European Federation of Pharmaceutical Industries and Associations

Tier B-C programs:

Issues to address for a Tier B development plan

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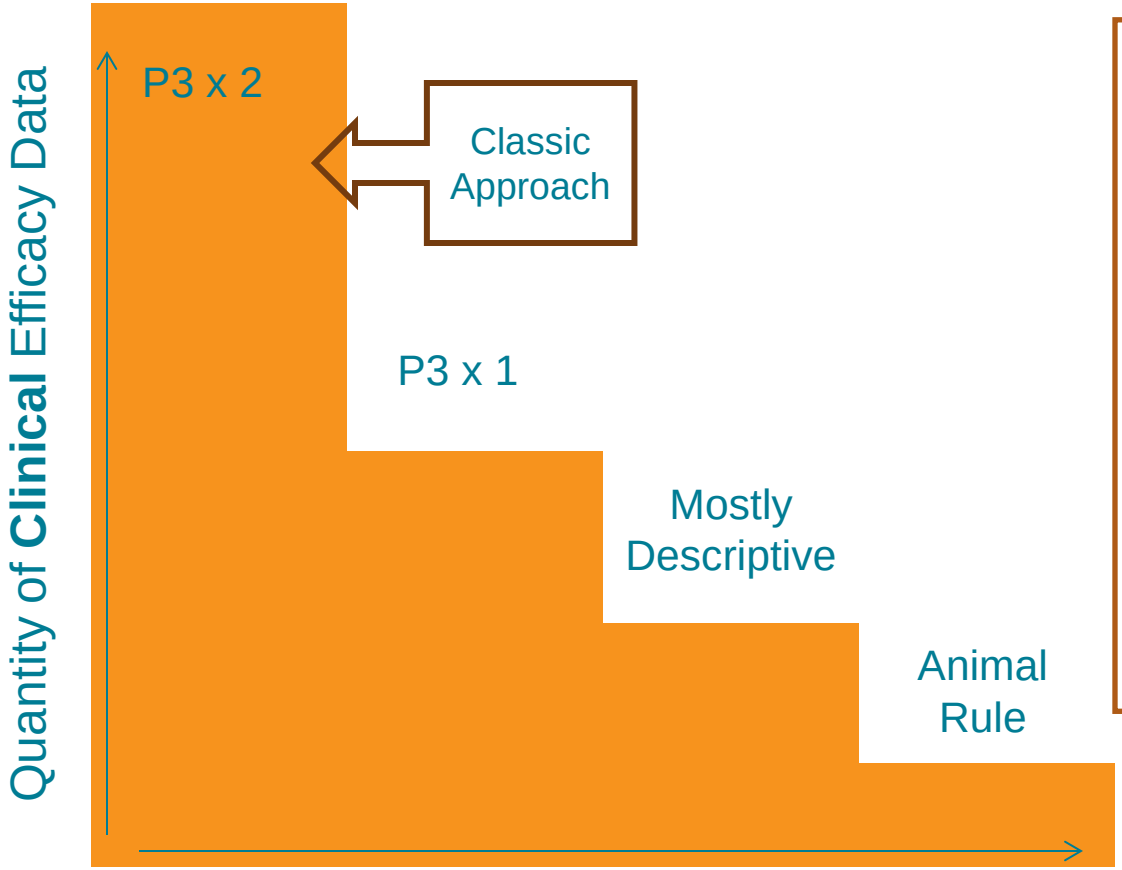
The paradigm gap

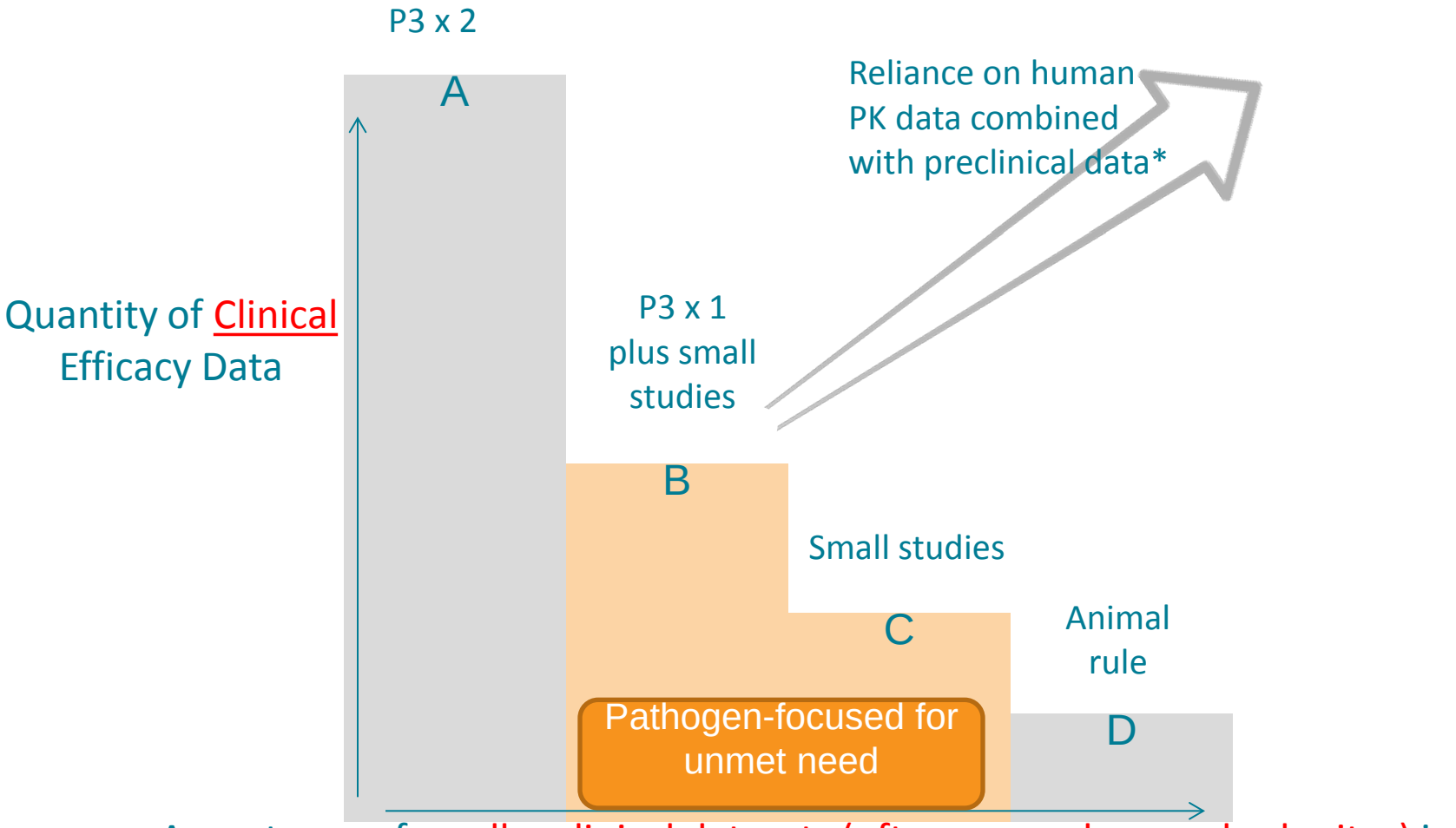
- For registration, we traditionally expect
  - Two substantial trials per indication (e.g., two UTI trials)
  - Typical size/trial: ~1,000 patients
- This presumes ready availability of substantial numbers of patients with the target disease
- But, what if the target disease includes a less common, but important, pathogen or type of resistance?
  - Less common pathogen: *Pseudomonas*
  - Emerging form of resistance: KPC or Metallo-ß-lactamase
- When only limited clinical data for these important subsets are possible, current paradigms give no easy way forward
  - Waiting for widespread resistance means we can't anticipate the epidemic

A tiered approach: Aligning feasibility and the quantity of clinical data with the unmet medical need



- The need for a tiered approach is real – there are real products at each tier that need a path forward
- Determination of the appropriate tier should be based on ***context***:
  - Feasibility
  - Unmet medical need
  - Strength of the preclinical data
  - By utilizing the totality of data, ***existing*** regulatory requirements can be met at each tier

A & D are familiar, B & C are new



Even Familiar Tier A is Evolving!

- FDA September 2012 Draft Guidance for Industry on Complicated Intra-abdominal Infections states (p.3, efficacy considerations regarding the number of clinical trials needed to support an indication):
- “A single persuasive adequate and well-controlled trial with supportive information can be provided as evidence of effectiveness in certain circumstances. For sponsors developing a drug for more than one indication for treatment of infections caused by similar bacterial pathogens, a single trial in cIAI and a trial in another indication can be provided as evidence of effectiveness.”

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 for non P3 study?	Yes	Yes
Reliance on nonclinical and PK (“totality of data”) approach?[4]	High	Even higher
Approach discussed in June 2012 EMA Addendum?	Yes	Implied

[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 Example

- Drug B: Preclinical data and human PK data are the foundation
  - Active vs. MDR Enterobacteriaceae, equally active vs. non-MDR strains
  - Detailed insight into microbiology, PK-PD, and dose justification
- Pivotal program: Two active treatment studies
  1. P3 study of Drug B vs. standard comparator
     - Single body site Y1, standard study design parameters (endpoints, margins)
     - Intended to show drug's effectiveness in treating serious infection
     - No expectation of enrolling sufficient MDR strains but because susceptibility (and thus, PK-PD math) is the same as for non-MDR strains, the results show implied efficacy against MDR pathogens
  2. Open-label study of Drug 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 (real infections, sick patients) and cross-site pattern of response
- From all studies: Safety data and PK data to show relevant exposures

Label that results

- Drug B is indicated for the treatment of Y1 in adults *(or children)* proven or strongly suspected to be caused by Drug B-susceptible strains of *(list of organisms)*.
- 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).

Additional labeling elements

- To reduce the development of drug-resistant bacteria and maintain the effectiveness of Drug B and other antibacterial drugs, Drug B should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.
  - When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy.
  - In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.
- Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to Drug B (see Microbiology).
  - Therapy with Drug B may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.

Summary thoughts

- Increasing medical need plus large trial size infeasibility means greater risk in not approving needed new antibiotics
- To address this, it is important to have a range of approaches to the data that can be generated
  - Tier A: Combinations of single trials may suffice
  - Tier B: A single appropriate and feasible Phase 3 trial plus limited clinical data on MDR pathogens across multiple body sites
  - Tier C: Limited clinical data sets across multiple body sites
- The label should reflect, as appropriate (Tier B and C), the limited data sets used for registration
- International harmonization should be a goal as this facilitates global feasibility and global registration