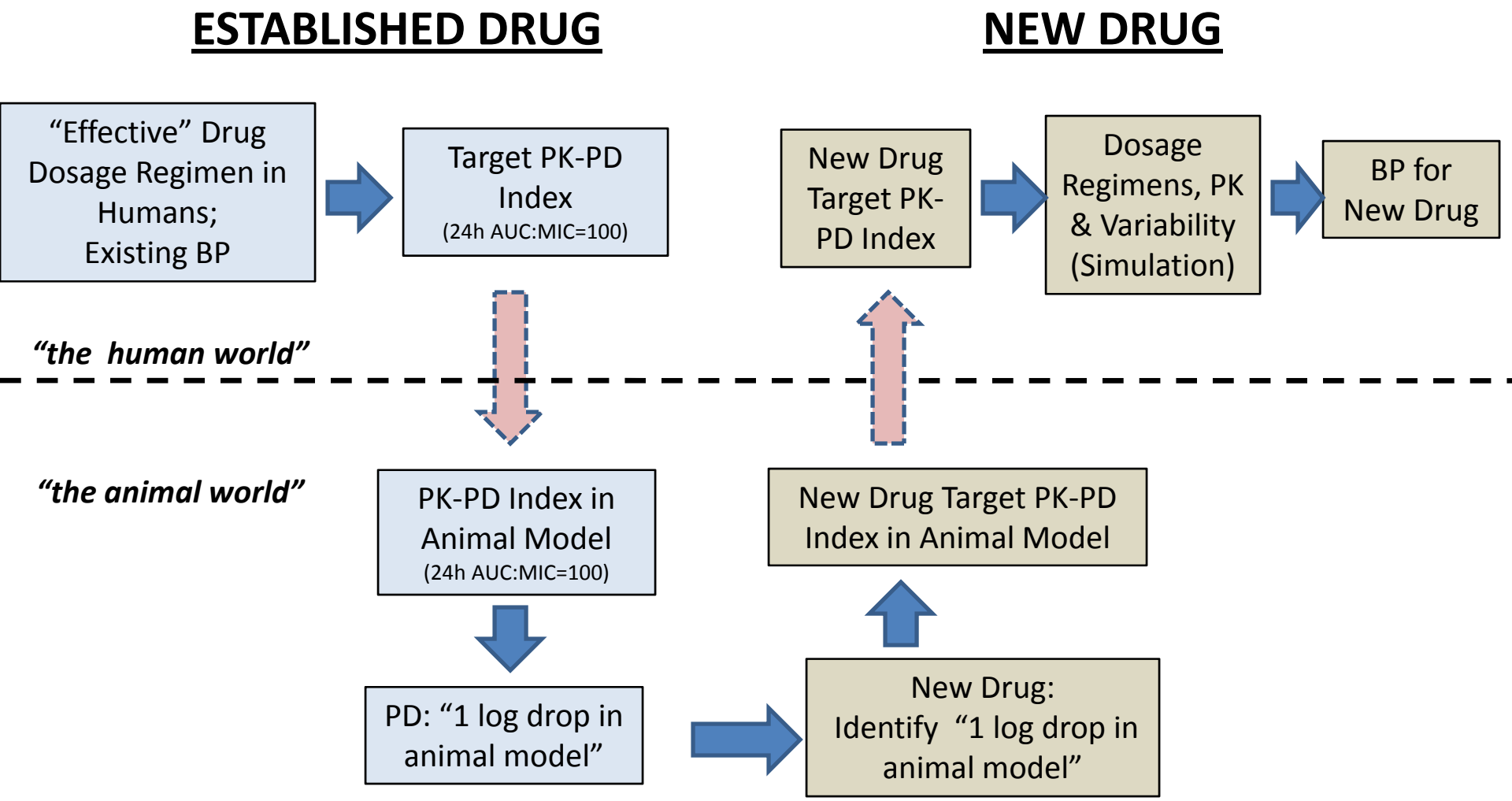
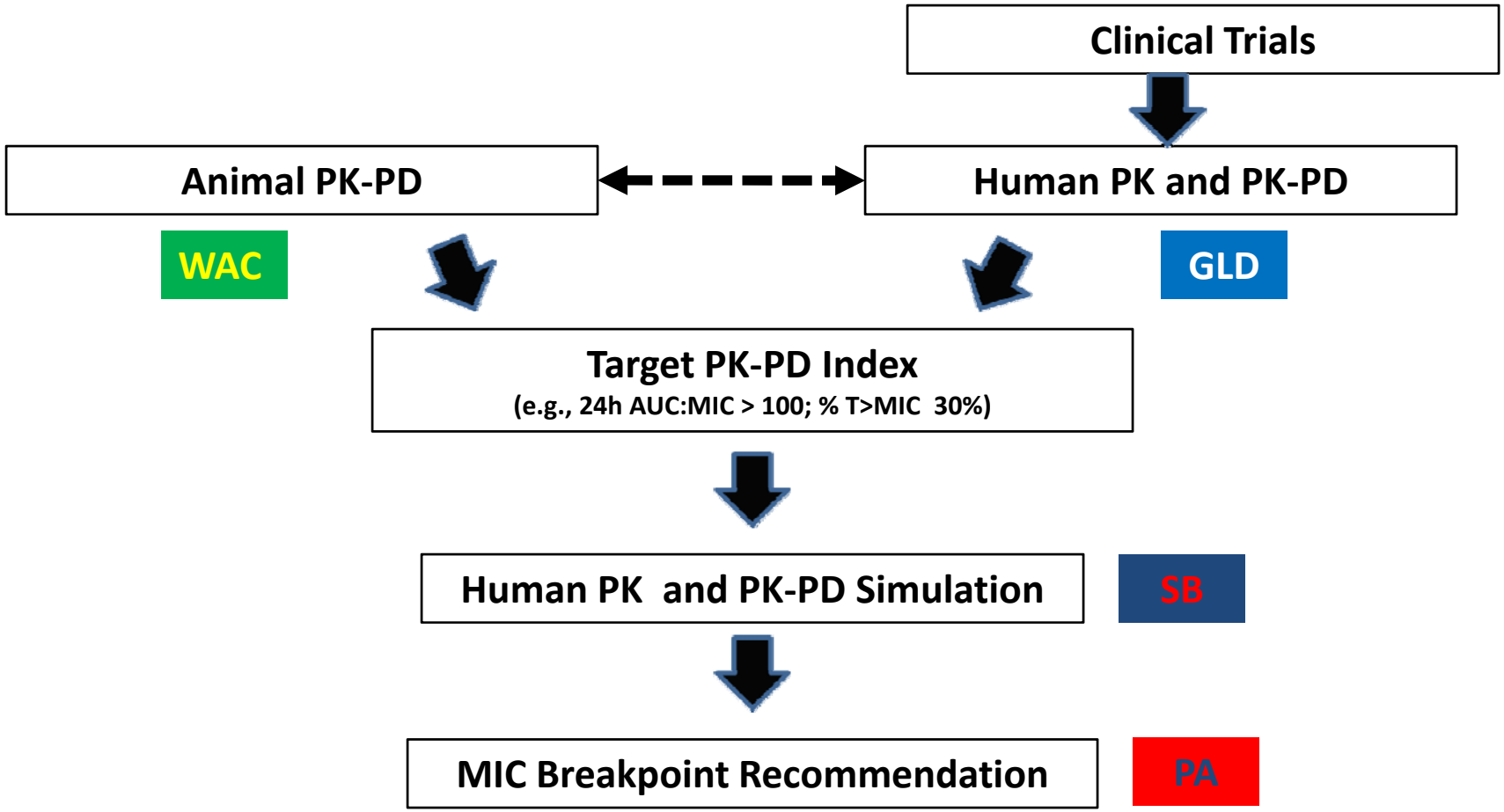


PK-PD as Decision Tool For BP Decisions

How Does it Fit Together?



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