ENGELBERG CENTER for Health Care Reform at BROOKINGS

Modernizing Antibacterial Drug Development and Promoting Stewardship

Engelberg Center for Health Care Reform
The Brookings Institution
Washington, D.C.
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Global Medicines Department, AstraZeneca

What are the essential requirements for a "pathogen-focused" program (or indication)?

- A program (indication) addressing **unmet need**

in which

- **Evidence of efficacy for a dosing regimen**

is based on

- Strong **PK-PD exposure-response predictions**

combined with

- **Limited clinical efficacy data**

possibly requiring pooling of

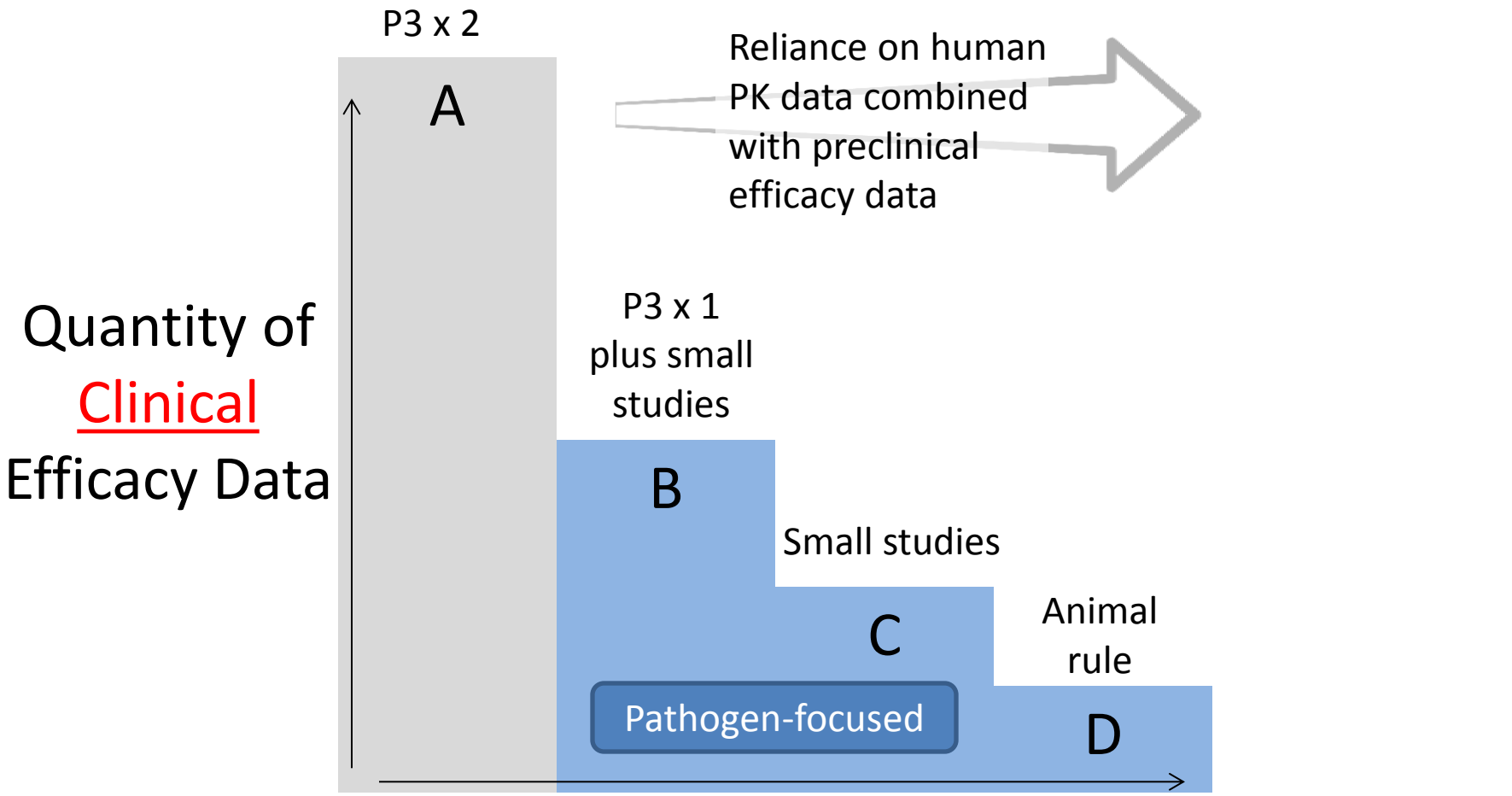
- Data gathered from **multiple body sites.**

Pathogen-focused pathways: Why do we need them?

- Enables development ahead of the epidemic
  - Large programs require substantial numbers of infected individuals
- Some agents can't otherwise be developed
  - By definition, programs focused on less common pathogens are limited in size
- Facilitates stewardship
  - Focused program → focused label → focused use
  - Consistent with draft legislation (ADAPT Act as proposed Dec. 2013)
- Reduced program cost & time
  - The economics of antibiotics are difficult
  - Program cost & time can be make or break

Pathogen-focused development

Taxonomy V1.0: The four tiers



Acceptance of smaller clinical datasets (often merged across body sites) in response to unmet medical need

Rex et al. Lancet Infect Dis 2013; 13: 269-75

Taxonomy V2.0 – Practical Applications

Five subcategories emerge

- NARROW(ER)-SPECTRUM AGENT
  - Relevant infection syndromes are truly monomicrobial OR relevant infection syndrome(s) are polymicrobial but is possible to show activity by adding Test drug to empirical combinations that otherwise lack activity. Two cases, one example for each:
    - **Tier B/Narrow-spectrum:** Agent for *N. gonorrhoeae*. Common pathogen. Approached as Tier B as a standard Phase 3 study of genitourinary gonorrhea. Depending on the comparator in the standard P3 study, it might be possible to enroll some types of resistant pathogens in this program OR it might be necessary to supplement with a program focused on enrolling highly resistant strains.
    - **Tier C/Narrow-spectrum:** Agent for *Acinetobacter*. Rare pathogen, always difficult. Approached as a Tier C program across multiple body sites. A small randomized study of a carbapenem + Test vs. Best Available Therapy readily shows activity of Test when the infecting *Acinetobacter* isolate is carbapenem-resistant.
- BROAD(ER)-SPECTRUM AGENT (developer focus on a specific organism or type of resistance)
  - Relevant infection syndrome(s) can be treated as monotherapy. Two cases, one example each:
    - **Tier B/Broad-spectrum/Multi-pathogen development:** Agent covering *Enterobacteriaceae* and approached as a Tier B program as a standard site Phase 3 study (e.g., intraabdominal infection) that would mostly enroll susceptible pathogen cases and that is supplemented with a program enrolling highly resistant strains.
    - **Tier C/Broad-spectrum/Single-pathogen development:** Agent covering *Enterobacteriaceae* but approached as Tier C and studied as if only active against a single specific difficult pathogen or mechanism of resistance.
- EXISTING AGENT WITH SPECIAL CIRCUMSTANCE INDICATION
  - **PK-PD-based modification:** Indication of a specific dosing regimen for a specific pathogen (e.g., higher dose for species with higher MICs). Requires PK-PD rationale, safety data at specific dosing regimen, and at least some consistent clinical data. The dosage modification may be limited to an indication or span indications.

Taxonomy V2.0 – Difficulties

- NARROW(ER)-SPECTRUM AGENT/Empirical monotherapy not possible
  - Relevant infection syndrome(s) are polymicrobial and it is difficult or impossible to show activity by adding new drug to empirical combinations that otherwise lack activity
  - **Example:** A narrow-spectrum agent for *K. pneumoniae.*
  - Without a stunning rapid point-of-care diagnostic, I see only three possible routes, all difficult:
    - Enroll after brief course of empirical therapy when it becomes apparent that a given infection is actually monomicrobial. Probably a small study.
    - Seek a setting where highly MDR strains (e.g., KPC *K. pneumoniae*) is so common that Test + carbapenem vs. colistin + carbapenem (or similar) makes sense and is likely to accrue a reasonable rate of MDR isolates. Probably a very small study.
    - Register as Tier D (animal rule): animal model efficacy + human PK and safety data
  - We need to talk about this one!
- NARROW OR BROAD AGENT/Must be used in combination but is not co-formulated
  - Reliable therapy requires a combination
  - **Example:** MICs of Test for relevant pathogens go from 1 to 0.01 when given with an aminoglycoside
    - This ideas is similar to testing a beta-lactam – beta-lactamase-inhibitor combination
  - Approach by treating the combination as a fixed entity that is only ever used in combination
- ANTIBODY-BASED THERAPEUTICS
  - Our understanding of PK-PD is less mature – how much can we rely on this approach?

Key enabler: Diagnostics

- The holy grail: We want to get as close as possible to
  - Rapid &
  - Point-of-care
- A diagnostic can most usefully
  - Make a diagnosis or detect a resistance mechanism
  - Make a *different* diagnosis
- Don’t expect perfection
  - Ruling out a diagnosis is hard
  - Empirical therapy will still be needed at times

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Christine Murray, Vice President,
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ACHAOGEN

PLAZOMICIN

An Example of a Streamlined Drug Development Program to Address an Unmet Medical Need

February 2014

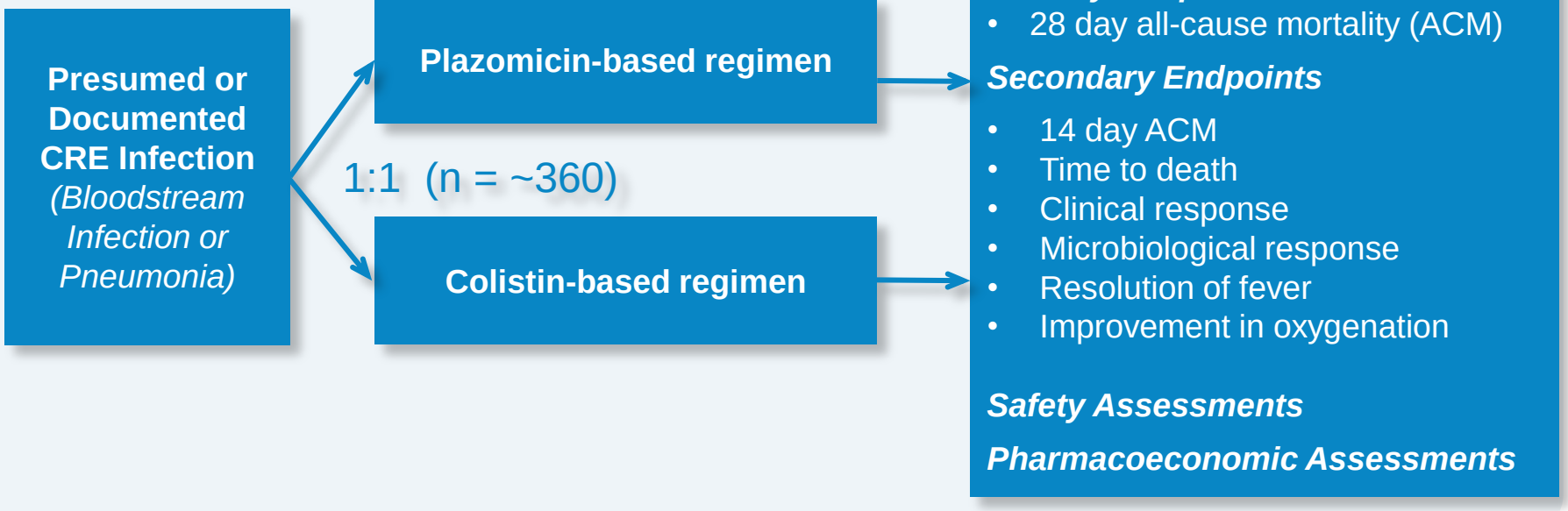
A Streamlined Development Program to Address an Unmet Medical Need

- Plazomicin, a novel aminoglycoside, engineered to overcome clinically relevant aminoglycoside resistance mechanisms
- Plazomicin's development program is focused on the treatment of serious bacterial infections due to multi-drug resistant (MDR) Enterobacteriaceae, including carbapenem-resistant Enterobacteriaceae (CRE)
  - Evidence-based rationale for Phase 3 includes in vitro activity, efficacy in animal models, and PK/PD exposure-response analyses
  - Phase 3 study will be conducted in the target unmet need population (i.e., patients with serious CRE infections)
  - A safety database of at least 300 patients is targeted to support initial registration
- Program is funded in part by a contract from the Biomedical Advanced Research and Development Authority (BARDA)

CARE (ACHN-490-007) Study Design Overview

COMBATING ANTIBIOTIC-RESISTANT ENTEROBACTERIACEAE

- *Pathogen-focused*
- *Randomized superiority study*
- *Primary mortality endpoint*



CARE (ACHN-490-007) Study Design
Key Features

- Selecting for patients most likely to demonstrate a survival benefit from an effective therapy
  - Patients with bloodstream infections and nosocomial pneumonia and type 2 carbapenem MIC ≥ 4 μg/mL
  - Meta-analysis of mortality in patients with carbapenemase-producing Enterobacteriaceae bloodstream infections supports study hypothesis of improvement in mortality
  - APACHE score between 15 and 30
- Both presumed and confirmed CRE infections will be enrolled if ≤72 hrs of empiric therapy.
  - Presumed infections are those with a high probability of being CRE based on diagnostic testing (eg, mass spectrometry or molecular testing)

New Paradigm for Antibacterial Drug Development Regulatory Considerations

- New regulatory guidance supportive of pathogen-focused approaches and streamlined programs:
  - FDA Guidance "*Antibacterial therapies for patients with unmet need for the treatment of serious bacterial diseases*"
  - EMA guidance *"Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections*"
- For sponsors, close interactions with Regulatory Agencies are critical to ensure alignment on a common development plan, details of study design, and smooth clinical trial application process
  - Study Design → FDA Special Protocol Assessment procedure, EMA Scientific Advice procedure
  - Clinical operations requires global reach → multiple regulatory agencies, national and local Ethics Committees and principal investigators

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Paul G. Ambrose, President,
Institute for Clinical Pharmacodynamics

PHARMACOMETRICS

An Opportunity to Increase the Certainty and Efficiency of Antibiotic Development Programs

7 February 2014

Paul G. Ambrose, Pharm.D, FIDSA
Institute for Clinical Pharmacodynamics
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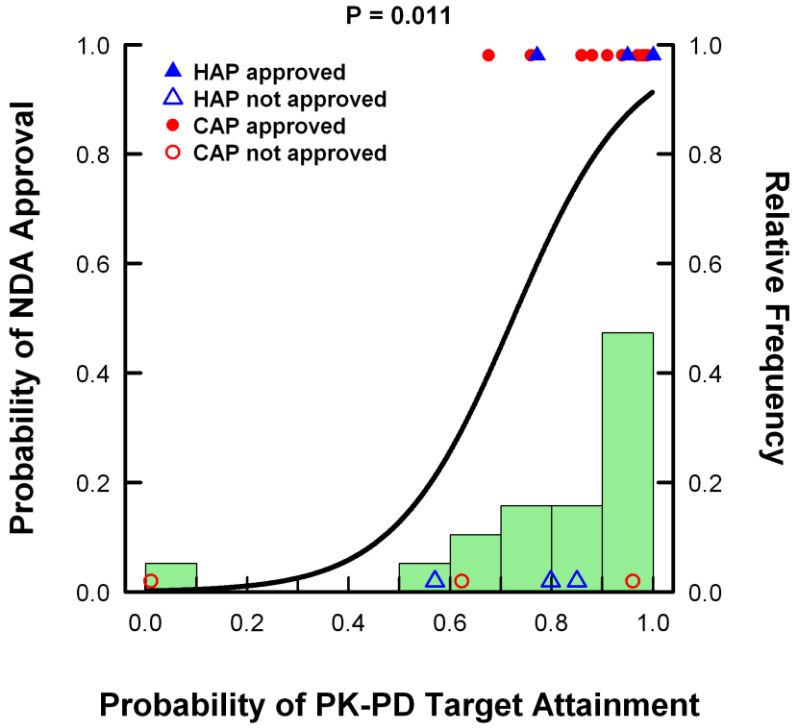
ICPD®
INSTITUTE FOR CLINICAL PHARMACODYNAMICS

PK-PD INFECTION MODELS
Do They Forecast Regulatory Approval?

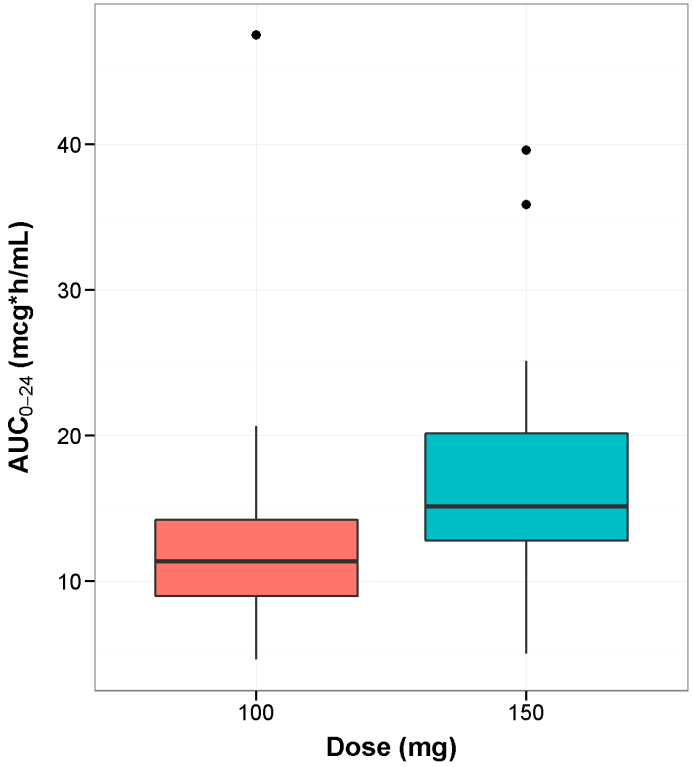


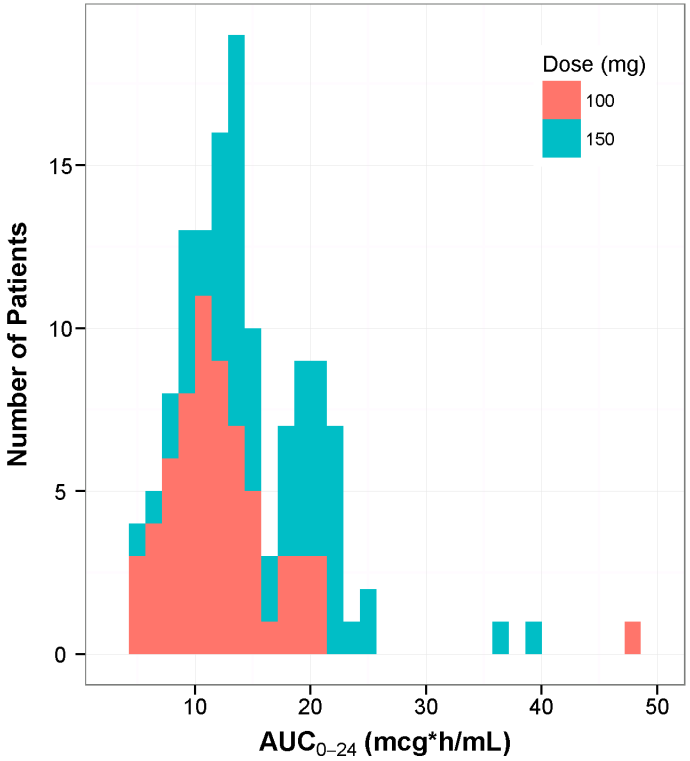
- Relationship between the regulatory approval and the probability of pre-clinical PK-PD target attainment (1996-2011)[1]
- Indications included community- and hospital-acquired pneumonia
  - 17 antibiotics in total, with 14 regulatory approvals and 6 failures

The Answer: YES! We can increase our probability of regulatory success by selecting PK-PD optimized dose regimens

1. Bulik CC, Bhavnani SM, Hammel JP, Forrest A, Dudley MN, Ellis-Grosse EJ, Drusano GL, Ambrose PG. Evaluation of the Probability of Regulatory Approval Based on Pre-Clinical PK-PD Target Attainment For Community-Acquired and Hospital-Acquired Pneumonia. A-295. 53rd InterScience Conference on Antimicrobial Agents and Chemotherapy. September 10-13, 2013, Denver CO.

TRADITIONAL PHASE 2 STUDIES
Can They Really Discriminate an Effective Dose?

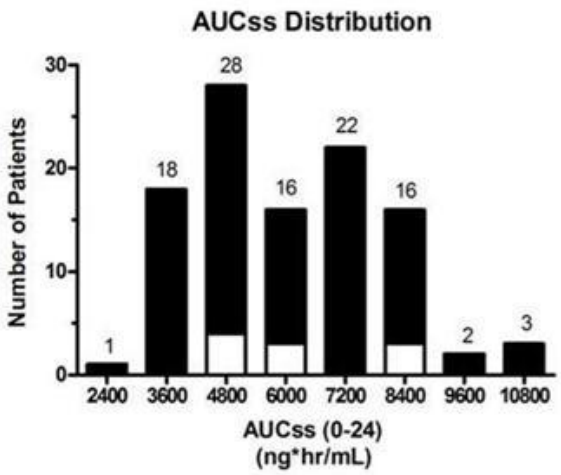


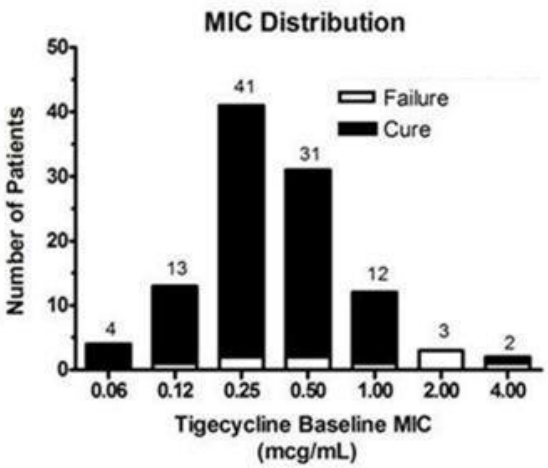


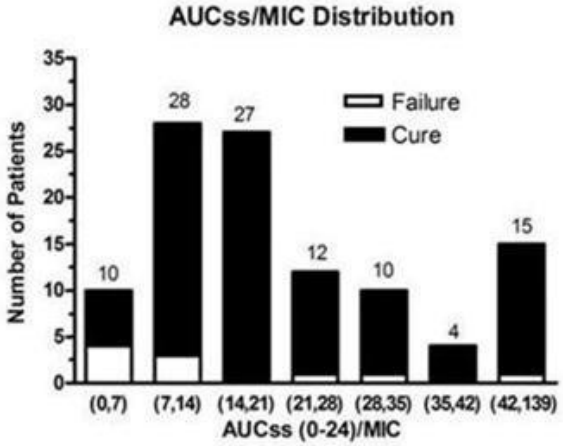
The Answer: It is impossible to discriminate between regimens by dose for PK-PD optimized regimens

Rubino CM, Xue B, Bhavnani SM, Prince WT, Ivezic-Schoenfeld Z, Wicha WW, Ambrose PG. Population pharmacokinetic analyses for BC-3781 using phase 2 data. ICAAC 2011, Abstract A2-024

EXPOSURE-RESPONSE
What Exposure Measure Drives Response?





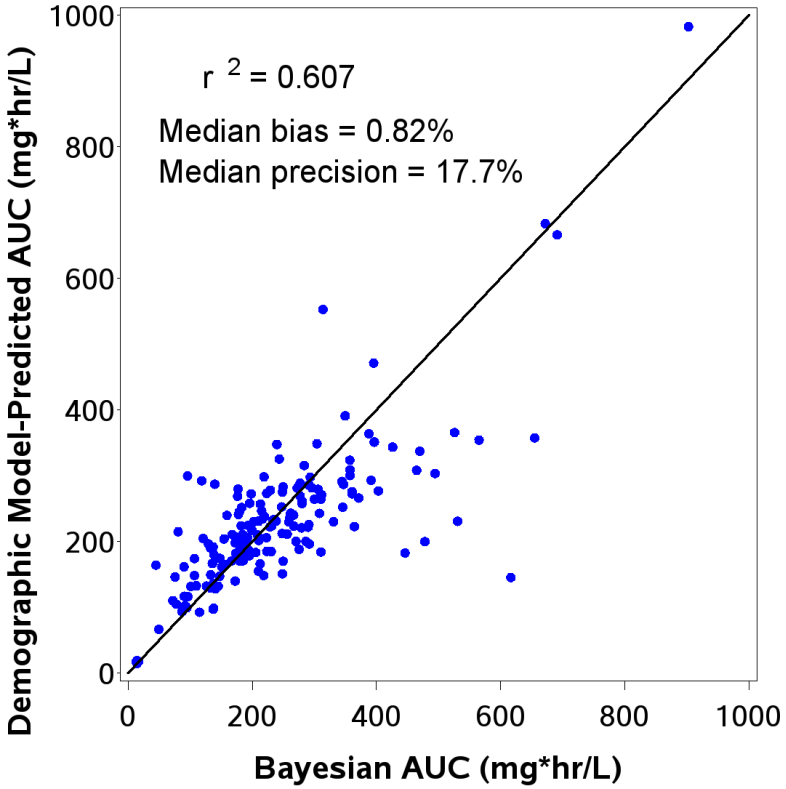


The Answer: Drug exposure indexed to MIC best captures the relationship between exposure and response

Ambrose PG, Bhavnani SM, Ellis-Grosse E, Drusano GL. PK-PD considerations in the design of hospital-acquired and ventilator-associated pneumonia: look before you leap! *Clin Infect Dis*. 2010;51(S1):103-110.

PHARMACOMETRICS

Does Drug Exposure Behave as a Baseline Variable?



The Answer: Yes! We can often predict exposure without bias with information known at baseline

Van Wart SA, Forrest A, Drusano GL, Bhavnani SM, Bulik CC, Kostrub CF, Ambrose PG, Louie A. Pharmacokinetic-pharmacodynamic analysis predicts a high probability of efficacy for plazomicin against serious infections caused by carbapenem-resistant Enterobacteriaceae. 52nd European Congress of Clinical Microbiology and Infectious Diseases. Berlin, Germany. April 27-30, 2013. [Abstract No. P 914].

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Joseph G. Toerner, Associate Director for Medical Affairs,
Office of Antimicrobial Products, CDER, FDA

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Afternoon Session: Facilitating Prudent Use of Commonly Prescribed Antibacterial Drugs – Stewardship and Benefit-Risk Considerations

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Review of Placebo-Controlled Trials

- ABS, ABOM, ABECB-COPD
  - Literature review
    - ABS: 19 trials, 5 showed treatment difference
    - ABOM: 12 trials, 5 showed treatment difference
    - ABECB: 15 trials, 6 showed treatment difference
  - Approximately 60% to 75% of the trials did not show a treatment difference over placebo
  - AIDAC: recommended placebo-controlled trials

ABS Hadley, et al, Laryngoscope 2010;120:1057-62

Efficacy MITT = 118	Placebo	Drug	Difference
Clinician improvement/ resolution	66.7%	78.1%	11.4% (P>0.05)
Symptom improvement (secondary)	42.4%	58.9%	16.5% (P>0.05)
Safety	**Placebo**	**Drug**	
Overall AE	6.9%	13.5%	
SAE	0	0	

ABECB Echols, et al, 48th ICAAC Abs L-662a

Efficacy	Placebo	Drug	Difference
Clinician improvement/ Resolution (ITT;N=398)	71%	80%	9% (P=0.05)
Clinician improvement/ Resolution (micro;N=163)	64%	80%	16% (P=0.03)
Safety	**Placebo**	**Drug**	
Worsening respiratory symptoms or pneumonia	4%	2%	

ABOM

Hoberman et al, NEJM 2011;364:105-15 (1)
Tähtinen et al, NEJM 2011;364:116-26 (2)

Efficacy	Placebo (1)	Drug (1)	Placebo (2)	Drug (2)
Parent reported outcome	54%	61% (P>0.05)	86%	93% (P>0.05)
Use of rescue antibacterial drugs (secondary)	23%	4%	33.5%	6.8%
Safety	**Placebo (1)**	**Drug (1)**	**Placebo (2)**	**Drug (2)**
Diarrhea	7%	24%	27%	48%
Perforated TM	4%	<1%	3%	<1%
SAE	1 (mastoiditis)	0	2 (pneumonia; bacteremia	0

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