Challenges of developing narrow-spectrum and adjunctive therapies

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Disclosures

- Employed by Spero Therapeutics, Cambridge, MA
- Shareholder GlaxoSmithKline

The opinions expressed in this presentation are my own and are not necessarily shared by Spero Therapeutics or my industry colleagues.

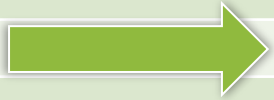
Agenda

- Past, Present, and Future
- Review of the Case Study
- Where we must go
- Conclusions

“The Past”

40 Years Since the Last Novel Gram Negative Class Approved

History of Antibiotic Discovery and Approval	
Year Introduced	**Class of Drug**
1935	Sulfonamides
1941	Penicillins
1944	Aminoglycosides
1945	Cephalosporins
1949	Chloramphenicol
1950	Tetracyclines
1952	Macrolides/ Lincosamides/ Streptogramins
1956	Glycopeptides
1957	Rifamycins
1959	Nitroimidiazoles
1962	Quinolones
1968	Trimethoprim
2000	Oxazolidinones
2003	Lipopeptides



Last Novel Class of Gram-Negatives

"The Present"

*Near-term Pipeline**

Gram-negative infection

- Bla-inhibitor combinations
  - Rempex/MedCo– Carbavance
  - Merck-- Imipenem/ Relebactam
- Tetracyclines
  - Tetraphase-- Evarvacycline
- Aminoglycosides
  - Achaogen-- Plazomicin
- Siderophore Cephalosporins
  - Shionogi-- S-649266

Gram-positive infection

- Ketolides
  - Cempra– Solithromycin
- Tetracyclines
  - Paratek-- Omadacycline
- Pleuromutilins
  - Nabriva-- Lefamulin

*For a complete list see:
http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development

“The *not so distant* Future”

Novel science advances against “threat” organisms/ infections

- Potentiators of an antibiotic
  - Facilitating access through the GNR outer membrane, inhibitors of efflux pumps, novel beta-lactamase inhibitors
- Single pathogen antimicrobials, e.g. *Pseudomonas aeruginosa* only
  e.g., Mab, small molecules, peptides, lysins, etc.
- Therapies that modify pathogen virulence
  e.g., transcription regulators, antagonists of type 3 secretion systems, anti-biofilm agents, etc.
- Novel delivery systems
  e.g., Liposomes, nanoparticles, aerosols, etc.
- Therapies that modify the host response
  Up regulate to augment pathogen clearance
  Down regulate to minimize inflammation and collateral damage

Antibiotic vs. Antibiotic Adjunctive Therapy

- Antibiotics are really amazing therapeutics
  - Treatment effects are huge (Placebo 30%, Treatment ~70-90%)
    - Is it really rational to expect to demonstrate an additional benefit in a clinical trial?
    - ”How much better could you be than cured?”

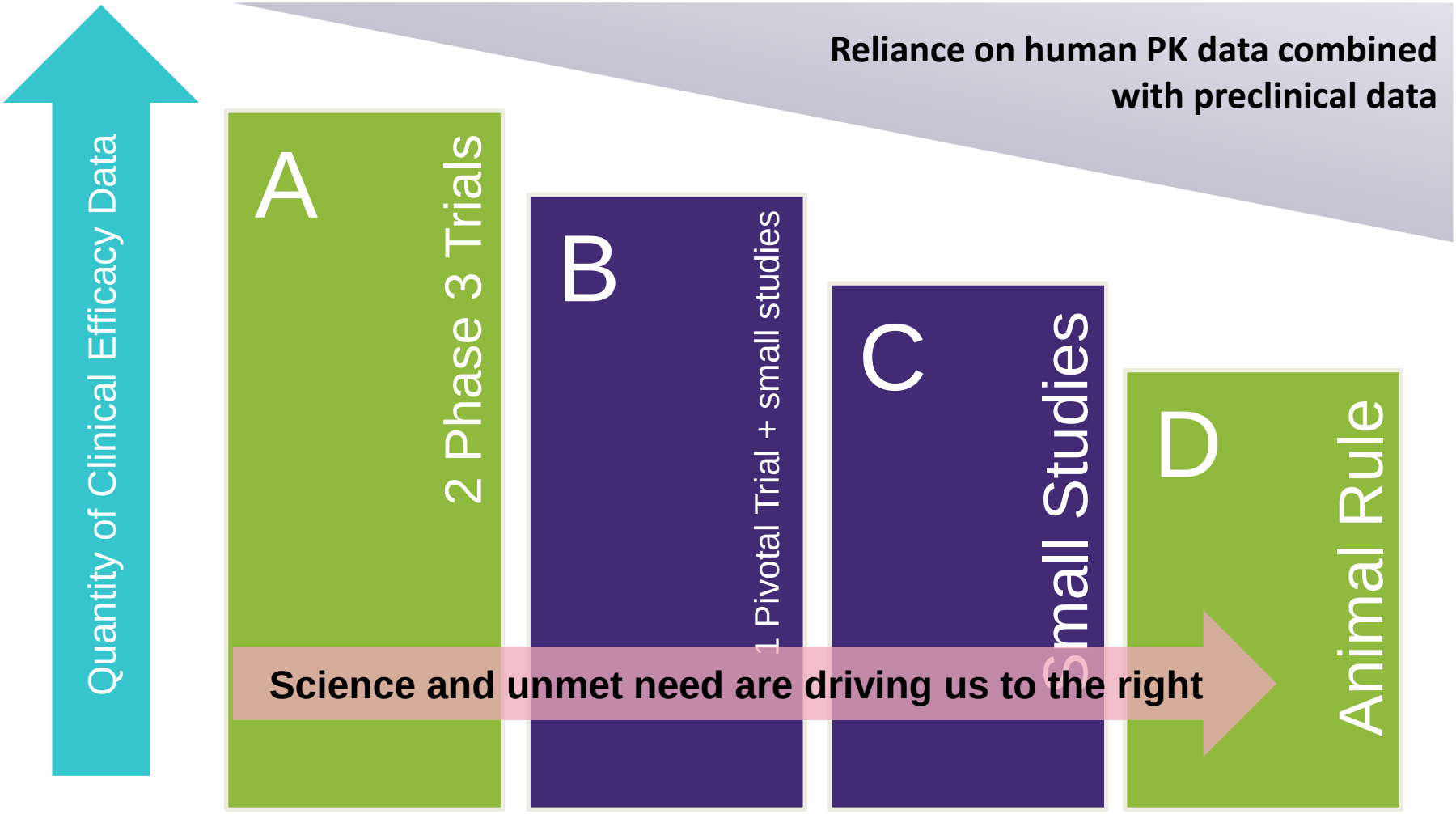
- A test therapeutic must make a successful clinical equipoise argument
  - Does it appear that the test therapeutic could be as good or better than the SoC antibiotic treatment?
    - A true state of **equipoise** exists when one has no good basis for a choice between two or more care options
  - Fortunately there are great translational models in antibacterial research
  - Therefore most “candidate antibacterials” can conduct non-inferiority trials

- Test therapeutics that cannot make this argument, e.g. most Mabs, antivirulence therapies, aerosol abx for VABP, etc.
  - Considered adjunctive to antibiotics, though they may bring great advances to modern medicine, e.g. rescue those who may have died
  - Development is particularly challenging, they must demonstrate an added benefit to abx, i.e. superiority (SoC + novel adjunct vs. SoC alone)

Pipeline agents Facing Development Challenges

- *Pseudomonas aeruginosa* MvfR inhibitor (anti-virulence)
  - Spero Therapeutics/Roche
- Multiple monocloncal antibodies
  - Arsanis (ASN200:*Escherichia coli,* ASN300: *Klebsiella pneumoniae)*
  - Astra Zeneca (Medimmune)– (MEDI3902 *P. aeruginosa*)
- Aerosol Therapies for VABP
  - Cardeas (aerosolized amikacin + fosfomycin)
  - Bayer/Nektar (aerosolized amikacin)
- *P.aeruginosa* macrocycle peptide antibiotic
  - Polyphor

So which way is clinical development heading?



A comprehensive regulatory framework to address the unmet need for new antibacterial treatments

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

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Case Study: Drug X-1

Injectable narrow spectrum agent *(P. aeruginosa)*

Strength

- Novel mechanism of action
- Potent, cidal activity
- Safety margin ≥ 4-fold
- Well distributed
  - 40% ELF/Plasma
  - Unchanged in urine
- Well tolerated in PH1-predictable PK
- + PoC in non-CF bronchiectasis study

Weakness

- Resistant subpopulation identified
  - MIC >4-fold higher
- P.a. infections not common in any particular body site
- Unclear development pathway
  - Rapid diagnostic not widely available

Frequency of *P. aeruginosa* (% of all enrolled)

	Lit.	Recent drug #1	Recent #2	Recent #3	Kollef
NP	20%[a, b]	13%	10%	23%	26%
cIAI	10%[c]	7%			
cUTI	3%[d]	4.30%	2.00%	2.40%	
ABSSI	Rare		Rare		

Chastre J et al. Crit Care Med 36:1089–1096, 2008, Brun-Buisson C et al.Clin Infect Dis 26;346-54, 1998, Lucasti C et al., Clin Ther 30:868-83, 2008, Naber KG et al. Antimicrob Agents Chemother. 53:3782-92, 2009, Kollef, M. H., J. Chastre, et al. 2014 Crit Care Med 42(10): 2178-2187

But note that non-standard VAP definitions were used

The painful math—borrowed from John Rex

- 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 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.

Practical Issues for Drug X-1

"Tier C" *P. aeruginosa* Specific Trials

Issues to Consider

- Design:
  - Non-inferiority is possible, but what site of infection, or
  - Pooling across infection sites?
    - VABP has highest incidence of P.a. (but still only 15-20%)
  - Limited choice of comparators/combinations? (Need to fill in spectrum gaps)
  - VABP guidelines recommend double coverage for P.a.
    - Impact of confounding

- Analysis:
  - Patients with P.a. infections typically sicker and have higher comorbidity
  - Endpoints are different across body sites
  - What NI margin could you use? Is discounting possible?
  - Or is inferential testing even possible?

- Enrollability
  - Is the trial feasible to enroll i.e. costs/time?
  - How much could a rapid diagnostic test help with enrollment?
  - Design acceptable to investigators?

Logistics of clinical research (All comers)

- Cost
  - cUTI, cIAI ~$50k/patient
  - HABP/VABP >$100K/patient
  - Costs are amplified when the # of sites increases
- Time
  - cUTI/cIAI enroll ~0.25 - 0.5pts/center/month
  - HABP/VABP enroll ~0.08pts/center/month
  - *Now consider that only a small fraction will have P.a*.
- Investigator fatigue
  - Site staff works hard screening patients to meet eligibility
  - Their effort is mostly compensated when they enroll a patient
    - Often have other trials that compete for their time and are easier to enroll
- Investor fatigue
  - Notoriously impatient
  - They have other choices when it comes to investment

Rapid Diagnostic to the Rescue??

- Have we oversold the value of rapid diagnostics?
  - Diagnostics do not create patients infected with target pathogens, they help identify them before culture results
  - Thus used for enrichment, they ***may*** save costs

- Logistics
  - Diagnostics often require hardware which must be purchased or leased
    - Other costs which must be factored include reagents and hardware maintenance
  - Site staff must be trained, and diagnostic companies are not working to your study timelines
    - If trained staff not present, patient enrollment can be compromised
  - QC must be maintained
  - Microbiologically evaluable population is based on + culture result
  - All of the above challenges are amplified if the diagnostic is investigational

- **Conclusion**- One must carefully weigh the value of diagnostics vs. other enrichment criteria

- **Aside–** Though a rapid diagnostic ***may*** be valuable in a clinical trial, it will be of great value in a stewardship role.

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Drug X-1 Clinical Development

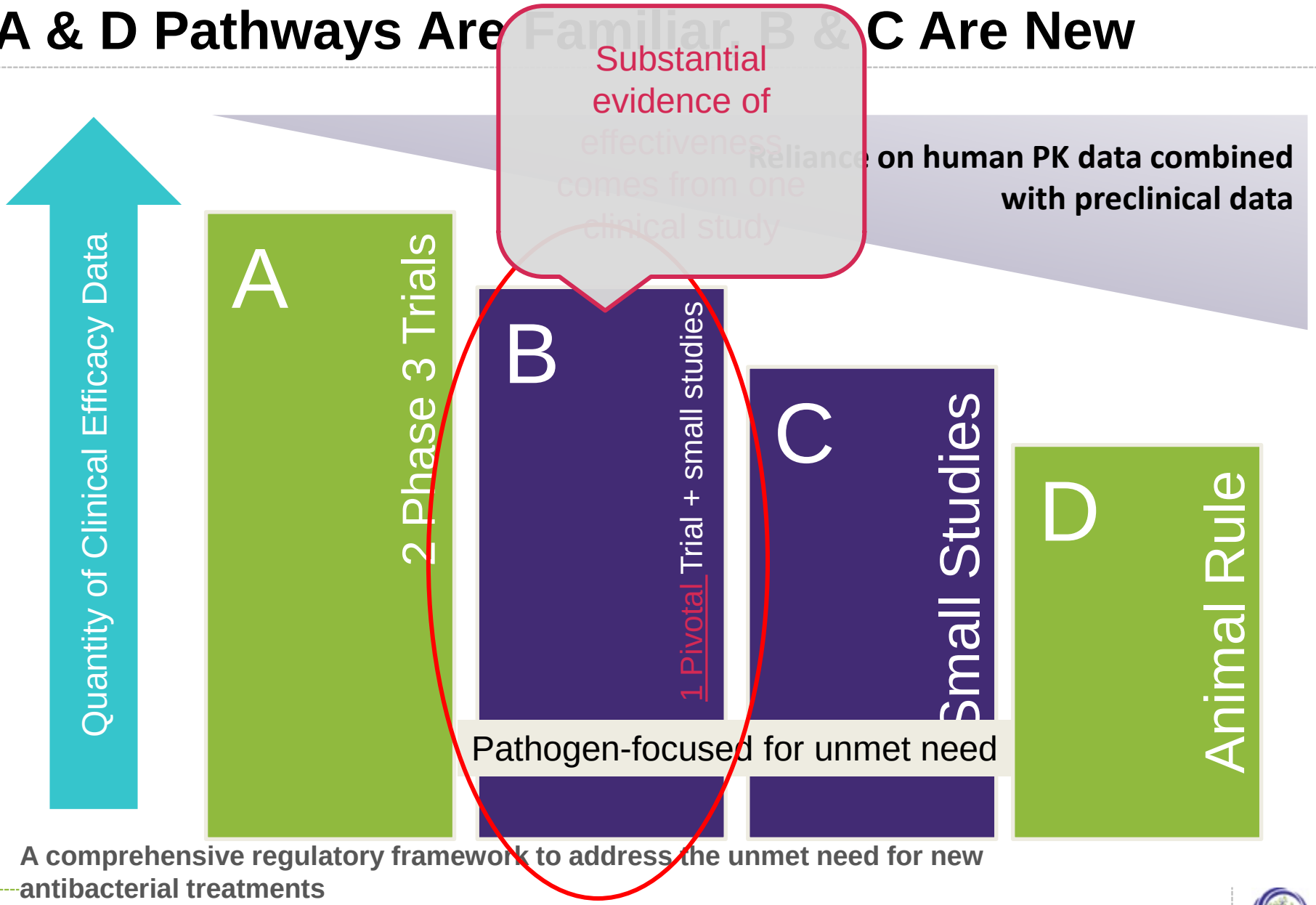
- Standalone Tier C programs have not yet been submitted for review
  - Small samples may not contain sufficient numbers of target pathogens to allow inferential testing, even with wide NI margins
  - Small samples from a sick population with many comorbidities could generate highly variable results—**increasing the risk of failure**

  (Tier B works well because it is feasible to enroll clinical studies of acute infection when the agent has a broad enough spectrum)

- What can readily be demonstrated for a narrow-spectrum agent like Drug X-1:
  - MoA, MIC range, potential for resistance—*in vitro* study
  - Target exposures for efficacy, from:
    - *in vivo* preclinical animal models of infection
    - *in vitro* hollow fiber experiments
  - Estimated dose to achieve target exposure in target population
  - Demonstrate PK/PD based on MoA in a small trial population (PoC)
  - Safety in a small population

- With the feasibility challenges highlighted for Drug X-1, can one expect that a clinical trial will meet the requirement for substantial evidence of effectiveness with any **predictable certainty?**

A & D Pathways Are Familiar, B & C Are New



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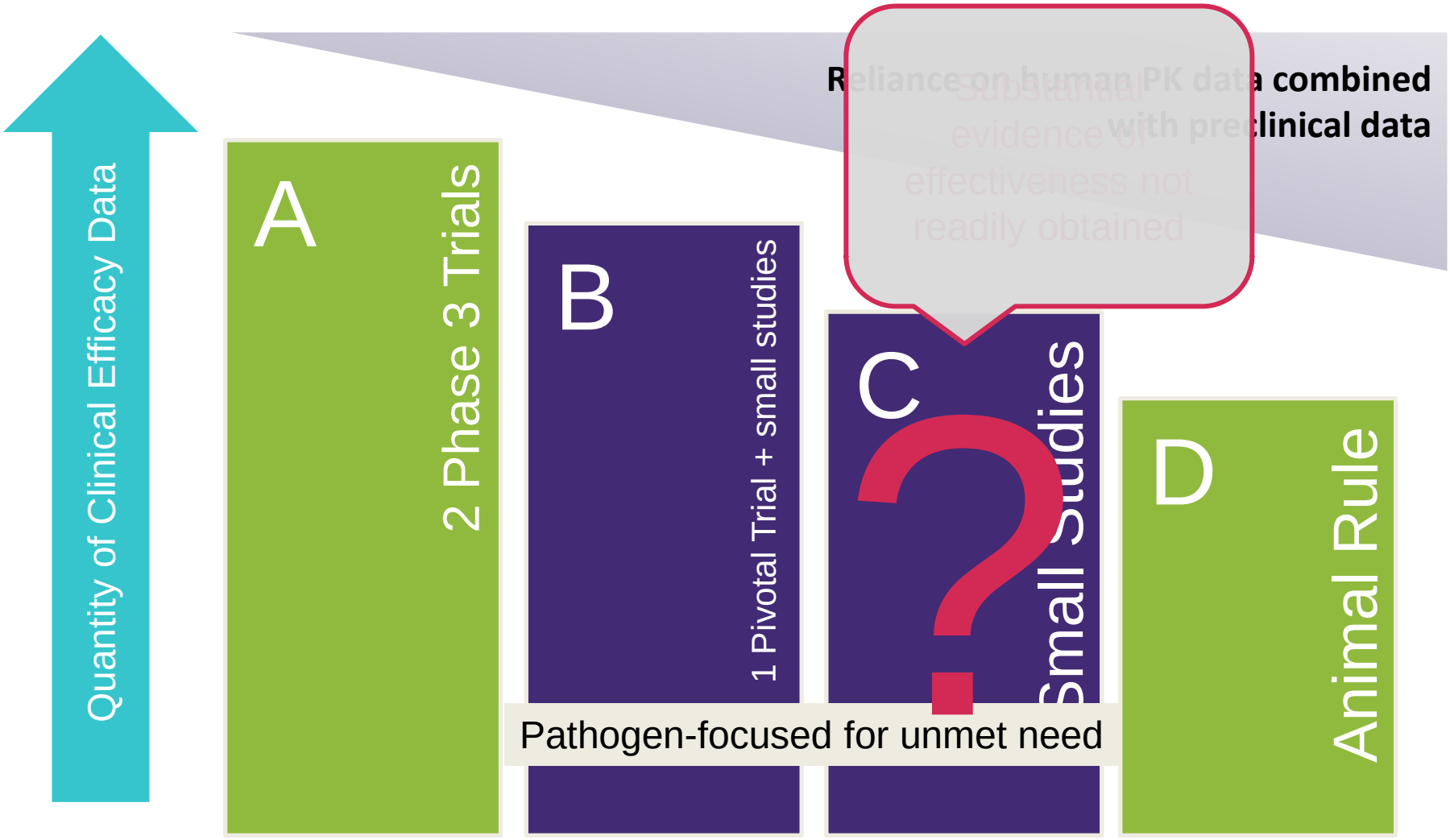

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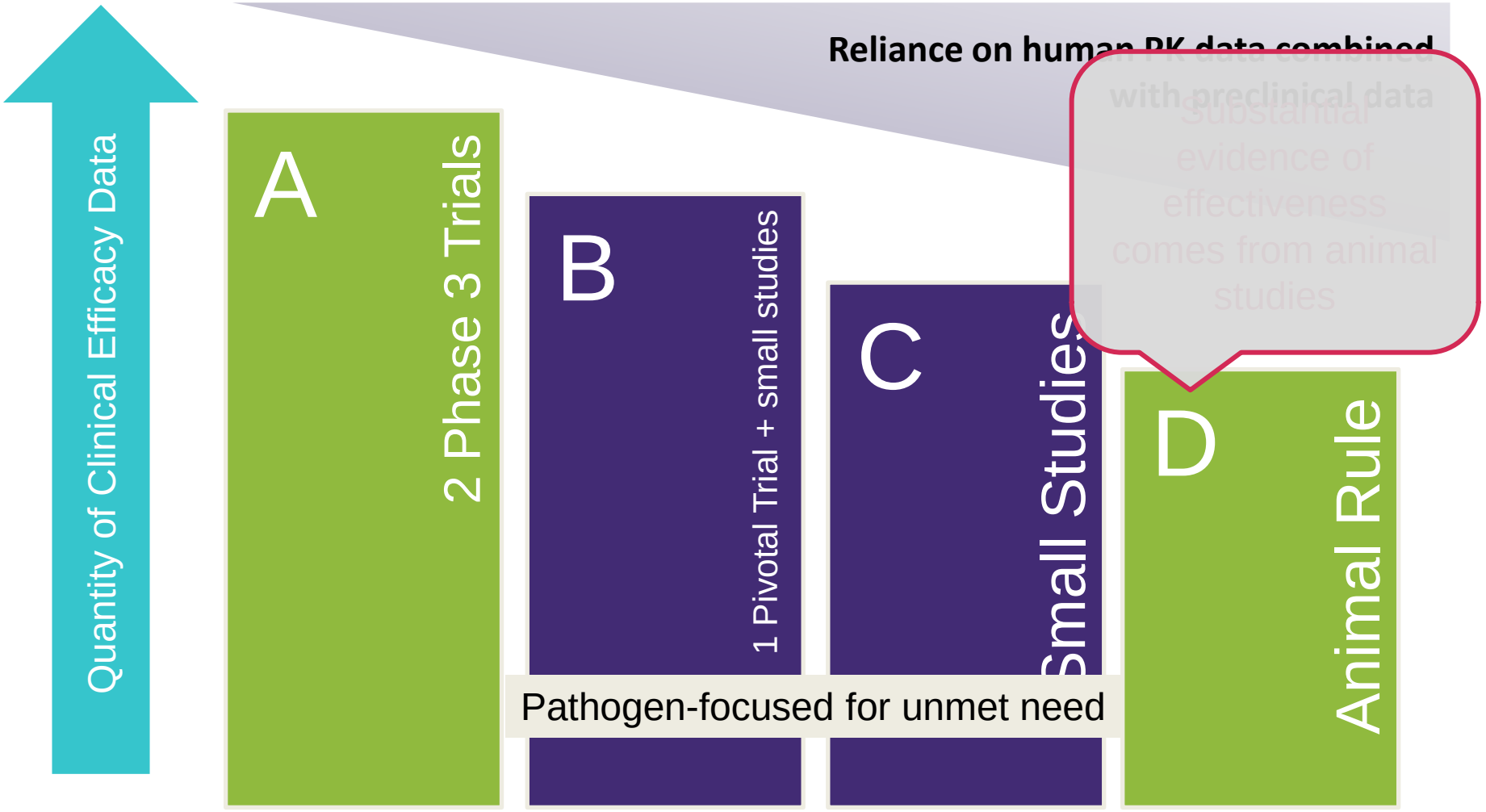

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Summary

Drug X-1 Clinical Development (Speaker's View)

- Drug X-1 has a novel MOA and the promising potential to address an important unmet medical need
  - Inappropriate therapy for *P. aeruginosa* is associated with increased mortality[1,2]
  - Increased mortality associated with MDR *P. aeruginosa*[1,3]
  - MDR *P. aeruginosa* more common than KPC and NDM in US
- A strong supportive data package has been generated for Drug X-1
- Given the challenges of recruiting a single-pathogen cohort along with the high degree of heterogeneity in the population, a **Tier C** approach to meet FDA statutory requirements for effectiveness **carries a high degree of unmanageable risk**
  - There is no way to argue that results of a Tier C study will favor chance of supporting approval vs. condemning to failure
- We need to consider an alternative approach
  - Could the "Animal Rule" help address this important unmet need …

1. Hirsch and Tam. *Expert Rev Pharmacoecon Outcomes Res*. 2010;10:441-51. 2. Lambert et al. *Lancet Infect Dis*. 2011;11:30-8.
3. Lautenbach et al. *Infect Control Hosp Epidemiol.* 2010;31:47-53.

Meeting the statutory requirements for a narrow-spectrum therapeutic

- When conduct of an adequate and well controlled clinical study is not ethical or **feasible,** than substantial evidence of efficacy can come from validated animal models
  - First we need to agree that a single pathogen P.a. clinical trial cannot meet the statutory requirement
  - If so, is there a validated animal model of P.a. infection?

- It is feasible to conduct **small** studies in the target patients with P.a. infections
  - Obtain PK to demonstrate that the given dose can generate efficacious target exposures in the population intended for use of the therapeutic
  - Provide descriptive statistics from such clinical trial
  - Collect safety data to support risk benefit analysis

- The Sponsor should present plans to conduct a “Field Study” to further support the benefit risk of the approved therapeutic

Conclusions

- Promising, narrow-spectrum agents are in the pipeline; the development path is currently unclear
- As basic science advances, translational challenges will continue to emerge
  - Establishing effectiveness in a clinical trial for adjunctive therapies may prove especially challenging
- Blending elements proposed under Tier C with the “Animal rule” may allow FDA approval of select narrow-spectrum therapeutics
- **Society is approaching a crossroads** in addressing antibiotic resistance and we are in danger of slipping backwards, losing a number of the scientific achievements accomplished as part of modern medicine in the 20th century
  - We must continue to advance and replenish the antibiotic pipeline, and find ways to test and approve novel, potentially useful therapeutics
  - **We can’t rely on or hope for *only* broadly-active anti-bacterial therapies**