

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

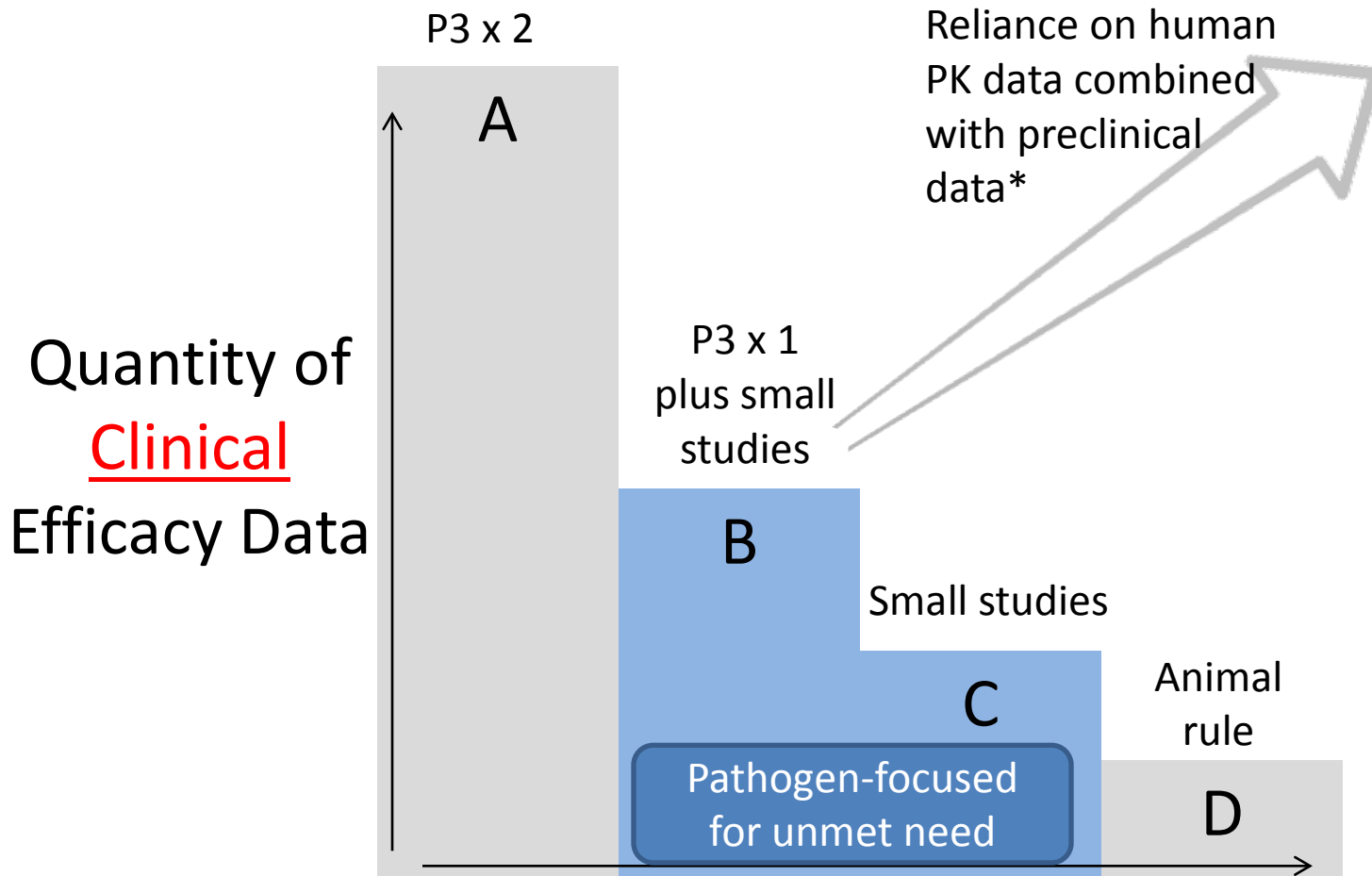


The paradigm gap

- 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- β -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, B & C are new



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

What might be in Tier B/C?¹

- Preclinical
 - Detailed² insight into microbiology, PK-PD, and dose justification
- **Tier C:** Three small comparative and descriptive studies...
 - Study #1: Prospective, randomized, open-label study of Drug X vs. BAT³ across multiple body sites (Y1, Y2, Y3). N \cong a few hundred
 - Study #2: Open-label study of Drug X (companion salvage study for Study #1)
 - Study #3: Observational study of (inadvertent) ineffective therapy for the target pathogen (estimates placebo effect, reference point for interpreting Study #1)⁴
- **Tier B variant:** P3 x 1 at one site + open-label MDR study (multiple sites)
- Case quality is key (microbiological proof, clear-cut syndrome)
 - “Usual strength” statistical inference testing not possible
 - Evaluating *totality-of-the-evidence* is critical: PK-PD, pattern across sites, etc.
- Target label:
 - Drug X is indicated for treatment of [Y1, Y2, Y3] when proven or strongly suspected to be caused by Drug X-susceptible strains of [list of pathogens].
 - As data for Drug X in these infections are limited, Drug X should be used only in situations where it is known or suspected that other alternatives are less suitable.

¹Rex et al. 2012, Proposal for a comprehensive regulatory framework to address the unmet need for new antibacterial therapies. *Submitted manuscript*.

²Mechanism of action understood, animal models reasonably mimic human disease at relevant sites, exposure-response in the animal studies informs human dose with adequate margin. ³BAT = Best Available Therapy, standardized insofar as possible. ⁴Might use existing data (e.g., Tigecycline PK-PD analysis in HAP-VAP [Ambrose et al., AAC 56:1466, 2012] provides a clear PK-PD estimate of placebo response rates) or pharmacometric proof from Study #1.

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 ideas¹ may really help here.*
- Adding a single P3 study (Tier B) is really helpful
 - Might well 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. To see something like this in print, see Lalonde RL, Kowalski KG, Hutmacher MM, et al. Model-based drug development. Clin Pharmacol Ther 2007;82:21-32.

To make this concrete

How would you develop this drug?

- Drug X is active vs. *Pseudomonas* and nothing else
 - If Drug X existed, knowing when to use would be simple
- Suitable study arms are possible
 - Drug X + 2nd agent with limited *Pseudomonas* activity (e.g., ertapenem¹) vs. a suitable comparator arm covering *Pseudomonas*
 - Drug X success for *P. aeruginosa* could be attributed to Drug X
- 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 evaluable cases (336/arm)
- Evaluable = culture-proven → 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 pts¹

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.

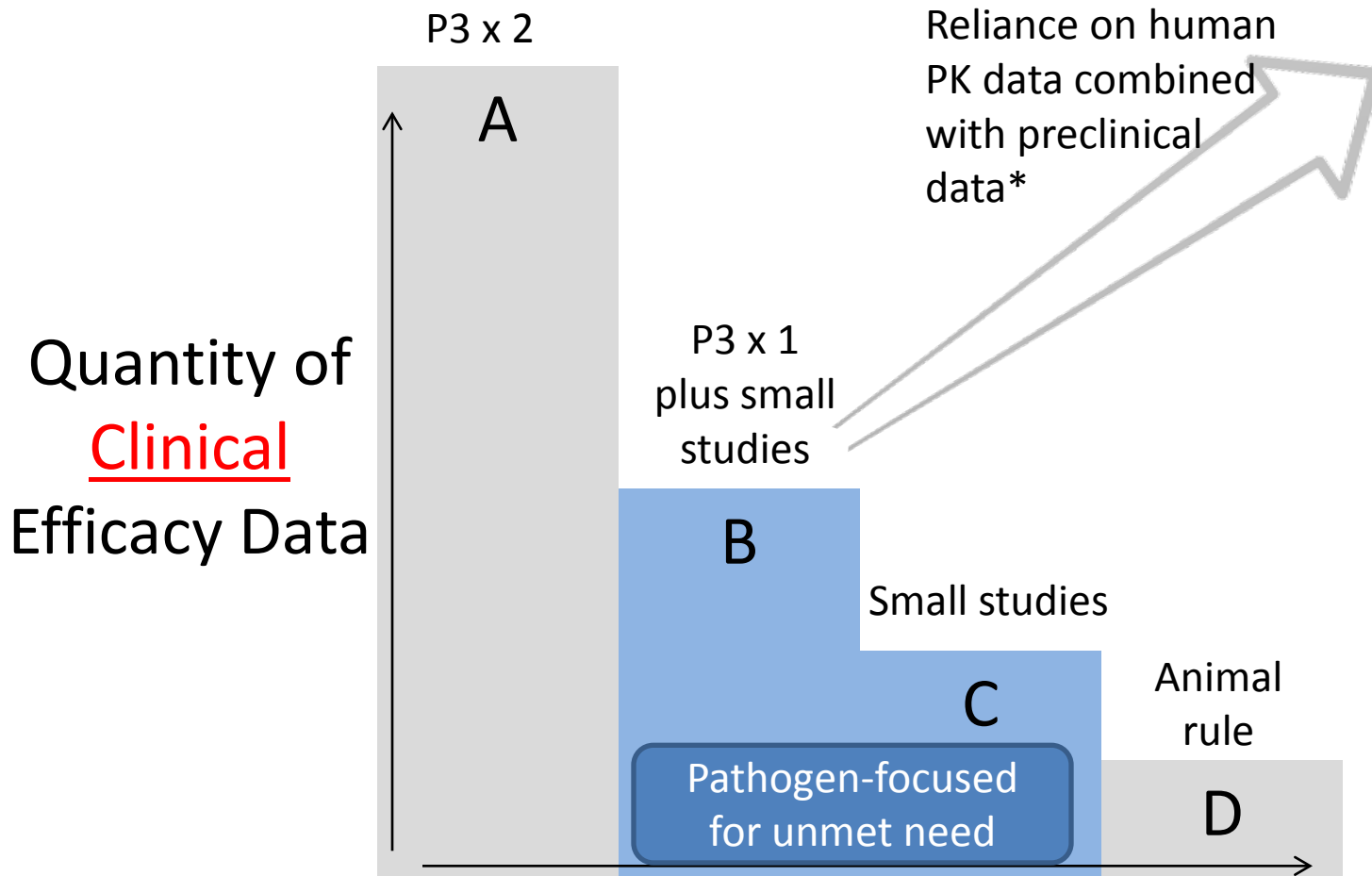
Can we adjust expectations?

- 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 rates $< 10\%$, the studies are simply impossible
 - Enriching via rapid predictive¹ 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 context² 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



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

BACKUP

Regulatory 101

- 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
- Subtle point for which we don't yet have good terminology
 - PS indication is written without reference to the underlying data
 - We could of course include a list of the sites for which data exist
 - Call this an “unmet need” indication? We need to think of a phrase.