Unique PK-PD properties of biotechnology-based therapeutics [mAbs] and First In Human dose considerations

[mAbs - monoclonal antibodies]

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Key questions to be addressed

Optimal characterisation of preclinical PK-PD relationships in a pharmacologically relevant species to enable selection of an appropriate starting dose and dose range for clinical studies

- How much drug (mAb) do we need to get to the target and for how long?
  - pharmacokinetics / delivery
- How will we know if it works - what are the required PD characteristics?
  - feasible dose and route of administration
  - feasible dosing frequency
- How will we know if it is safe – what is the potential safety liability?

1 what is relevant?
- affinity / potency
- target expression / turnover
- downstream markers
Outline of the presentation

– Historical background
  - FDA guidance - pros and cons
  - TGN1412 incident - Northwick Park, Mar-06
  - Minimal Anticipated Biological Effect Level (MABEL)
  - EMEA guideline - risk mitigation

– PK-PD model based approach to characterise Ab-ligand binding
  - typical behaviour of mAb-ligand binding models
  - dose – response relationships
  - examples: soluble and cell surface targets

– Justification of safe starting dose in man
  - NOAEL and MABEL

– Summary
Paracelsus 1493 – 1541

Alle Ding' sind Gift und nichts ohn' Gift; allein die Dosis macht, das ein Ding kein Gift ist.
"All things are poison and nothing is without poison, only the dose makes a thing be poison."
... ... 500 years later

Guidance for Industry and Reviewers
Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers
July 2005
FDA 2005 guidance - Summary

[Step 1] Determine “No Observable Adverse Effect Level” (NOAEL)

[Step 2] Convert NOAEL to a “Human Equivalent Dose” (HED)
- generally normalised to body surface area (low MW NCEs)
- mg/kg normalisation recommended for proteins >100K daltons

[Step 3] Select HED from the most appropriate species
- additional factors: metabolism, receptors, binding epitopes …
- default: most sensitive species (lowest HED)

[Step 4] Apply a safety factor (>10-fold) to give a:
“Maximum Recommended Starting Dose” (MRSD)

[Step 5] Adjust MRSD based on the pharmacologically active dose (PAD)
FDA 2005 guidance - Summary

Pro
- simple to use
- supported by historical evidence (mainly conventional NCEs)

Con
- primary focus: NOAEL
- secondary focus: pharmacologically active dose
- over simplified scaling to man
- focus on dose not exposure
- one algorithm fits all
- step 5 (PAD) often ignored
mAbs – *high species specificity*

- adverse effects are often a direct consequence of exaggerated pharmacology - “on target” effects
- safety assessment is critically dependent on an understanding of risks associated with target and downstream pathways
- focus on pharmacological activity taking into account adverse events at higher dose levels

**NB** reliant on robust measures of pharmacology (**PD biomarkers**):
- **target** (eg receptor occupancy or ligand binding)
- **mechanism** (eg downstream signalling)
- **outcome** (eg clinical response)
TGN1412 incident - Northwick Park

Two drug trial men critically ill

Two men remain critically ill and four others are in a serious condition after suffering a violent reaction while taking part in a clinical drugs trial.

All are still in intensive care in Northwick Park Hospital, north-west London, after falling ill on Monday.

Sir Gordon Duff

November 2006
Recommendation from Duff report

10. A broader approach to dose calculation, beyond reliance on ‘No Observable Effect Level’ or ‘No Observable Adverse Effect Level’ in animal studies, should be taken. The calculation of starting dose should utilise all relevant information. Factors to be taken into account include the novelty of the agent, its biological potency and its mechanism of action, the degree of species-specificity of the agent, the dose-response curves of biological effects in human and animal cells, dose-response data from in vivo animal studies, pharmacokinetic and pharmacodynamic modelling, the calculation of target occupancy versus concentration and the calculated exposure of targets or target cells in humans in vivo.

The ‘Minimal Anticipated Biological Effect Level’ (MABEL) approach is one good model for achieving this. (See BIA/ABPI report and stakeholder submission.)

Expert Scientific Group – Phase I clinical trials Nov 2006
Risk mitigation strategies

Factors affecting risk:
- mode of action
- nature of the target
- relevance of animal species and models
Risk mitigation strategies

For investigational medicinal products for which factors influencing risk according to section 4.1 have been identified, an additional approach to dose calculation should be taken. Information about pharmacodynamics can give further guidance for dose selection. The ‘Minimal Anticipated Biological Effect Level’ (MABEL) approach is recommended. The MABEL is the anticipated dose level leading to a minimal biological effect level in humans. When using this approach, potential differences of sensitivity for the mode of action of the investigational medicinal product between humans and animals need to be taken into consideration e.g. derived from in-vitro studies. A safety factor may be applied for the calculation of the first dose in human from MABEL as discussed below.

The calculation of MABEL should utilise all in vitro and in vivo information available from pharmacokinetic/pharmacodynamic (PK/PD) data such as:

i) target binding and receptor occupancy studies in vitro in target cells from human and the relevant animal species;
ii) concentration-response curves in vitro in target cells from human and the relevant animal species and dose/exposure-response in vivo in the relevant animal species.
iii) exposures at pharmacological doses in the relevant animal species.

Wherever possible, the above data should be integrated in a PK/PD modelling approach for the determination of the MABEL.
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  - typical behaviour of mAb-ligand binding models
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- **Summary**
A simple mAb PK model

- iv dose
- elimination mAb
- slow clearance
- \( V \sim 7L \)
- \( t_{\frac{1}{2}} \sim 300 \text{ h (human)} \)

FcRn protects IgG from degradation & explains long serum half-life

Roopenian and Akiles.  
Nature Reviews Immunology 2007; 7: 715
A simple mAb-ligand PK-PD model

- **mAb “A”**
  - Elimination mAb
  - Dose

- **ligand “B”**
  - Elimination ligand

- **mAb – ligand complex “C”**
  - Elimination mAb – ligand complex

- **slow clearance**
  - \( V \sim 7L \)
  - \( t_{1/2} \sim 300\ h \)
**mAb PK-PD ligand binding models**

**Soluble target:**
mAb-ligand complex tends to take on the elimination characteristics of the mAb

**Cellular target:**
mAb-ligand complex tends to take on the elimination characteristics of the ligand (TMDD apparent)

Lowe PJ et al: On setting the first dose in man: Quantitating biotherapeutic drug-target binding through PK and PD models
Basic & Clin Pharmacology & Toxicology 2009; 106: 195-209
Components of the PK-PD model

- Inherent pharmacokinetics of the mAb and clearance of the mAb-ligand complex:
  - PK of monoclonal antibodies will generally follow “typical IgG behaviour” and scale reasonably well to man and/or exhibit Target Mediated Disposition and be dependent on the amount of target present and its rate of turnover

- Binding affinity and potency against the target ligand:
  - species differences understood during characterisation of the mAb
  - once “maximum” ligand binding is achieved then increasing the dose will primarily increase the duration of response

- Expression and turnover of the ligand:
  - key drivers of the extent and duration of response
  - species differences often not well understood
    - healthy individuals vs disease often not well understood
Potential benefits of a model based approach

- “simple” mathematical representation of known biology
  also represents components of the model which cannot be measured
  (e.g., low circulating level of free ligand)

- Sensitivity analysis
  elements of the model which are key drivers of the desired outcome
  (e.g., affinity / potency)

- Hypothesis testing
  the ability to test assumptions prior to experimental design, leading to better
  pre-clinical studies
Example 1: “Typical PK-PD behaviour” – cell surface ligand

anti-CD11a mAb – Raptiva (efalizumab)

Increasing dose:
change in IgG kinetics

Increasing dose:
increases duration of effect

Example 2: target suppression in safety assessment

A single dose of 100mg/kg is capable of maximal suppression of the target ligand for >75 days

**NB** consequence for repeat dose GLP tox and recovery period
Example 2: target suppression in safety assessment

4wk GLP toxicology study  cell surface ligand

Conclusion:
- 16wk recovery period is appropriate to characterise the PK (and hence the PD effect) for this molecule (4wk study 40 mg/kg/wk)
- NB assumption! target turnover is not affected by drug treatment
Example 3: “Typical PK-PD behaviour” – soluble ligand

anti-IL1β mAb – Ilaris (canakinumab)

simulation 0.1, 0.3, 1, 3 and 10 mg/kg
Example 4: target suppression in safety assessment

- soluble ligand

- humanised mAb; high affinity against soluble target
- $K_d$ man < cyno (~10-fold)
- “typical IgG kinetics”
- target ligand can be measured in the systemic circulation
- mAb acts as a “capture system”:
  - mAb-ligand complex (detected in serum) is a biomarker for suppression of free ligand via a PK/PD model
Example 4: target suppression in safety assessment

4wk GLP toxicology study

soluble ligand

PK-PD model:
- exposure and total ligand
  - pre-clin exposure data conform to a 2-compartment model
  - increase in total ligand fitted to ligand binding model
  - PK-PD model allows estimation of free ligand (target suppression)

PK (exposure)  PD (total ligand)

Concentration

Time (days)

Dose: 3

DOSE: 3

Dose: 20

DOSE: 20

Dose: 120

DOSE: 120
Example 4: target suppression in safety assessment

- pre-clin exposure data adjusted to man
- binding affinity in PK-PD model adjusted to man

Monte-Carlo simulation

MABEL

Monte-Carlo simulation
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NOAEL and MABEL

NOAEL – No Observable Adverse Effect Level

FDA – “highest dose level that does not produce a significant increase in adverse effects”

“an effect that would be unacceptable if produced by the initial dose of a therapeutic in a phase I clinical trial conducted in adult healthy volunteers”

MABEL - Minimal Anticipated (Acceptable) Biological Effect Level

minimal exposure / dose level that is anticipated to produce an acceptable biological effect

“an effect that would be considered acceptable if produced by the initial dose of a therapeutic in a phase I clinical trial”
**FIH dose calculation**

<table>
<thead>
<tr>
<th>Toxicology (exposure)</th>
<th>Pharmacology (response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1] NOAEL 100 mg/kg</td>
<td>[5] PAD / MABEL</td>
</tr>
<tr>
<td>[2/3] HED 100 mg/kg</td>
<td>- justify based on pharmacology</td>
</tr>
<tr>
<td></td>
<td>- (demonstration of max pharmacology in pre-clinical species)</td>
</tr>
<tr>
<td></td>
<td>- adjust for anticipated <em>exposure</em> in man?</td>
</tr>
<tr>
<td>[4] Apply &gt;10-fold safety factor 10 mg/kg *</td>
<td>- include anticipated duration of effect</td>
</tr>
<tr>
<td></td>
<td>- adjust for <em>inter-species differences in affinity / potency</em></td>
</tr>
</tbody>
</table>

"Maximum Recommended Starting Dose"

- define anticipated safety window based on NOAEL and MABEL

1 mg/kg

* - NB an additional factor may be added based on uncertainty of data / prediction and relative risk
Summary:

calculation of starting and incremental doses in FIH studies

- Important to understand target mechanism, pharmacology and limitations of the preclinical data for predicting human safety and efficacy
  - target concentration and turnover, affinity, potency across species

- Estimate the clinical starting dose for FTIH study using both toxicology (NOAEL) and pharmacology (MABEL)
  - no simple algorithm for MABEL – case by case

- Design the clinical study to mitigate risk
  - PK/PD data from initial and subsequent dose cohorts can aid dose escalation in FTIH study
  - consider stopping rules, exposure limitations based on pharmacology AND toxicology
Thank You