Considerations for the development of biological medicinal products

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- **Nonclinical study requirements for biologicals**
- **Special considerations**
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- **Estimating first in human dosing**

Biological medicinal products (biologics)

- **Pharmaceuticals derived from living organisms such as:**

  Humans, animals, plants, microorganisms

  and/or by biotechnology methods (recombinant DNA techniques/cell culture)

Biologics include

- **Modified human proteins**
- **Monoclonal antibodies**
- **Cytokines & growth factors**
- **Antagonist/inhibitor (peptide based)**
- **Blood products**
- **Vaccines**
- **Hormones**
- **Advanced therapy medicinal products (cell/gene therapy and tissue engineered products)**

Recommendations for biologics may in part be applicable to other types of medicinal products e.g. oligonucleotides.

What's so special with biologics?

Often

- **Large molecules**
- **Species-specific**
- **Long acting (mAbs), intermittent dosing**
- **Degraded/catabolized**
- **Potentially immunogenic**
- **Limited distribution**
- **Toxicity: exaggerated pharmacology**
- **Complex temporal effects, not necessarily linear**
- **Complex manufacturing and control but simple formulations for parenteral use**

Nonclinical guidance

- **ICH guideline S6 (R1)-**preclinical safety evaluation of **biotechnology-derived** pharmaceuticals med addendum of 2011. EMA/CHMP/ICH/731
- **ICH M3 (R2)** Nonclinical safety studies for the conduct of human clinical trials with pharmaceuticals *guidance on timing and study requirements for different phases of development*
- Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products **(**EMEA/CHMP/SWP/28367/07)

+ additional product specific non-clinical guidance (e.g. vaccines, advanced cell therapy medicinal products) or advanced cancer (ICH S9)

Nonclinical evaluation of biologicals- objectives

Same aims as for small molecules

- **Provide support for effect in humans**
- **Identify safe human dose (exposure)**
- **Identify target organs and information on irreversibility/reversibility**
- **Provide guidance for safety monitoring/risk management**

-> benefit/risk assessment

General nonclinical program adapted to a biological medicinal product

PHARMACOLOGY

Primary pharmacodynamics
Secondary pharmacodynamics (receptor screening generally not of value)
Safety pharmacology (part of repeated dose)

PHARMACOKINETICS

AD*M*E ~~Pharmacokinetic drug interactions (nonclinical)~~

TOXICITY

Single dose toxicity
Repeat-dose toxicity
~~Genotoxicity~~*Carcinogenicity (to be adressed)*
Reproductive and developmental toxicity
Local tolerance (part of repeated dose)
Other toxicity studies (e.g. immunotoxicity)
~~Phototoxicity~~ Tissue cross reactivity (mAbs)

- **Timing of study follows M3 with a few exceptions**

Product related issues often impact nonclinial package

Considerations when evaluating biologics

Evaluating safety of biologics, special considerations

- **Toxicity often due to exaggerated pharmacology (on-target)**
  - e.g. anti-CD20 antibody->B cell depletion->increased risk for infections.

  Characterization of Pharmacology and PK/PD relationships is important
- **Off-targets toxicity/class related effects**

  Antibodies -> Fc-part related effects (e.g. cytokine release) or immunogenicity.

  Oligonucleotides: well-known sequence unspecific, back-bone related toxicity (e.g. coagulation inhibition and complement activation)

Use pharmacologically relevant species

- **Identify pharmacologically relevant species**

- **Characterize potential differences in potency**

Target expression
Sequence homology

Binding characteristics

Functional assays
Human vs animal cell assays

***In vivo* pharmacology**

Study requirements depend on available relevant species

- **Rodent and non-rodents <u>both relevant</u>:**
  General toxicity studies in <u>two</u> species.
- **Rodents <u>not</u> relevant - or feasible:**
  One species sufficient. Common that monkey is the only relevant species.
- **Similar findings in short term studies in rodents and non-rodents:**
  One species sufficient for long-term toxicity studies. Use rodent unless justified

Study requirements, cont.

Special situations:

- **Target expressed at no/low levels in healthy animals:**
  Incorporating safety endpoints in proof-of- concept (disease model) study may be of value.
- **No relevant species available.**
  Homologous molecule, transgenic animals,
  human cell assays (each have pros and cons, justify if used)
- **Gaps in knowledge.**
  Possible to manage in the protocol and acceptable for the indication?

Dose selection for nonclinical safety studies:

Pharmacokinetic-Pharmacodynamic relationships can assist dose selection

High dose selection: select highest of the following:- dose needed to reach maximal pharmacological effect, or a 10-fold exposure margin to clinical exposure (unless justified).

Differences in binding/potency should be taken into account.

Frequency and route of administration: mimic intended dosing (but adjust taking PK into account)

Duration of safety studies

Duration should support duration of clinical trial (ICH M3).
2 week repeated dose toxicity studies minimum for up to 2 w long FIH trial. 6-months studies generally sufficient for chronic administration.

Recovery animals: to assess reversibility of effects not delayed toxicity. Long $t_{1/2}$ should be considered

Provide rational for study design

Immunogenicity

Human proteins often immunogenic in animals.
Development of anti-drug antibodies (ADA) may impact exposure and -> pharmacodynamics/toxicity.

Kinetics: *increased or reduced clearance of the drug*
Effect/pharmacodynamics: e.g. *Neutralization (of effect)*
Toxicity: *e.g. antibody mediated immune reactions. Under-estimation of toxicity, cross-reactivity to endogenous proteins*

- **Collect samples.** Analyse if ADA development is indicated by PK or Toxicity data.

- Take into account in the assessment of nonclinical data.(e.g. to explain findings and/or that animals have been adequately exposed)

Not predictive of immunogenic potential in humans

Safety pharmacology

- **Evaluated as a part of repeated dose toxicity studies.** Separate studies if concerns needs to be addressed

- hERG test normally not appropriate for biologics

Local tolerance/toxicity (e.g. injection site reactions)

- **Evaluated as part of repeated dose toxicity studies**

Development and Reproductive Toxicology studies

- **If both rodent and non-rodent (e.g. rabbit) relevant and feasible** -> **ICH M3 applies**. Differences in placental transfer should be taken into consideration.
- **Monkey should only be used if it is the only relevant species. If so:**
  - **different timing** - generally prior to phase III or MAA depending on placental transfer during organogenesis or other cause of concern)
  - **no requirement for mating studies -** fertility evaluated in repeated dose toxicity studies
  - **one well designed study** (e.g. enhanced pre- and postnatal development study, ePPND).

Genotoxicity testing

- **Generally not required for biologicals** *limited risk for DNA interaction*
- **Recommended for oligonucleotides that contain non-natural chemical modifications (if not previously documented for oligos of this class).**

Carcinogenicity

- **Biologicals may be non-genotoxic carcinogens**
- **Standard models generally not appropriate for biologics.** "when an assessment is warranted the sponsor should design a strategy to address this issue. " (ICH S6)

Specific assays

- **Tissue cross reactivity (for antibodies):**
  - human tissue panels
  - animal tissue panels (not for species selection but may be of value for assessment of toxicity)
  - TCRs may not always be feasible

- **In vitro assessment of risk for antibody mediated reactions**
  - complement activation
  - Antibody mediated cell cytotoxity (ADCC)
  - cytokine release assays

Additional modifications to the nonclinical program?

Common that the nonclinical program (or a study) requires additional modifications due to product-specific issues

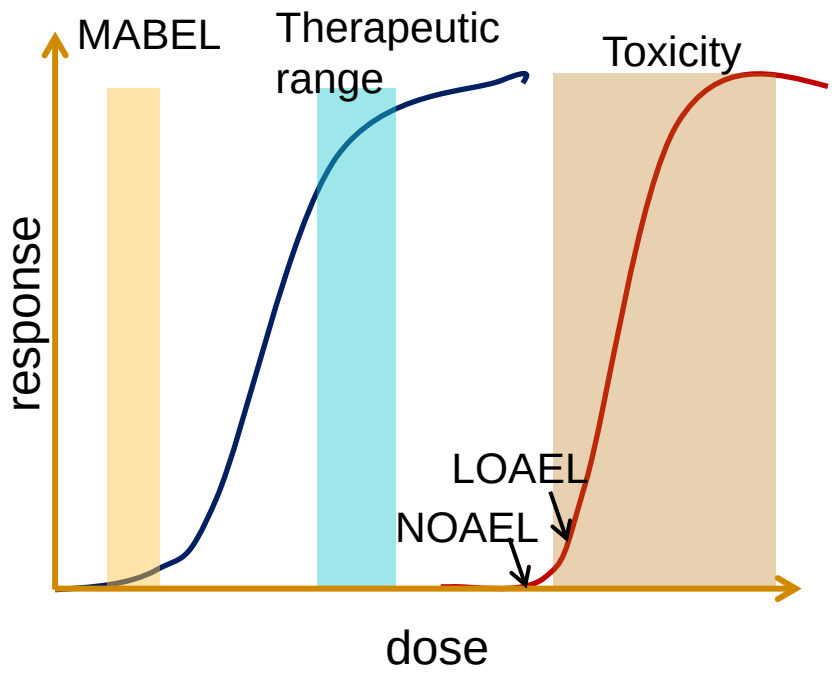
(e.g. no relevant species available, immunogenicity, safety findings)

→discuss deviations from guidelines with the regulatory agencies (national or central advice)

First-in-human dose

Optimal starting dose:

- **No toxicity**
- **Low/no pharmacodynamic response**
- **Measurable plasma concentration**
- **Sufficiently high to attain study objectives within reasonable time**

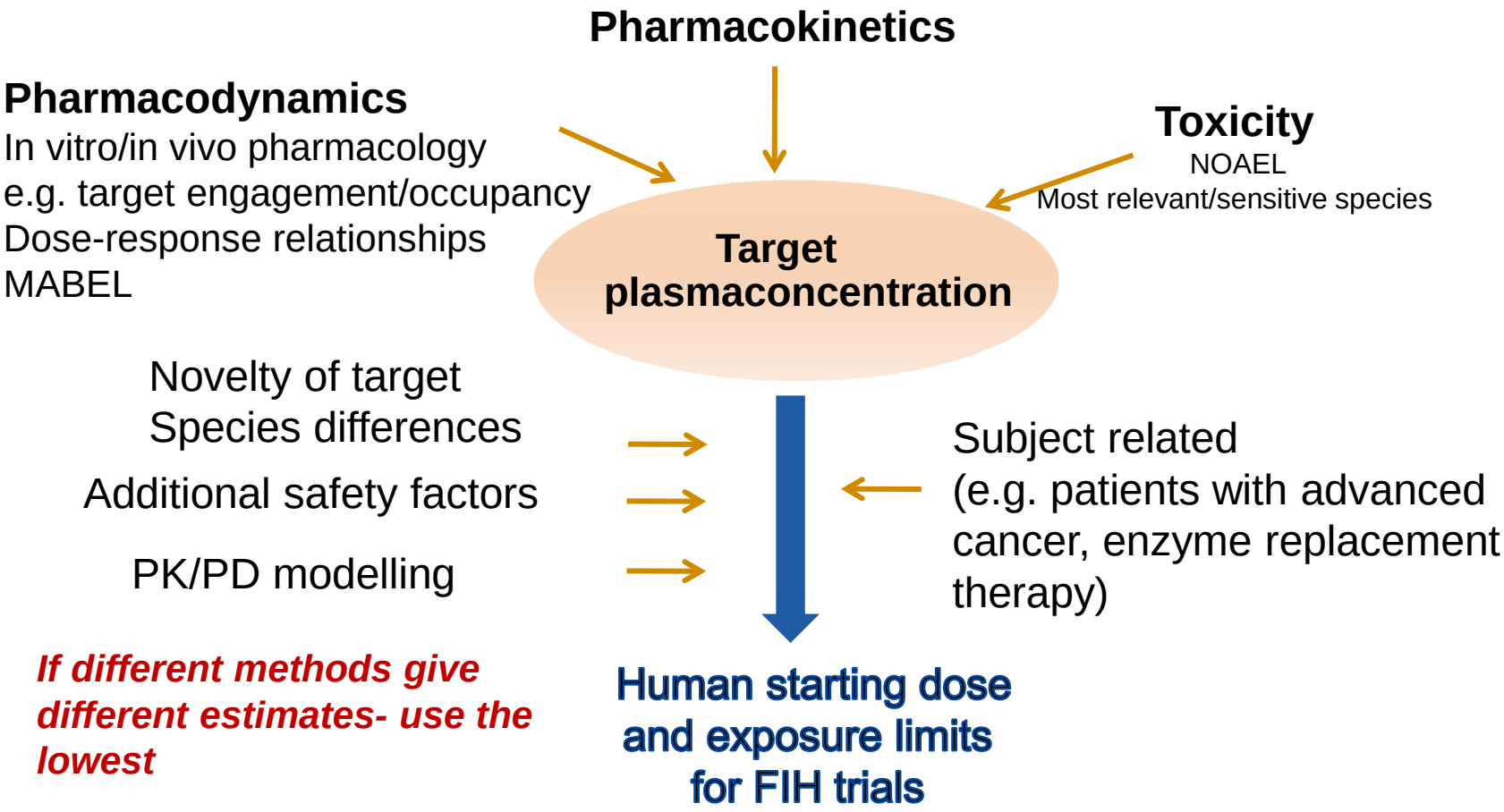


HED *human equivalent dose:* Based on (NOAEL) allometric body surface scaling

vs

MABEL *minimal anticipated biological effect level:*
Based on pharmacological effect (PK/PD relationship)

Consider all relevant data



….then use emerging clinical PK data to verify/adjust dose escalation steps

Take home message

- **Toxicity often on-target related**
- **Use relevant animal species**
- **Immunogenicity- may impact interpretation of animal data. Collect samples, analyze for ADA if needed.**
- **Product-specific issues often requires adaptations of study program: discuss with regulatory agencies**
- **Use all relevant nonclinical information when estimating human dose**