European Federation of Pharmaceutical Industries and Associations

Clinical Exposure-Response Relationships

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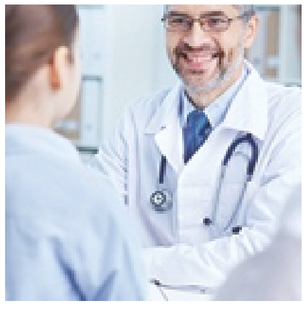

EMA PK-PD Workshop

12-13 Nov 2015

Clinical E-R in Development Process (Section 4.5)

- E-R provides an important step in the overarching pharmacometrics package within drug development
  - Utilized for a priori analyses and data exploration
  - Aims to quantify key effects against an exposure range
- E-R is grounded by individual drug or drug class pharmacologic/toxicologic properties
  - Safety analyses (important, but not discussed in Guideline)
  - Efficacy analyses

4.5.1 Potential Value of E-R relationships (Slide 1 of 4)

- *"…used to describe interplay of MIC, PK and outcome…identify clinical PK-PD indices and clinical PDTs to support adequacy of dose regimens selected from nonclinical PK-PD indices and PDTs." (Lines 468-472)*

- **EFPIA recommendation: It may, at times, be possible to reduce programmatic requirements**
  - **Example, Sponsors with a known class agents having contemporary nonclinical data (PDT and MIC distributions), and confident knowledge of population variance (from small patient Phase 1 or adequate inflated variance in PK models) may facilitate sufficient data to proceed into Phase 3**
  - **Suggested language: "Depending on prior class knowledge, nonclinical PDTs may sufficiently define target to reduce traditional programmatic requirements (e.g. dose finding, Phase 2)"**

4.5.1 Potential Value of E-R relationships (Slide 2 of 4)

"…it may not be feasible to describe the E-R relationship for all…. "(Lines 473-474)

- We agree that there are well-delineated limitations in some settings:
  - Limited number of clinical patients
  - Small numbers of failures prevent robust analyses
    - Failures by MIC may actually follow population MIC distribution if dosing is generally adequate
  - Patient Confounders
    - Non-surgical interventions or adjunctive treatments
    - Underlying host factors/ patient severity
      - Immune function
    - High mortality 'noise' in some disease states
      - Death is always a failure of the antibiotic, attributable or not

4.5.1 Potential Value of E-R relationships (Slide 3 of 4)

… limitations, continued:

- Microbiologic challenges
  - Inability to obtain and/or identify organisms in all disease states
  - Debate regarding causative organisms in mixed infections
    - Which pathogen or MIC is selected for ER? Select the pathogen with the highest MIC? Or most commonly associated pathogen?

- **EFPIA recommendation:**
- **We agree with and support retention of the language noting the limitations of E-R analyses.**
- **Although such analyses should be attempted by Sponsors, it may not be possible to derive clinical PDTs in all settings, supporting reliance on nonclinical targets.**

4.5.1 Potential Value of E-R relationships (Slide 4 of 4)

Already licensed agents (Lines 486-493):

- *"….unlikely ER relationships can be used to support changes to dose regimens unless new efficacy studies are conducted … consider offering stored samples to interested parties."*

- **EFPIA recommendation: This section is unclear as it relates to E-R analyses. Please expand and clarify intentions**

4.5.2 Analyses of E-R relationships

- *"…E-R relationships are confined to patients with documented outcomes, adequate PK and …MICs of the test agent…" (Lines 495-497)*
  - Typical assessments (dichotomous):
    - Micro/clinical responses at TOC
    - Improvement in biomarkers (continuous, time-to-event)
      - PaO_2/FiO_2 ratios, defervescence, decrease in wound size

- **EFPIA recommendation:**
  - **We appreciate the flexibility in model and statistical approaches based upon Sponsor's data exploration.**
  - **Consider this additional language: "Sponsors are encouraged to explore alternative endpoints in E-R analyses to support dose justification and effect size estimations."**

4.5.3 Application of E-R relationships (Slide 1 of 2)

- "*The ER relationship can be used to identify the highest MIC of the test agent that can be treated with confidence using a selected dose regimen, further supporting the initial predictions…" (Lines 510-512)*

- **EFPIA Response: Appreciates EMA consideration in that E-R supports predicted PTA, but it may not fully reflect successful response rates due to multitude of potential confounding factors.**
  - **While ER analyses may be supportive to breakpoint analyses, PTA ≠ response rate**
    - **Difficult to accrue meaningful number of isolates at high MICs**
    - **Confusing results- - e,g, 3 at a highest MIC: 1 cure, 1 failure and 1 indeterminate**
    - **Discussed further in Topic 6**

4.5.3 Application of E-R relationships (Slide 2 of 2)

- **EFPIA recommendation: Suggest EMA consider additional application for E-R analyses, when achievable**
  - **E-R may be of assistance for difficult indications (e.g., nosocomial pneumonia) or those in which NI margins are not well defined (e.g., bloodstream infections, osteomyelitis, diabetic foot infections, etc…)**
  - **Consider this additional language particularly for indications where knowledge base is less: "Sponsors are encouraged to consider E-R analyses, and other pharmacometric-based analyses, for estimation of treatment effect sizes and hence, as a support in selection of non-inferiority margins (see also Section 4.7)."**

Conclusions

- E-R analyses provide an important step toward a comprehensive pharmacometric data package

- E-R analyses should be encouraged for alternative applications (e.g. exploring alternative endpoints, support of treatment effect sizes, etc..)

- The noted limitations in deriving an E-R relationship in all settings, as well as the flexibility for Sponsor approaches to E-R analyses is appreciated

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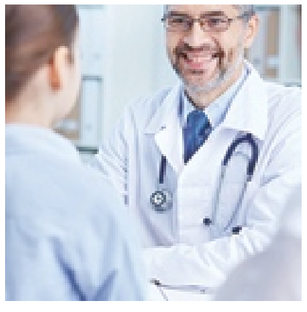
Thank you!





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