Novel Approaches to Further Antibacterial Drug Development: New Approaches to the Clinical Development Program

An industry view

John H. Rex, Infection Clinical Vice President

AstraZeneca Pharmaceuticals

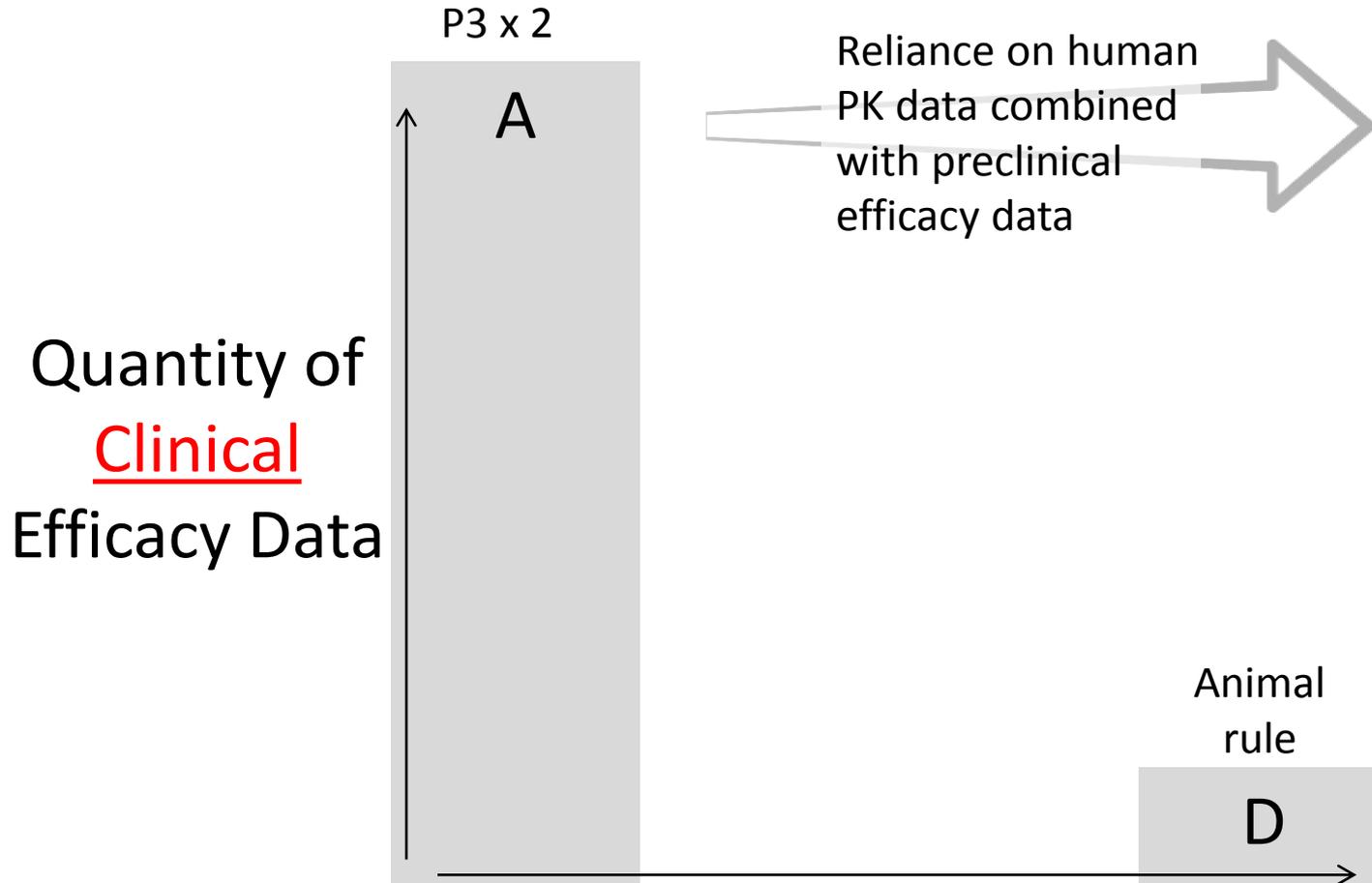*john.rex@astrazeneca.com*

The paradigm gap

- For registration, we traditionally expect
  - Two substantial trials per indication (e.g., two UTI trials)
  - Typical size & cost/trial: ~1,000 patients, ~$50-70m

- This presumes ready availability of substantial numbers of patients with the target disease

- But, what if the target disease includes requirement for a specific less common pathogen or type of resistance?
  - Less common pathogen: *Pseudomonas*
  - Emerging form of resistance: KPC or Metallo-ß-lactamase

- When only limited clinical data are possible, current paradigms give no easy way forward
  - Waiting for widespread resistance means we can't anticipate the epidemic
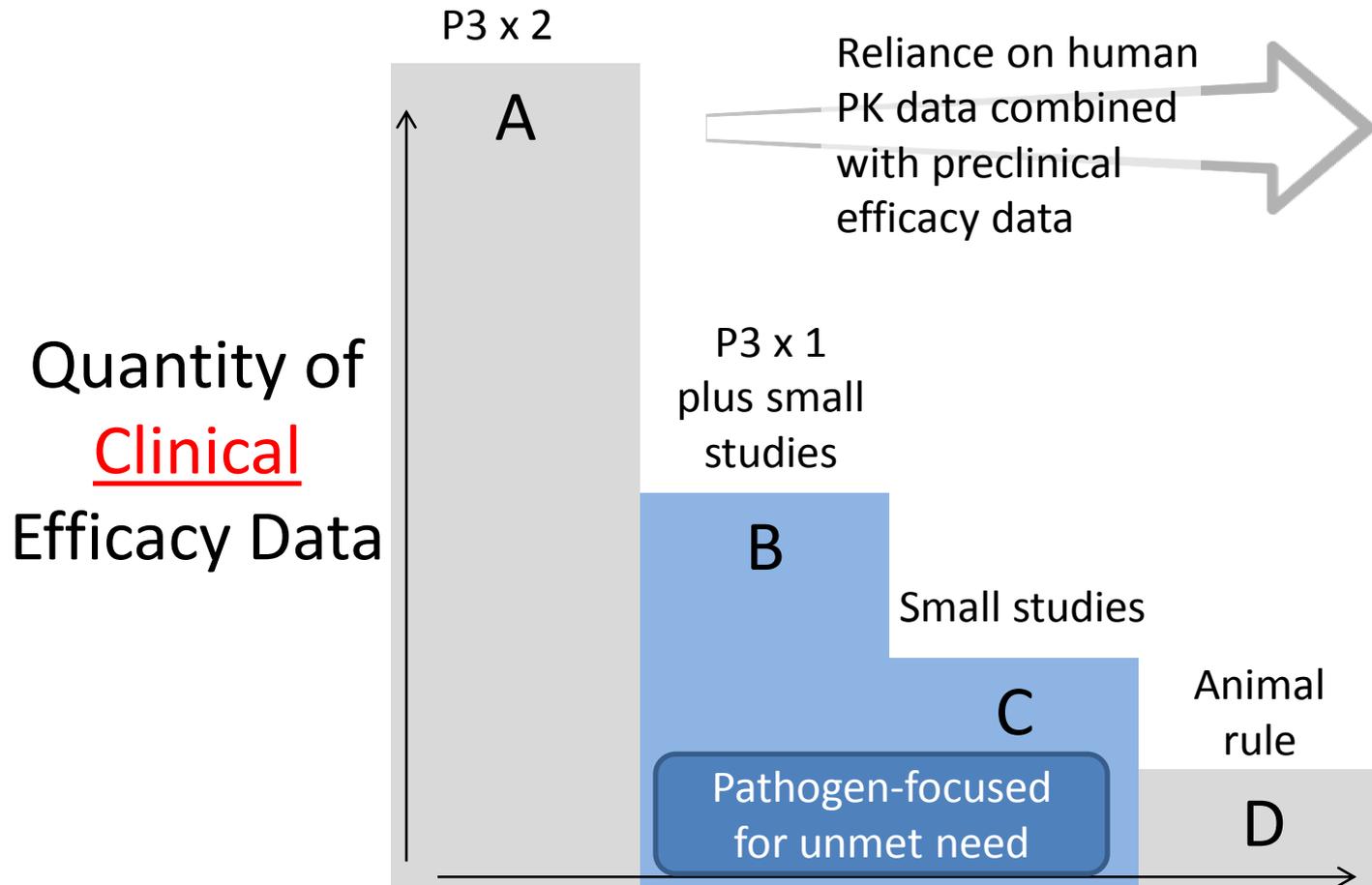
Addressing unmet need via Four Tiers
A & D are familiar...

P3 x 2

A

Reliance on human PK data combined with preclinical efficacy data

Quantity of **Clinical** Efficacy Data

Animal rule

D

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

Addressing unmet need via Four Tiers
A & D are familiar, B & C are new

P3 x 2

A

Reliance on human PK data combined with preclinical efficacy data

Quantity of
Clinical
Efficacy Data

P3 x 1 plus small studies

B

Small studies

C

Animal rule

Pathogen-focused for unmet need

D

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

Tier Overview: Preclinical

Attribute	Tier B	Tier C
Example spectrum	**Broad** with MDR pathogen coverage	**Narrow** MDR pathogen coverage
Example target pathogen	MDR Enterobacteriaceae (also covers if non-MDR)	*Pseudomonas aeruginosa* **only**
Challenge in studying MDR pathogen in large numbers?	Yes	Yes
Detailed insight into:		
Microbiology including mechanism of action and resistance?	Yes	Yes
Animal models that mimic human disease?	Yes	Yes
Exposure-response in animals?	Yes	Yes

Tier Overview: Clinical

Attribute	Tier B	Tier C
Detailed PK/PD justification of dose selection in humans[1]	Yes	Yes
Can do "standard" P3 study vs. *susceptible* organisms?	Yes[2]	No
Randomized comparative data generated?	Yes (single body site, vs. standard comparator)	Yes (multiple body sites, vs. BAT[3])
Able to do "usual strength" statistical inference testing?	Yes, but only in the standard P3 study	No
Pooling of data across infection sites proposed?	Yes	Yes
Reliance on a totality-of-evidence approach?[4]	High	Even higher

[1]Mechanism of action understood, animal models reasonably mimic human disease at relevant sites, exposure-response in the animal studies informs human dose with adequate margin, PK known in healthy volunteers and relevant patient groups. [2]This provides relevant efficacy data if MDR pathogens have same susceptibility to new agent as do non-MDR pathogens. [3]BAT = Best Available Therapy, standardized insofar as possible. [4]All drug reviews consider the totality of evidence, but the reliance on such things as PK-PD predictions and pooled responses across sites will be very high here.

Tier B/C Development Programs[1]

- **Tier B:** Two active treatment studies (one large, one small)
  - Standard Phase 3 study of Drug B vs. standard comparator at standard body site
    - No expectation of enrolling any resistant pathogens!
    - Data are relevant because activity of Drug B vs. MDR and non-MDR is the same
  - Open-label salvage study of Drug B for MDR pathogens

- **Tier C:** Two small active treatment studies + one observational study
  - Prospective, randomized, open-label study of Drug C vs. BAT[2] across multiple body sites (Y1, Y2, Y3) in known (or high-risk) MDR settings. N $\cong$ a few hundred
  - Open-label companion salvage study of Drug C for MDR pathogens (no BAT exists)
  - Observational study of (inadvertent) ineffective therapy for the target pathogen (estimates placebo response rate, reference point for active therapy studies)[3]

- Target label (see also detailed examples in appendix):
  - Drug BC is indicated for treatment of *[Y1, Y2, Y3]* when proven or strongly suspected to be caused by Drug BC-susceptible strains of *[list of pathogens]*.
  - As data for Drug BC in these infections are limited, Drug BC should be used only in situations where it is known or suspected that other alternatives are less suitable.

[1]Detailed examples in appendix. [2]BAT = Best Available Therapy, standardized insofar as possible. [3]There is no easy way to provide a good control group: Ineffective therapy does not mean no therapy and also might quickly be replaced with active therapy. One might also use modern data (pharmacometric estimates of placebo response rates: AAC 56:1466, 2012), pharmacometric analyses with the new drug, or historical estimates of true placebo response rates.

Risks

- The ideas of Tier B/C carry risks
  - Small datasets → more risk from patient heterogeneity
  - Often going to be enrolling in settings of serious illness
  - There will be a lot of confounding / confusing signals

- With fewer safety & efficacy data...
  - Less depth for subset analyses to explain small variations
  - Less context for safety signals
  - *Note: Tier B/C is about efficacy. The sponsor may very well need to find ways to supplement the safety database. Model-based drug design ideas[1] may really help here.*

- Adding a single P3 study (Tier B) is really helpful
  - Will enroll only *susceptible* strains of the target pathogen
  - Even so, very useful source of context for data ambiguities
    - Activity against susceptible isolates (and even other species) gives insight
  - Combined with open-label data on resistant strains of the target pathogen, a compelling story for the drug's activity could be made

1. E.g., Lalonde RL, Kowalski KG, Hutmacher MM, et al. Model-based drug development. Clin Pharmacol Ther 2007;82:21-32.

The reason for Tier C
How would you develop this drug?

- Drug C is active vs. *Pseudomonas* and nothing else
  - If Drug C existed, knowing when to use would be simple

- Suitable study arms are possible
  - Drug C + 2nd agent with limited *Pseudomonas* activity (e.g., ertapenem[1]) vs. a suitable comparator arm covering *Pseudomonas*
  - Drug C + ertapenem success for *P. aeruginosa* can be attributed to Drug C

- The problem is the rate of cases of *Pseudomonas*
  - Must usually enroll before culture result becomes available
  - Typical rates: HAP-VAP: 22%[2, 3], cIAI: 11%[4], cUTI: 3%[5]

- This creates a significant trial problem…

[1]Only about 10% of *P. aeruginosa* isolates have an ertapenem MIC below the generally accepted susceptible breakpoint of 1 mg/L. [2]Chastre J et al. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: A multicenter, randomized study. Crit Care Med 36:1089–1096, 2008. [3]Brun-Buisson C et al. Treatment of ventilator-associated pneumonia with piperacillin-tazobactam/amikacin vs. ceftazidime/amikacin: A multicenter, randomized controlled trial. Clin Infect Dis 26;346-54, 1998. [4]Lucasti C et al. Efficacy and Tolerability of IV Doripenem Versus Meropenem in Adults with Complicated Intra-Abdominal Infection: A Phase III, Prospective, Multicenter, Randomized, Double-Blind, Noninferiority Study. Clin Ther 30:868-83, 2008. [5]Naber KG et al. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. Antimicrob Agents Chemother. 53:3782-92, 2009

The painful math

- Assume some typical general parameters
  - An endpoint with about a 20% failure rate
  - A non-inferiority margin of 10%, power of 90%
  - You need ~672 <u>evaluable</u> cases (336/arm)

- Evaluable = <u>culture-proven</u> → so now we need…
  - If 22% *P. aeruginosa*, need 3,064 (1,532/arm)
  - If 11% *P. aeruginosa*, need 6,128 (3,064/arm)
  - If 3% *P. aeruginosa*, need 22,466 (11,233/arm)

- Certainly big enough for the safety database!
  - But, not feasible for actual development
  - Recent HAP-VAP trial took 5 years to enroll ~1,200 pts[1]

1. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in Methicillin-Resistant Staphylococcus aureus Nosocomial Pneumonia: A Randomized, Controlled Study. Clin Infect Dis 2012;54:621-9.
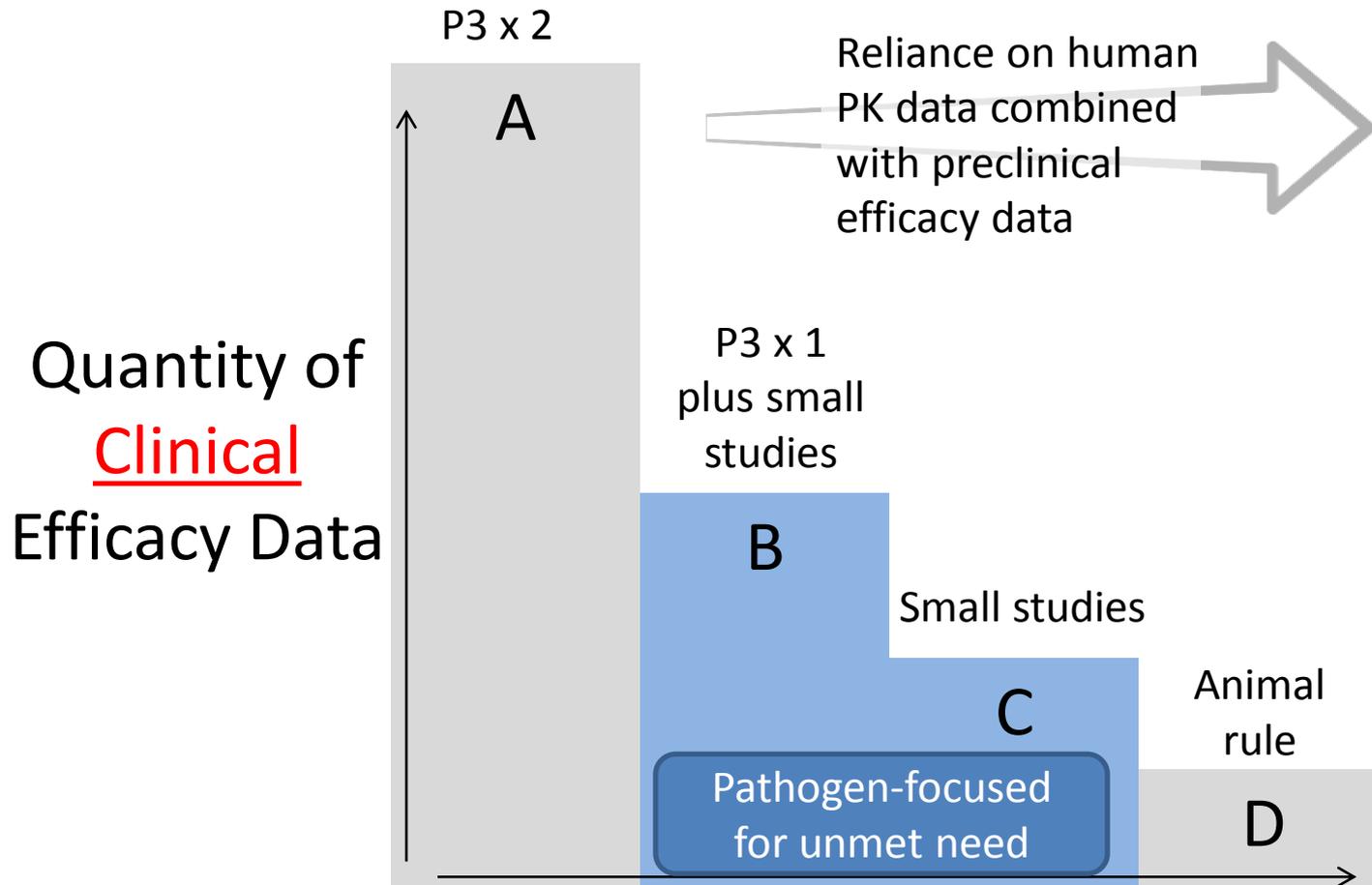
Can we adjust expectations?

- It is possible to design slightly smaller trials…
  - More generous non-inferiority margin, alpha, or power
  - But, sizes are still ~ several thousand patients/study
  - At pathogen rates < 10%, the studies are simply impossible
    - Enriching via rapid predictive[1] diagnostics might help in the future

- This is just not a way forward
  - A small margin, high power, aspirational design that is never completed offers little benefit to anyone

- We need to approach from a different place
  - Smaller studies seen in context[2] offer powerful consistency
  - → A logical basis for approval in setting of unmet need

1. Predictive diagnostic: A test result that increases the likelihood of a given result from a definitive diagnostic. Example: A positive result on a PCR for a *P. aeruginosa* gene product should increase the likelihood of growth of *P. aeruginosa* from a related specimen. A predictive diagnostic would help a developer enrich the enrolled population for patients of interest.
2. Other data available would include the preclinical in vitro database, the preclinical in vivo efficacy demonstrations and likely PD targets, and the demonstration that human dosing covers the desired PD target(s). In short, the available confirmatory evidence will show how and why the drug should work. The clinical data then need provide only the final confirmation of efficacy as well as the safety information.

Addressing unmet need via Four Tiers
A & D are familiar, B & C are new

P3 x 2

A

Reliance on human PK data combined with preclinical efficacy data

Quantity of Clinical Efficacy Data

P3 x 1 plus small studies

B

Small studies

C

Animal rule

Pathogen-focused for unmet need

D

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

Summary: Mind the gap

- An approach to the paradigm gap is suggested
  - Tier B & C: focused mostly on the pathogen
  - Implementation is not simple: Challenges to overcome
  - Implementation carries risks for developers, regulators, and users

- But, we must act: New options are desperately needed[1]
  - By acting quickly to create approaches to describe and manage the uncertainty of small data packages,
  - We will provide patients with timely access to urgently needed, life-saving antibiotics and
  - Avoid the paradoxical situation of being forced in the future to accept even greater degrees of therapeutic uncertainty as antimicrobial resistance progresses.

[1]Hersh et al., Clinical Infectious Diseases 54:1677, 2012. Among 562 respondents in a 2011 survey of the Emerging Infections Network (EIN), 64% reported using colistin during the previous year and 63% reported caring for a patient with an infection resistant to all available antibacterials.

Appendix

Detailed Tier B and Tier C examples

Pathogen-specific indications

Tier B: Detailed Example

- Drug B
  - Active vs. MDR Enterobacteriaceae; equally active vs. MDR and non-MDR strains
  - Detailed (see notes on Tier C example) insight into microbiology, PK-PD, and dose justification
- P2 program: Dose-ranging study of drug B (e.g., two doses) vs. comparator at site Y1
- P3 pivotal program
  - Study B-1: P3 study of B vs. standard comparator to show general activity
    - Single body site Y1, standard study design (endpoints, margins). No expectation of enrolling (any) MDR strains, but because susceptibility (and thus, PK-PD math) is the same as for non-MDR strains, the results show relevant efficacy.
  - Study B-3: Open-label study of B for infections due MDR strains
    - Body sites include Y1 but also sites Y2 and Y3
    - Analysis limited to simple descriptive statistics. Key will be case quality and cross-site pattern of response
  - Study B-9: Observational study of (inadvertently) ineffective therapy for the target pathogen (estimates placebo effect, reference point for interpreting Study B-3)
  - From all studies: PK data (at site if possible) to show comparable exposures
- Label that results
  - Drug B is indicated for the treatment of Y1 proven or strongly suspected to be caused by Drug B-susceptible strains of *(list of organisms)*. Drug B was studied in a single clinical trial of patients with Y1 [See Clinical Studies]. Drug B is only indicated in situations where other therapy is not available or appropriate (e.g., because of resistance to other available therapies).
  - Drug B is indicated for the treatment of Y2 and Y3 proven or strongly suspected to be caused by Drug B-susceptible strains of *(list of organisms)*. Drug B was studied in a limited number of patients with these conditions. Assessment of efficacy was based in part on attaining drug levels associated with therapeutic effect in Y1 and animal models of infection. Drug B is only indicated in situations where other therapy is not available or appropriate (e.g., because of resistance to other available therapies).

Tier C: Detailed Example

- Drug C
  - Active only for *P. aeruginosa*
  - Detailed[1] insight into microbiology, PK-PD, dose justification
- Phase 2 Program: None. The size of any reasonable P2 program ≈ the P3 program
- P3 pivotal program
  - Study C-2:[2] Prospective, randomized, open-label study of Drug C vs. BAT[3] across multiple body sites (Y1, Y2, Y3). N ≅ a few hundred (?)
    - Limited ability to go beyond simple descriptive statistics. Key will be case quality (real infections, sick patients) and cross-site pattern of response
  - Study C-3: Open-label study of Drug C (companion salvage study for study C-2)
  - Study C-9: Observational study of (inadvertently) ineffective therapy for the target pathogen (estimates placebo effect, reference point for interpreting Study C-2)
  - Throughout: Use any available patient enrichment tools (rapid tests, etc.)
  - From all studies: PK data (at relevant body sites as possible) to show comparable exposures
- Label that results
  - Drug C is indicated for the treatment of Y1, Y2, and Y3 proven or strongly suspected to be caused by Drug C-susceptible strains of *Pseudomonas aeruginosa*. Drug C was studied in a limited number of patients with these conditions. Assessment of efficacy was dependent on the use of external controls and also in part on attaining drug levels that were associated with therapeutic effect in animal models of infection. Drug C is only indicated in situations where other therapy is not available or appropriate (e.g., because of resistance to other available therapies).

[1]Mechanism of action understood, animal models reasonably mimic human disease at relevant sites, exposure-response in the animal studies informs human dose with adequate margin. [2]There is no Study C-1: for ease of discussion, study numbers are aligned across the Tier B and C examples. [3]BAT = Best Available Therapy, standardized insofar as possible.

Pathogen-specific indications

- Classic antibacterial indication: Drug, site, bugs:
  - Drug X is indicated for Infection Y when proven or strongly suspected to be caused by Drug X-susceptible strains of *[list of pathogens]*.

- Pathogen-specific indication
  - Drug X is indicated for *infections* proven or strongly suspected to be caused by Drug X-susceptible strains of *[list of pathogens]*.

- Pathogen-specific is not new…
  - Linezolid is indicated for infections due to vancomycin-R *E. faecium*

- What is new is the idea of registering *only* in this way
  - Linezolid also has classic indications in pneumonia, skin