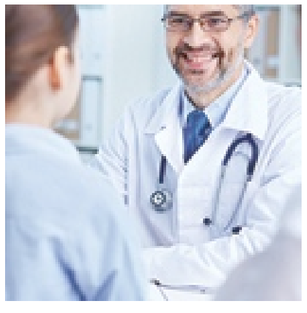
European Federation of Pharmaceutical Industries and Associations

Topic 1 – Nonclinical models to identify PK-PD indices and PD Targets - Industry Perspective

Kevin Krause, *on behalf of the EFPIA team*





EMA PK-PD Workshop

12-13 Nov 2015

Introduction

- Non-clinical in vitro and in vivo models set the foundation for a robust PK/PD and dose justification story
- Each model type has its own advantages and should be used in situations where the output can best answer a specific question being asked about a given drug
- Therefore, defining a hierarchal approach to PK/PD that works for all drugs is not possible

Both In Vitro and In Vivo Models have Advantages (1 of 2)

- *Lines 273-282:* "In-vitro models have several advantages over animal models. In particular, in-vitro models make it possible to: ..."
- We agree that in vitro models do have some advantages over in vivo models, however these do not necessarily apply to all drugs
- **EFPIA recommendation: We suggest adding "may" in front of "…have several advantages…" to allow for alternate pathways for agents where good in vitro – in vivo correlations are not observed.**

Both In Vitro and In Vivo Models have Advantages (2 of 2)

- *Lines 273-282:* "In-vitro models have several advantages over animal models. In particular, in-vitro models make it possible to: ..."
- We also believe that there are advantages to in vivo models that are not mentioned in the in vivo section.
- **EFPIA recommendation: Suggest adding an introductory statement to the Animal Models section (beginning on line 290) that says "There are also some distinct advantages to in vivo models that may make them more suitable for early investigations, including**
  - **Well established methods for defining PK/PD targets**
  - **Linkage between in vivo efficacy and clinical response has been established"**

The Use of In Vitro Models as a Recommended Starting Point

- *Lines 253-256: "In general, the use of in-vitro models is recommended initially so that…"*
- This assumes that in vitro and in vivo models provide the same answer
  - This can be especially challenging for novel antibacterial classes where there is no historical basis for the PD profile or the PK/PD driver of efficacy, or
  - When more robust growth can be achieved in vitro than in vivo, or
  - In instances where in vitro resistance is greater than in vivo observations
- **EFPIA recommendation: We suggest replacing "recommended initially" with "may be used initially or in conjunction with" to remove the suggestion of a hierarchical approach to PK/PD program design.**

The Specific Advantages of In Vitro PK/PD Models

- *Lines 273-289:* "In-vitro models have several advantages over animal models. In particular, in-vitro models make it possible to: ..."

- **EFPIA recommendation: We suggest adding a 5th bullet after line 286 that says "Use a data-driven approach to justify alternative PK/PD indices that may be appropriate for a given drug"**

In Vitro Models and Resistance

- *Lines 283-284:* "Study the relationships between rates of emergent resistance, drug exposure and duration of therapy"
- We agree that in vitro model systems are a convenient way to study the potential for emergence of resistance,
- However, emergence of resistance in vitro does not always correlate with in vivo or clinical resistance.
- **EFPIA recommendation: Suggest changing the above text to "Study the relationships between rates of emergent resistance, drug exposure, and duration of therapy. It may be useful to evaluate these relationships in multiple models of infection to aid in selecting a dose that suppresses or limits the potential for resistance development"**

Continued Flexibility in Experimental Design and Contents of PK/PD data Package is Critical

- Allows for development of a dose justification story that makes sense for each individual drug
- Creates an environment where contemporary methods can be used to build a story that supersedes previous work on the class

Conclusions

- The value of in vitro and in vivo models as building blocks of a well thought out dose justification story stems from the ability to be flexible in the use of these models
- Flexibility in design also allows for introduction of novel PK/PD technologies, concepts, targets and approaches to data analysis
- A well-designed and comprehensive PK/PD data set should complement a robust clinical data package, so again, flexibility on the PK/PD side is necessary in order to keep up with more creative trial designs and approval pathways that are currently being explored.

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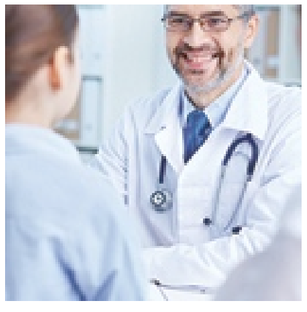
Thank you!





EFPIA Brussels Office
Leopold Plaza Building * Rue du Trône 108
B-1050 Brussels * Belgium
Tel: + 32 (0)2 626 25 55
www.efpia.eu * info@efpia.eu