Demonstration of Relevance of the Animal Model

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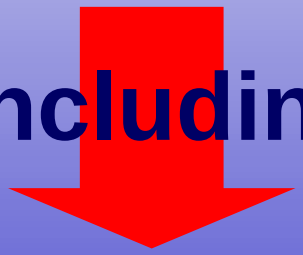
Guideline Purpose

To Assist Sponsors in The Transition From Non-Clinical Into Early Clinical Development



including

FIM dose

Calculation of MABEL

should utilise all relevant *in vitro* and *in vivo* available information from PD/PK data, eg:

- i) receptor binding and receptor occupancy
- ii) concentration-response curves
- iii) exposures at pharmacological doses in the **relevant species**.

Integrated in a PK/PD modelling approach

(FIM

WHY?

«higher concern» at FIM

Because…..

- Nonclinical studies performed in such nonrelevant models may:
  - Not reproduce the intended PD effect in Humans
  - Lead to misinterpretation of PK (and PD) results
  - Miss relevant toxic effects

Search for & Demonstration of

Relevant
(Animal Models)

Is of High Relevance

should be documented & justified

The Demonstration of Relevance Includes:

- Comparison of pharmacodynamics.
- Comparison of pharmacokinetics.
- Cross-reactivity studies using human and animal tissues.

Comparison of Pharmacodynamics

- **should include**
  - the target structure
  - binding
  - Target occupancy
  - functional consequences (incl. cell signalling)
  - functionality of additional functional domains

More explicit requirements

vs

ICH-S6 Guideline!

If NO Relevant Species Exist

- The use of relevant Tg animals expressing the human target
- The use of homologous proteins

Is Strongly Recommended

Comments

- Comparison of target structure (primary, secondary, tertiary?)
- Not all targets are receptors
- Cross reactivity studies are mainly for MAbs
- Concerns on the use of Tg animals (comparison to human situation suggested)

Comments

The extent to which relevant species is relevant Should be discussed

i.e.

discussion of the limitations

of available species and models

to predict human safety is suggested