European Federation of Pharmaceutical Industries and Associations

Topic 2: PK data for supporting PK-PD analyses

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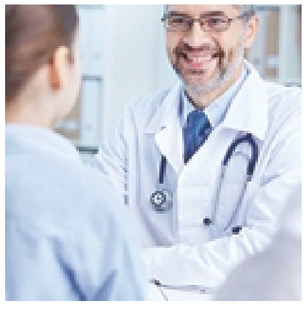

EMA PK-PD Workshop

12-13 Nov 2015

4.3 Clinical PK data to support PK-PD analyses; Title (slide 1/1)

- Section title: “Clinical PK data to support PK-PD analyses”
- EFPIA comment:
  - We agree with the need to obtain appropriate clinical PK data to allow conduct of population PK analyses
  - Also need appropriate clinical PD data to allow conduct of population exposure-response analyses (Topic 4)
    - Traditional efficacy endpoints: microbiological/clinical response at the ToC visit (or an early time point)
    - Non-traditional markers of improvement: temperature, symptom assessments, Pa02/Fi02 ratios, other biomarkers?
- **EFPIA recommendation:**
  - **Add “PD data” to the title and a section describing the appropriate PD data to support exposure-response analyses”**

4.3.2 PK data from patients; Lines 344 – 350 (slide 1/2)

- Line 344 – 350: “In initial studies with a test antimicrobial agent in infected patients…it is recommended that intensive PK data are obtained from a subset and sparse sampling PK data are obtained from the total study population assigned to the test agent. The PK data obtained from patients typical of the intended target population in terms of site of infection and severity of infection (but regardless of pathogen susceptibility) should be used to update the POPPK model. The updated model can then support repeat PK-PD analyses to confirm or reject the sufficiency of the dose regimen before proceeding to larger studies in patients.”
- EFPIA comment:
  - We agree that an early read of the PK in patients is important so that the population PK model generated with healthy volunteer data can be updated with patient specific data and used to confirm the dose/exposure for larger clinical studies.
  - We do not agree with specifying the sample design. The guidance should point to the need for a sample design that allows development of a robust model and accurate/precise PK parameter estimates to be obtained.

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4.3.2 PK data from patients; Lines 344 – 350 (slide 2/2)

- **EFPIA recommendation:**
  - **“PK data should be obtained from patients typical of the intended target population in terms of site of infection and severity of infection (but regardless of pathogen susceptibility) as early as possible in development and should be used to update the POPPK model based on healthy volunteer data. The updated model can support repeat PK-PD analyses and simulation to confirm or reject the likely sufficiency of the dose regimen before proceeding to larger studies in patients.”**

  - **“The PK sampling design to be used in clinical studies (sparse sampling and/or intensive sampling) should be selected to allow accurate/precise PK parameter estimates to be obtained. Optimal sampling design can be used to select sample times and the sample design can be validated with clinical trial simulation.”**

4.3.2 PK data from patients; Lines 354 – 360 (slide 1/1)

- Lines 354 – 360 (protein binding): “Initially this may be evaluated *in vitro*… Further estimates should be obtained during a study with radiolabelled test agent (if conducted) or from samples collected during clinical PK studies. The data collected from infected patients should suffice support a robust estimation of unbound (free) concentrations of the test agent that can be used for PK-PD analyses.”
- EFPIA comment:
  - If a drug is not highly protein bound (fu > 20%) and there is no *in vitro* evidence of concentration-dependent binding, further study is not needed.
  - Non-linear binding may need to be addressed by measuring free concentration in a study or using a model-based approach [Singh et al. CP&T 2014; 95(suppl.1):S87]
    - technical difficulties in measuring protein binding may be a issue
- **EFPIA recommendation:**
  - **“The degree of binding of the test agent to human plasma proteins in the presence of clinically relevant concentrations should be assessed. Initially, this is typically done *in vitro*. For drugs with non-linear binding, if technically feasible, further assessment may be necessary during drug development.”**

4.3.3 Topic 2 - Other relevant data; Lines 361 – 363 (slide 1/2)

- Line 361 – 363: “As relevant to the test agent and its intended clinical uses, total and free test agent concentration-time data should be presented for specific body fluids and related to plasma/serum levels using compartment PK modelling.”
- EFPIA comments:
  - We agree with the importance of obtaining drug concentration data at bodily sites more relevant to the site of infection in both preclinical animal efficacy studies and in human.
  - We would not specify “free” as free drug is not always specifically assayed for (e.g., ELF).
  - We want to note that an assessment of the extent of drug penetration can be obtained through compartmental and non-compartmental methods.
    - e.g., rapid distribution and a “complete” composite profile
  - We remain concerned about the limitations and use of data obtained at body sites outside of plasma.

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4.3.3 Topic 2 - Other relevant data; Lines 361 – 363 (slide 2/2)

- EFPIA comments (using ELF as an example):
  - We are concerned about limitations of the data (BAL collection methodology, sampling limitations, drug/urea assay quality) and their influence on variability.
  - Based on this, we do not think simulations for PTA can routinely be meaningfully computed for ELF.
  - ELF/plasma exposure ratios could be used to account for differences in lung penetration between animals and human and to justify a plasma-based PD targets.
- **EFPIA recommendation:**
  - **“As relevant to the test agent and its intended clinical uses, test agent concentration-time data should be presented for specific body fluids and related to plasma/serum levels.”**

4.3.3 Topic 2 - Other relevant data; Lines 375 – 379 (slide 1/2)

- Line 375 – 379: “For test agents that will be used to treat patients receiving positive pressure ventilation (PPV) the potential for this to affect PK of the test agent should be considered before commencing studies in infected patients. If an effect of PPV on PK cannot be ruled out based on the physicochemical properties of the test agent it is important that the issue is evaluated either in a dedicated study or in an initial cohort of infected patients within a larger study.”
- EFPIA comments:
  - Please describe where the concern with PPV on PK has arisen.
  - Is it related to a potential impact of PPV on hemodynamics resulting in changes in drug distribution/elimination?
    - If so, are there non-clinical data including *in vivo* models that have indicated such an effect?

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4.3.3 Topic 2 - Other relevant data; Lines 375 – 379 (slide 2/2)

- EFPIA comments (continued):
  - Is the concern related to sepsis physiology frequently observed in patients on PPV?
  - If the concern is related to augmented renal clearance, should this be considered independent of PPV, as ARC is sometimes observed in patients who are not on PPV?
  - Can the agency propose examples of how a dedicated study would be designed to address the potential for PPV to affect PK?
  - How does one determine if PPV will affect the PK of a test agent based on the physicochemical properties?
- **EFPIA recommendation:**
  - **This section should be significantly revised or stricken**

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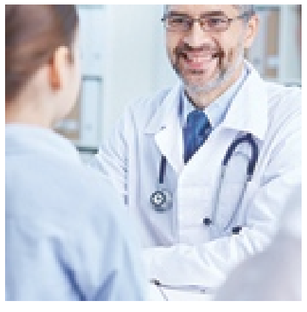
Thank you!





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Back-up Slides

4.3.3 Topic 2 - Other relevant data (ELF)

- EFPIA comment:
  - ELF/plasma exposure ratios could be used to account for differences in lung penetration between animals and human and to justify a plasma-based Pd target.

    For example:
    - a plasma-based target is obtained in an animal pneumonia model; lung penetration data are also obtained (ex, E/P = 100%)
    - TAR simulations for human dose selection are conducted based on the plasma-based target
    - the human E/P = 50%; the dose is altered (doubled) based on the different animal and human lung penetrations