European Federation of Pharmaceutical Industries and Associations

Drugs for MDR Pathogens:
Issues in Development

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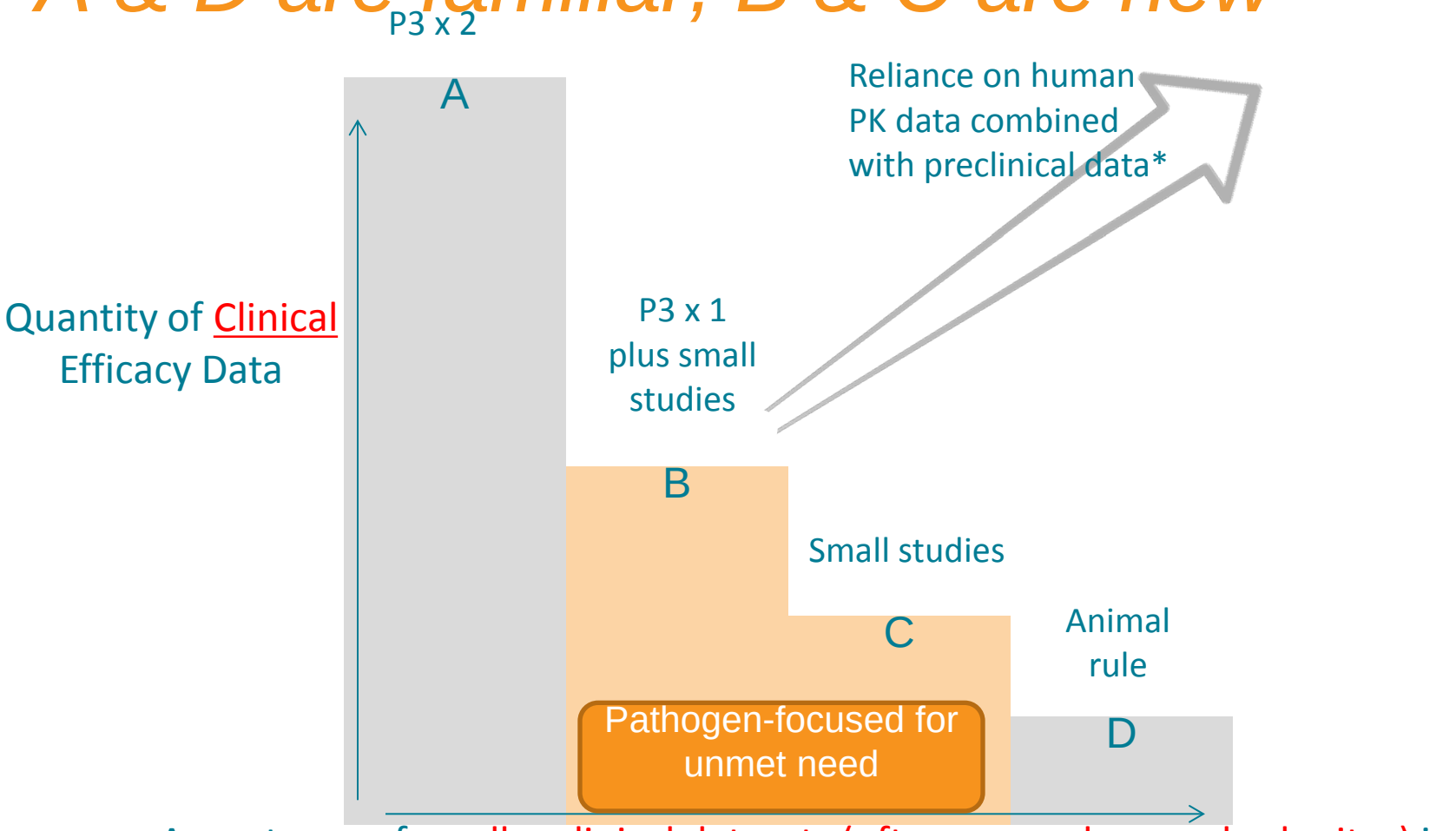
MDR Pathogens: Development Overview

- The EFPIA WG proposes an expedited approach to antibacterial development for MDR pathogens
- This approach includes pathways for
  - Broad spectrum (Tier B)
  - Narrow spectrum (Tier C)
- These approaches emphasize the use of the “totality of data”
  - A comprehensive pre-clinical program
  - A contribution from data in patients infected with less resistant (non-MDR) strains of the pathogen(s) of interest
  - A more focused clinical development program informed by the above
- In the following slides I will review some considerations to maximize success of these programs

A & D are familiar, B & C are new



It’s all about Benefit-Risk

- High unmet need for new MDR therapies justifies accepting more uncertainty regarding efficacy and safety in product development.
  - Without this, we’ll see a continuing increase in unmet need
  - These greater levels of uncertainty can be managed & described
- Efficacy
  - Increased utilization of pre-clinical and early clinical data
  - At least some controlled data in the clinical trials
- Safety
  - Usual preclinical assessments
  - Safety data from all trials to identify AEs in the 0.5-1.0% range
- SmPC to focus on situations where both potential benefit and tolerance of unexpected safety events are greater

Key Themes to Explore

- Managing Uncertainty: Beyond preclinical and human PK data
  - Contribution of data from patients infected with non-MDR strains
    - If a new drug has similar activity on MDR and non-MDR pathogens,
    - The PK-PD math is thus the same for MDR and non-MDR strains,
    - And thus patients infected with non-MDR strains are informative
  - Multiple ways to collect and interpret MDR data
    - Both pooling across body sites and external controls are needed
    - Patients with MDR pathogens may be acquired from the above non-MDR trial, from a dedicated MDR trial, and via expanded access
- Other issues
  - Options to superiority are needed
  - Seriousness vs. severity
  - Harmonization

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Pooling Across Body Sites

- A dedicated MDR study will need to enroll patients with infections involving different body sites
- Pooling this data can facilitate its analysis but should have a rationale based upon:
  - Clinical pharmacology of the drug
  - Adequate tissue penetration and drug levels at key body sites
  - Similarity of infecting organisms across the different sites
- A control or controls will place results into context
  - General issues of controls will be discussed on following slides
  - This issue will be explored in even greater detail in the Tier C talk
  - Statistical methodology should be agreed before trial initiation

Data from Controlled Trials

- Data on treatment response of patients infected with MDR organisms should be collected and placed in context.
- A control provides both context and “insurance” for unexpected results obtained with the investigational agent
  - MDR patients may be sicker and have greater underlying disease
  - A control facilitates consideration of these factors when assessing drug performance
- A randomized MDR study would be an effective way to address these issues but concerns with this approach exist
  - Limitations in numbers of patients who can be enrolled,
  - Heterogeneity of best available therapy (BAT) regimens
  - Potential logistical issues: These studies are difficult to run
- External controls are an important alternative approach (next slides)

External Controls: Definitions

- External including historical controls
  - An external control is data collected from patients not directly included within the trial of the investigational agent
  - A historical control is a subset of this and is composed of patients treated and/or observed at some time in the past. Such a group may for instance be able to provide placebo/no treatment data to aid in interpretation of current treatment results
- Historical and contemporary controls can each provide useful although different perspectives.
  - Information on size of treatment effect
  - Comparison to current therapies
- Contemporary controls for studies of patients infected with MDR pathogens are a necessary component because resistance patterns, supportive care and other factors are changing,

External Controls: Methods

- Rigor will be important in developing external control data
- To maximize both its value and credibility an external control should
  - Be composed of contemporary patients
  - Have a protocol and case report form (CRF) for identifying and enrolling patients
  - Enroll patients from similar or identical clinical centers who were treated just prior to availability of the investigational agent
  - Have the patient-level data available to evaluate comparability with investigational arm and these data should be similar in key demographic and disease related characteristics

EFPIA are keen to work with EMA to validate methods using historical control data or to develop new methods to collect contemporary, external control data

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Options to Superiority are Needed

The problem of Drug #2 (and #3 and #4…)

- Once we have Drug #1, the unmet need doesn't go away.
- All candidates will have some component of intrinsic superiority
  - Any new therapeutic agent should address an unmet medical need
- But, showing superiority on a hard endpoint is not routinely possible
  - Cannot deliberately study vs. an ineffective comparator
  - May be possible when there are high levels of resistance to existing therapies and studies include only patients with more severe illness
- A trial in that population might show superiority of the new drug
  - Might initially be possible vs. a drug like colistin (nephrotoxic)
  - Softer endpoints (time to bacterial clearance or clinical improvement, as discussed in the EMA Guidance) might be helpful
  - But will become more difficult if comparator is a newly approved drug
  - And, resistance is dynamic and patients complex: drugs with different MOA, metabolism/excretion and DDI profiles are valuable options
- **An option based upon non-inferiority is essential**

Seriousness vs. Severity of Illness

- It is tempting to call for studies only in “severe” infection
  - EMA Guidance uses severity scales (CAP), specified distributions of disease forms (HAP/VAP), and underlying etiology (cIAI).
- Not all patients with serious infection are severely ill when first observed: But all are at risk for progression
  - Untreated pneumococcal pneumonia has a very high mortality
- Patients with MDR pathogens can differ in degree of underlying illness and use of concomitant medications
  - Studies in non-MDR infections may not serve as a complete surrogate
- Thus, clinical program must accrue a representative patient group
  - **All should have established infection with the pathogen of interest**
  - **Some but not all will be severely ill at entry**

Regulatory Harmonization

- Need for regulators to agree on the basics of program and study design to facilitate a global program:
  - Increase efficiency of the program through use of totality of data
  - Agreement on principal studies that serve as a basis for approval for a drug targeting serious infections due to resistant organisms
- At the level of an individual study
  - Within relevant target indications (CABP, HAP/VAP, cIAI)
    - Endpoints, prior antibiotics, methodology for determining NI.
  - Within the MDR Study
    - Agreement on pooling across body sites
    - Flexibility on comparator and use of external controls
    - If there is a randomized control, agreement on management of patient with comparator-resistant isolates in control arm
    - Ideally agreement on approach to use of rapid diagnostics

Summary

- MDR development focuses on an unmet need
- A totality of evidence approach expedites development while enhancing the strength of evidence supporting the new drug
- Development approaches must anticipate the problem of Drug #2: To meet the challenge of evolving resistance patterns there must be feasible pathways for both the initial and subsequent drugs that do not require a demonstration of superiority on a hard endpoint
- To provide these new therapies it will be necessary to accept greater uncertainty regarding efficacy and safety but some of the associated risk can be mitigated
- Harmonization of regulatory requirements is an essential component of this paradigm