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

[mAbs -monoclonal antibodies]

Peter Lloyd

Head of Pharmacokinetics-Pharmacodynamics

Novartis Biologics

Key questions to be addressed

Optimal characterisation of preclinical PK-PD relationships in a pharmacologically relevant[1] 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

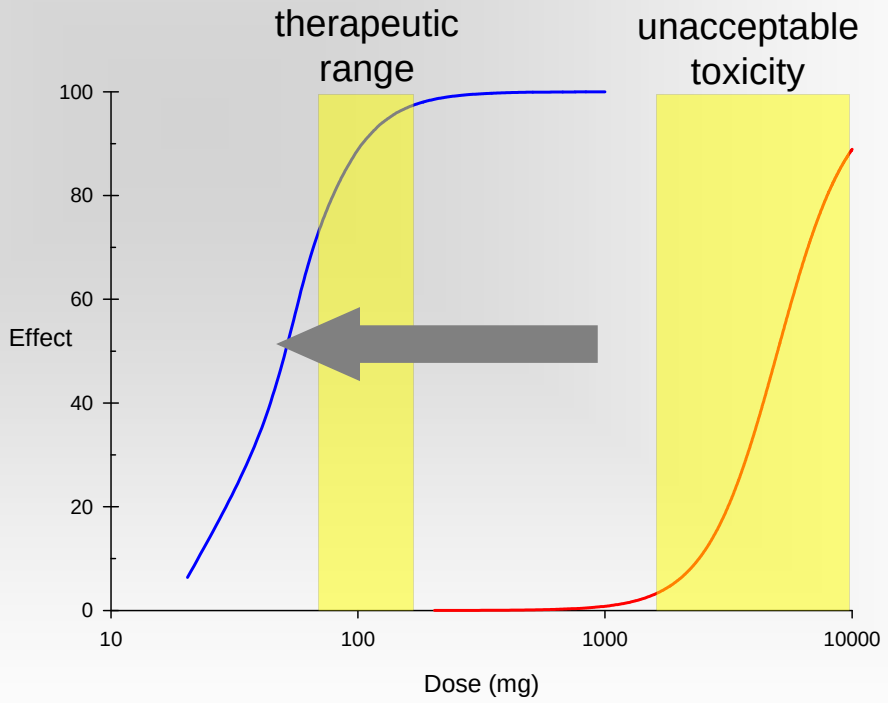
- **Historical background**
  - FDA guidance - pros and cons
  - TGN1412 incident - Northwick Park, Mar-06
  - Minimal Anticipated Biological Effect Level (MABEL)
  - EMEA guideline - risk mitigation
- **PK-PD model based approach to characterise Ab-ligand binding**
  - typical behaviour of mAb-ligand binding models
  - dose – response relationships
  - examples: soluble and cell surface targets
- **Justification of safe starting dose in man**
  - NOAEL and MABEL
- **Summary**

Historical background

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."

Geigy
1758
Johann Rudolf Geigy-Gemuseus (1733-1793) begins trading in "Materials, Chemicals, Dyes and Drugs of all Kinds" in Basel.



... ... 500 years later

U.S. Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

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

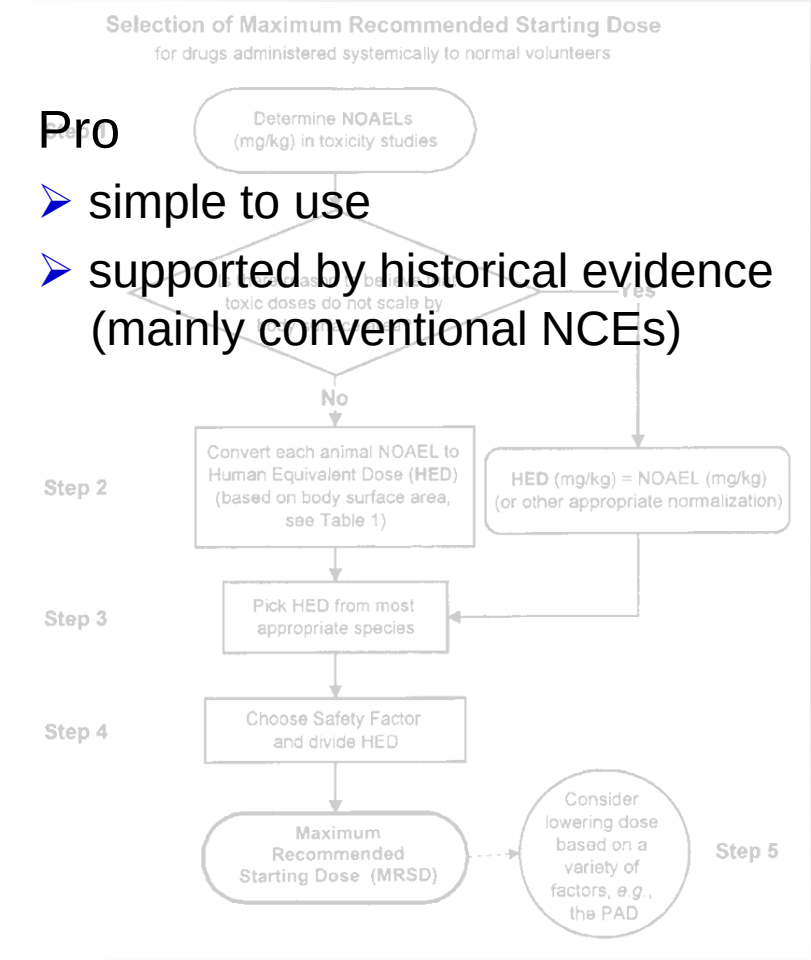
[Step 3] Select HED from the most appropriate species

- 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



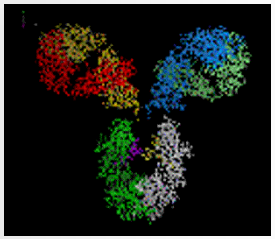
Pro

- 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

BBC Home | Search | Explore the BBC

UK version | International version | About the versions | Low graphics | Accessibility help

BBC NEWS | LIVE BBC NEWS CHANNEL | News services Your news when you want it

News Front Page
World
UK
England
Northern Ireland
Scotland
Wales
Business
Politics
Health
Education
Science & Environment
Technology
Entertainment
Also in the news
Video and Audio
Have Your Say
Magazine
In Pictures
Country Profiles
Special Reports

Last Updated: Wednesday, 15 March 2006, 22:37 GMT

E-mail this to a friend | Printable version

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.

The six are being treated at Northwick Park hospital

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

BBC LONDON
BBC London
Sport, travel, weather, things to do, features and much more

SEE ALSO:
- 'They say he needs a miracle' 15 Mar 06 | Health
- Making a career out of drug tests 15 Mar 06 | London
- Q&A: Drug trials 15 Mar 06 | Health
- Six taken ill after drug trials 15 Mar 06 | London
- Confusion over drug trial rights 26 Feb 06 | Health
- Woman died on cannabis drug trial 12 Dec 05 | South Yorkshire

RELATED BBC LINKS:
- Clinical trials

Expert Scientific Group on Phase I clinical trials

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

European Medicines Agency

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

effective 01-Sep-07

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:

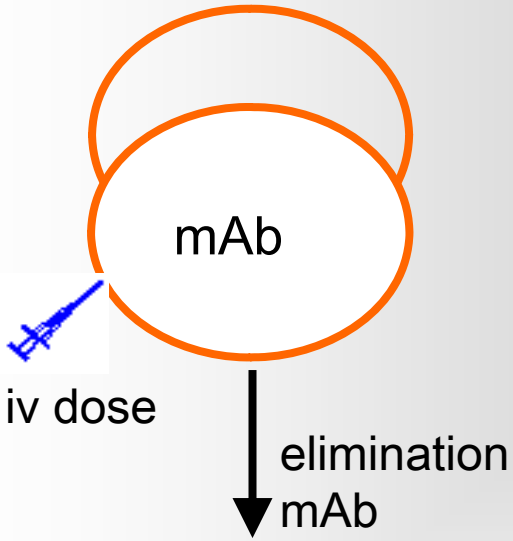
i) target binding and receptor occupancy studies *in vitro* in target cells from human and the relevant animal species;
ii) concentration-response curves *in vitro* in target cells from human and the relevant animal species and dose/exposure-response *in vivo* in the relevant animal species.
iii) exposures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

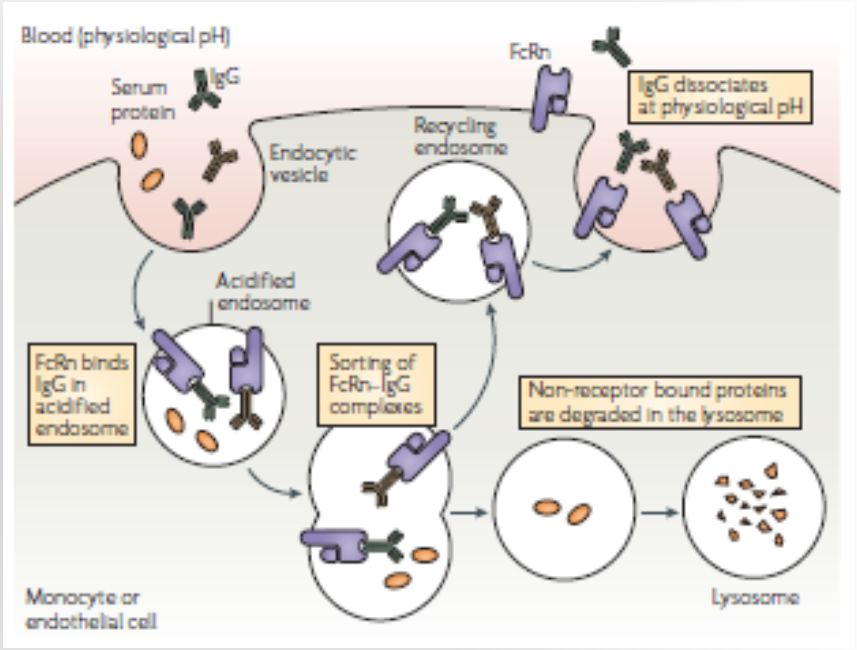
Wherever possible, the above data should be integrated in a PK/PD modelling approach for the determination of the MABEL.

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**

A simple mAb PK model



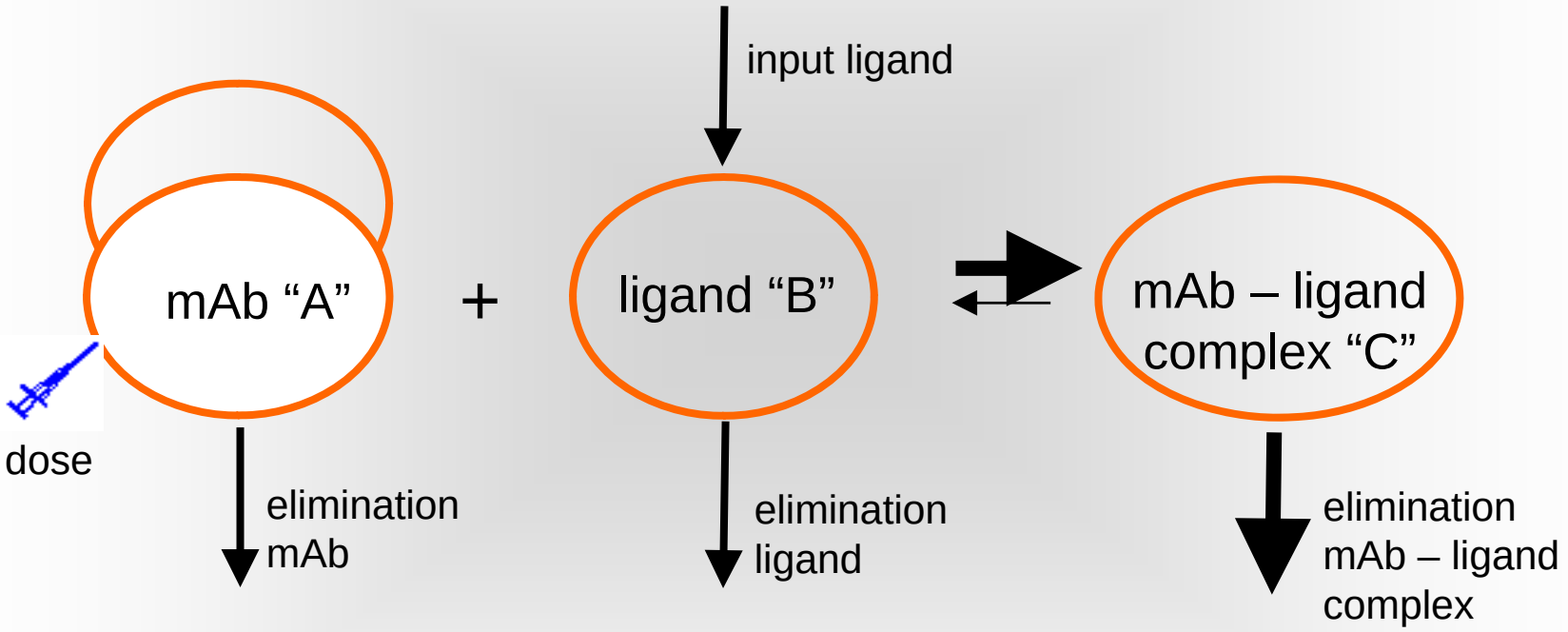


FcRn protects IgG from degradation & explains long serum half-life

slow clearance
V ~ 7L
$t_{½}$ ~ 300 h (human)

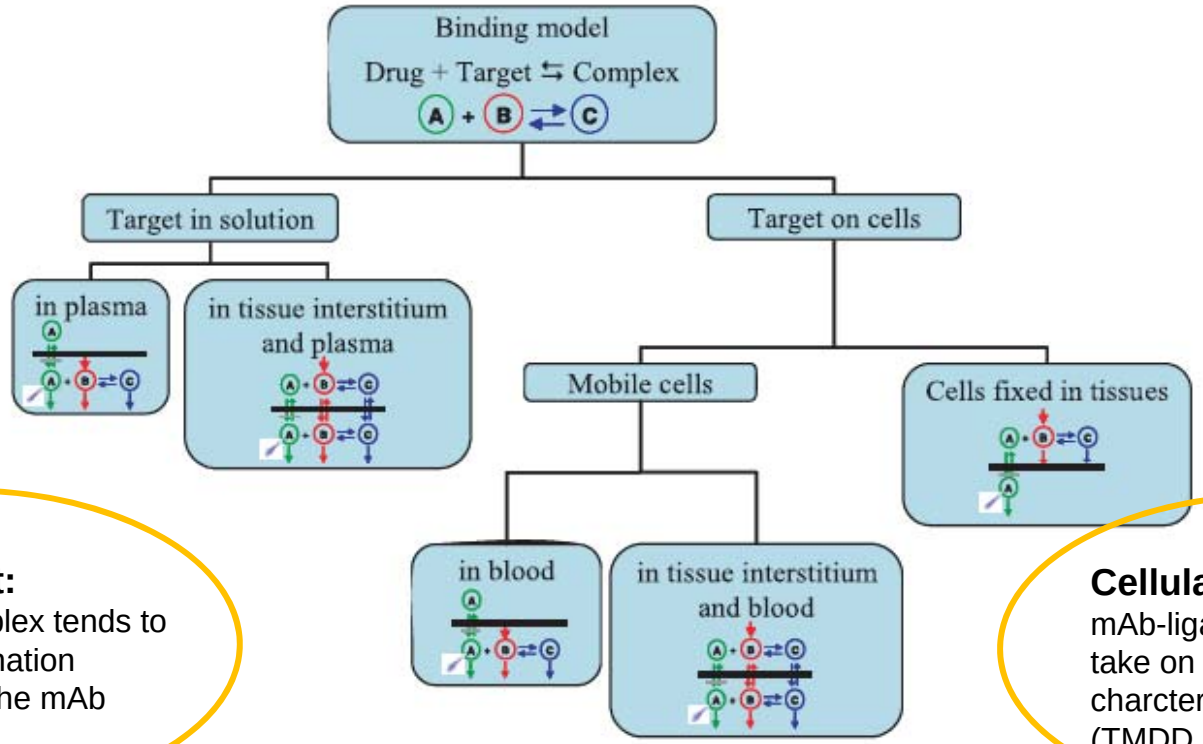
Roopenian and Akilesh.
Nature Reviews Immunology 2007; 7: 715

A simple mAb-ligand PK-PD model



slow clearance
V ~ 7L
$t_{½}$ ~ 300 h

mAb PK-PD ligand binding models



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

Cellular target:
mAb-ligand complex tends to take on the elimination charcteristics 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

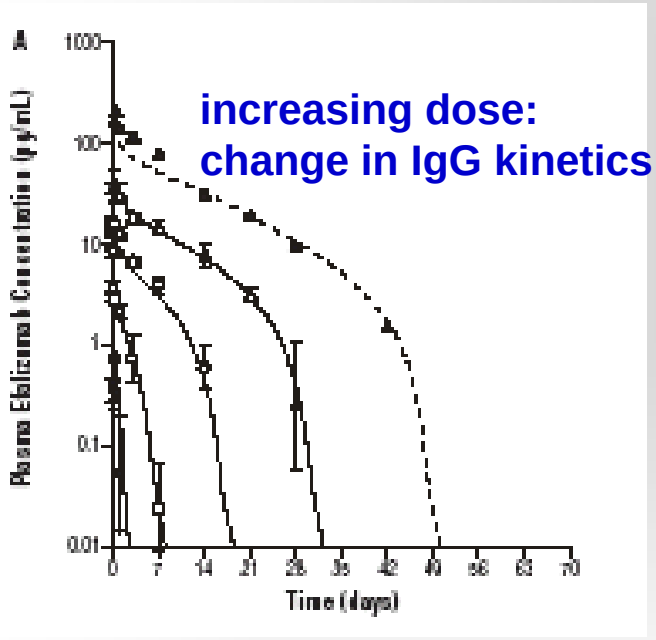
- Inherent pharmacokinetics of the mAb and clearance of the mAb-ligand complex:
  - PK of monoclonal antibodies will generally follow “typical IgG behaviour” and scale reasonably well to man and/or exhibit Target Mediated Disposition and be dependent on the amount of target present and its rate of turnover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

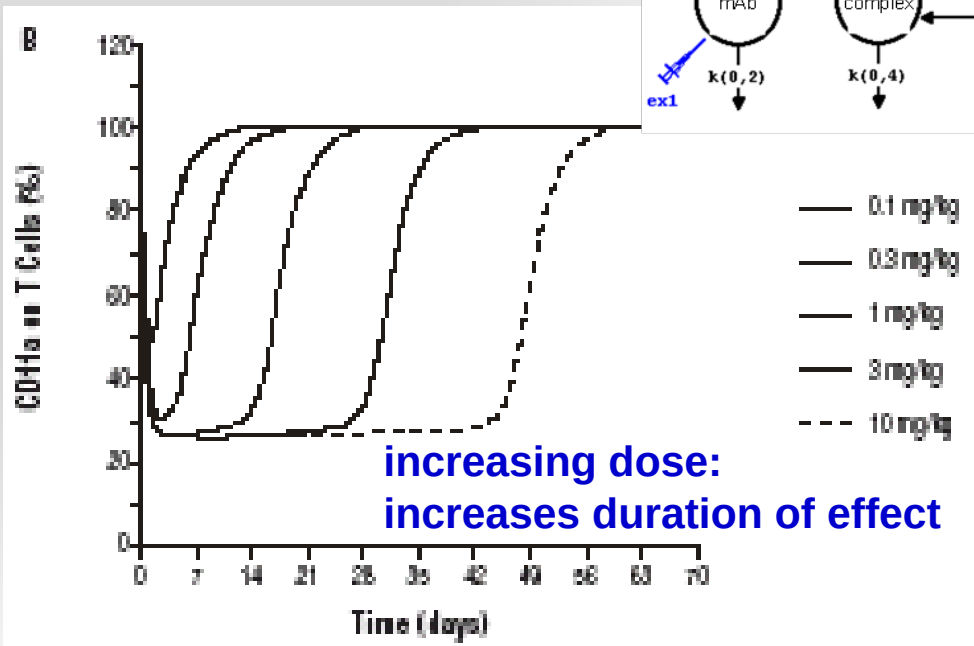
Potential benefits of a model based approach

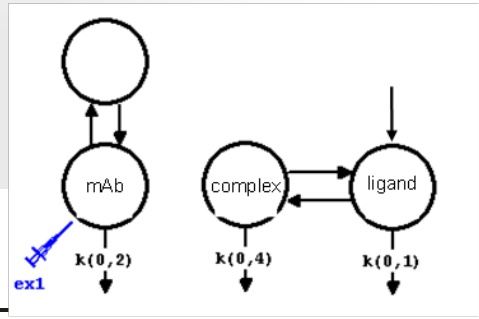
- “simple” mathematical representation of known biology
  - also represents components of the model which cannot be measured (eg low circulating level of free ligand)
- sensitivity analysis
  - elements of the model which are key drivers of the desired outcome (eg affinity / potency)
- hypothesis testing
  - 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)



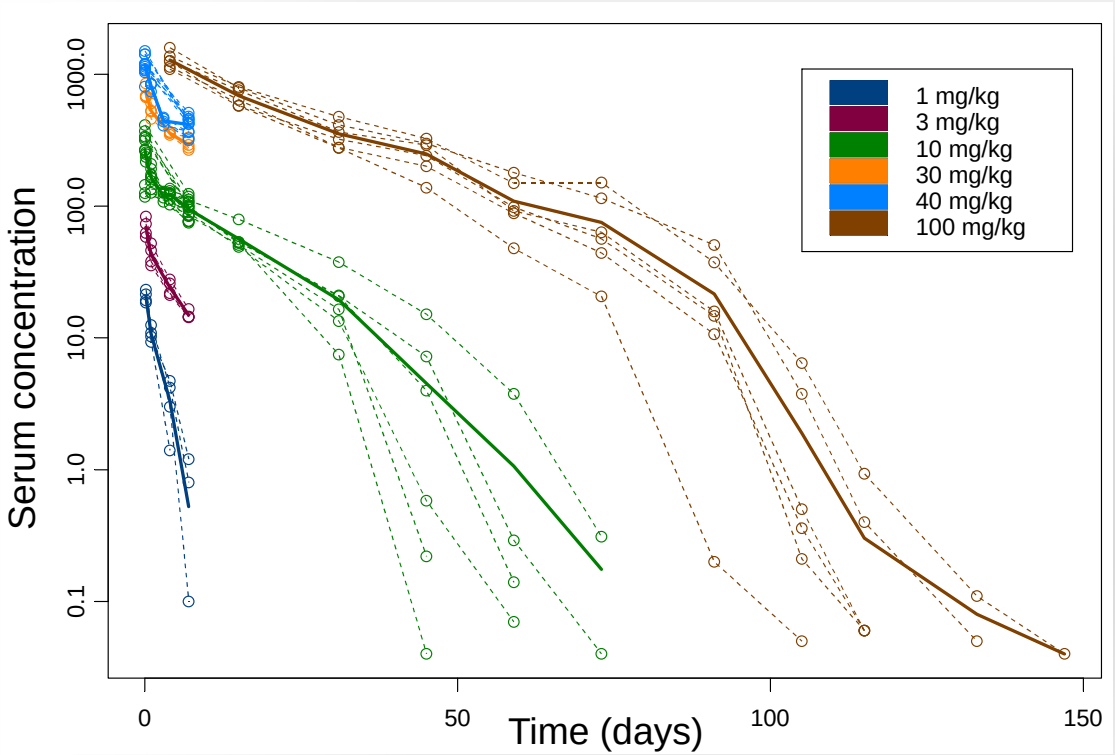


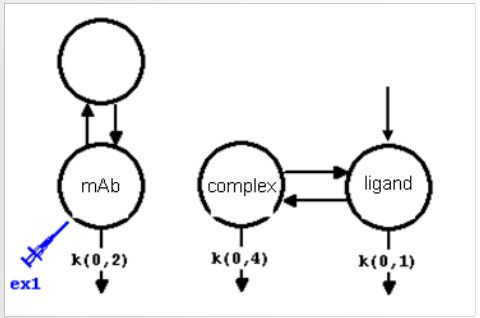


Joshi et al An overview of the pharmacokinetics and pharmacodynamics of efalizumab: a monoclonal antibody approved for use in psoriasis
J Clin Pharmacol 2006; 46: 10-20

Example 2: target suppression in safety assessment

cell surface ligand



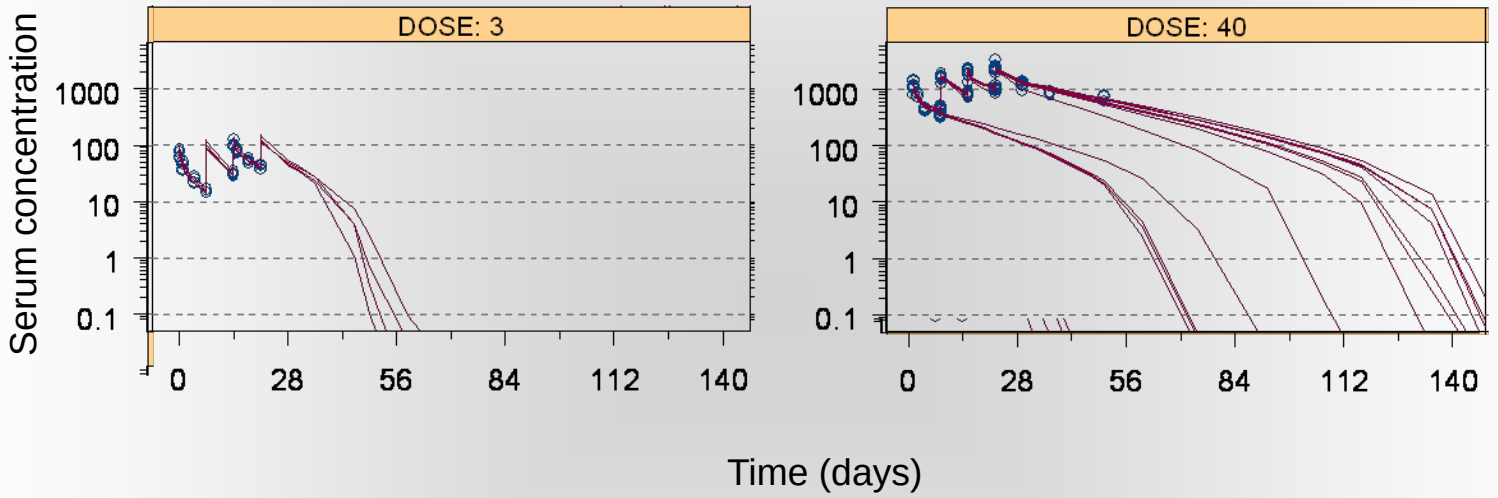


A single dose of 100mg/kg is capable of maximal suppression of the target ligand for >75 days

NB consequence for repeat dose GLP tox and recovery period

Example 2: target suppression in safety assessment

4wk GLP toxicology study **cell surface ligand**



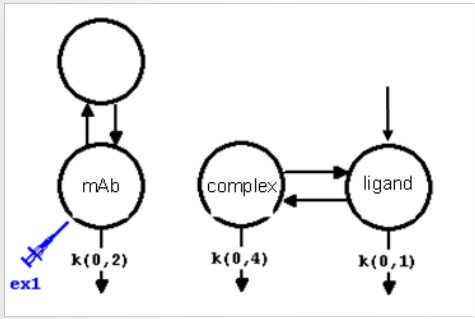
Conclusion:

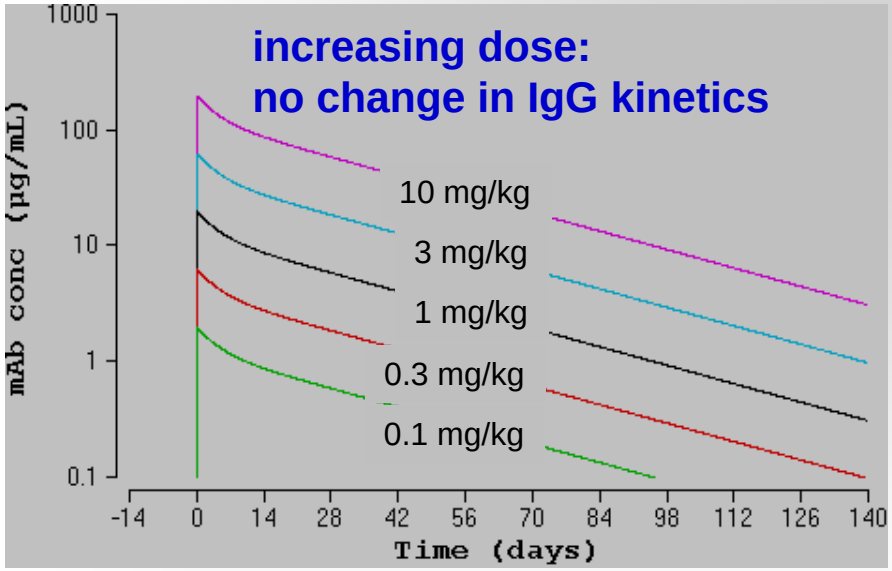
- 16wk recovery period is appropriate to characterise the PK (and hence the PD effect) for this molecule (4wk study 40 mg/kg/wk)
- *NB assumption!* target turnover is not affected by drug treatment

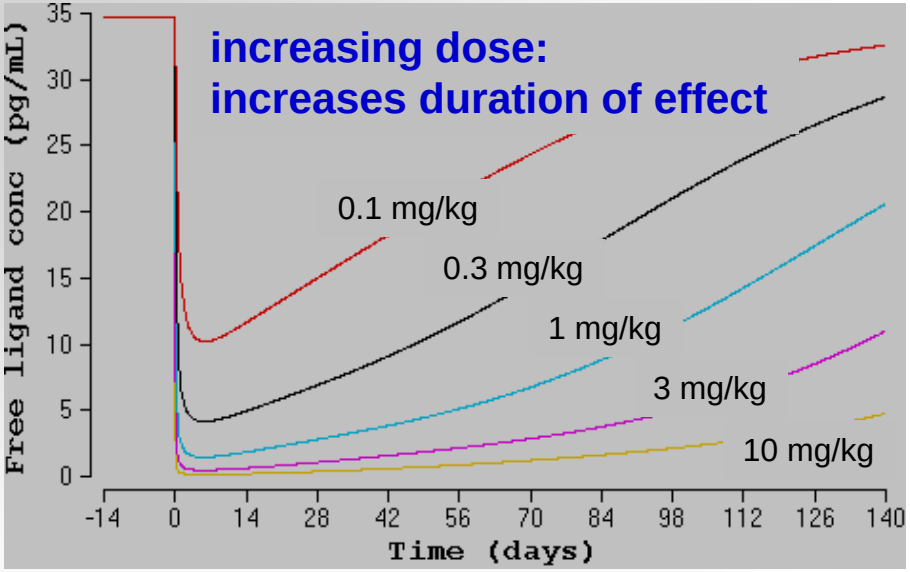
Example 3: “Typical PK-PD behaviour” – soluble ligand

anti-IL1β mAb – Ilaris (canakinumab)

simulation 0.1, 0.3, 1, 3 and 10 mg/kg

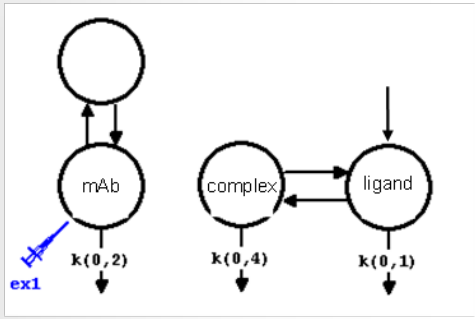






Example 4: target suppression in safety assessment

soluble ligand



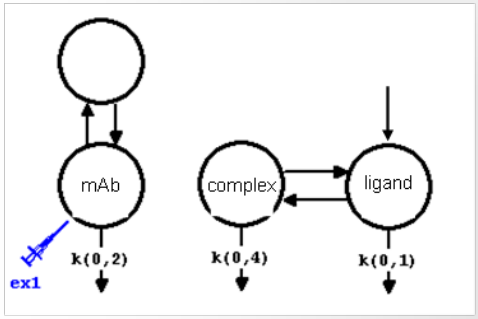
- humanised mAb; high affinity against soluble target
- K_d man < cyno (~10-fold)
- “typical IgG kinetics”
- target ligand can be measured in the systemic circulation
- mAb acts as a “capture system”:

  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

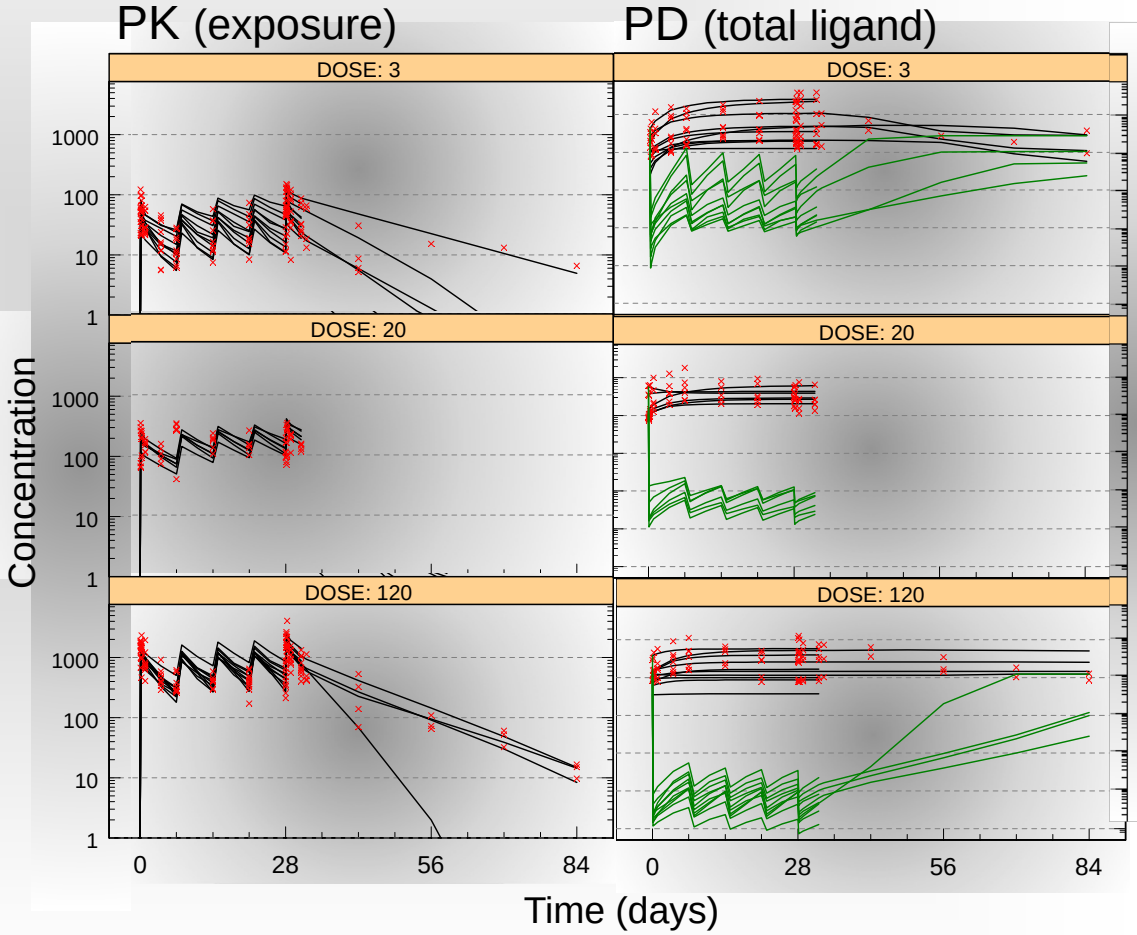
4wk GLP toxicology study

soluble ligand



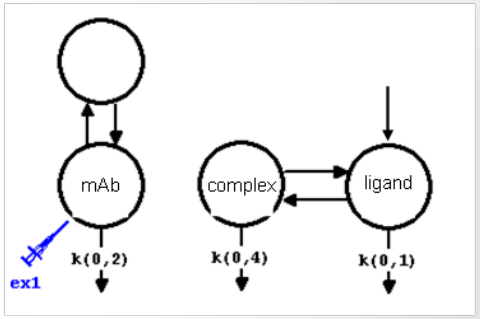
PK-PD model:
exposure and total ligand

- 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)*



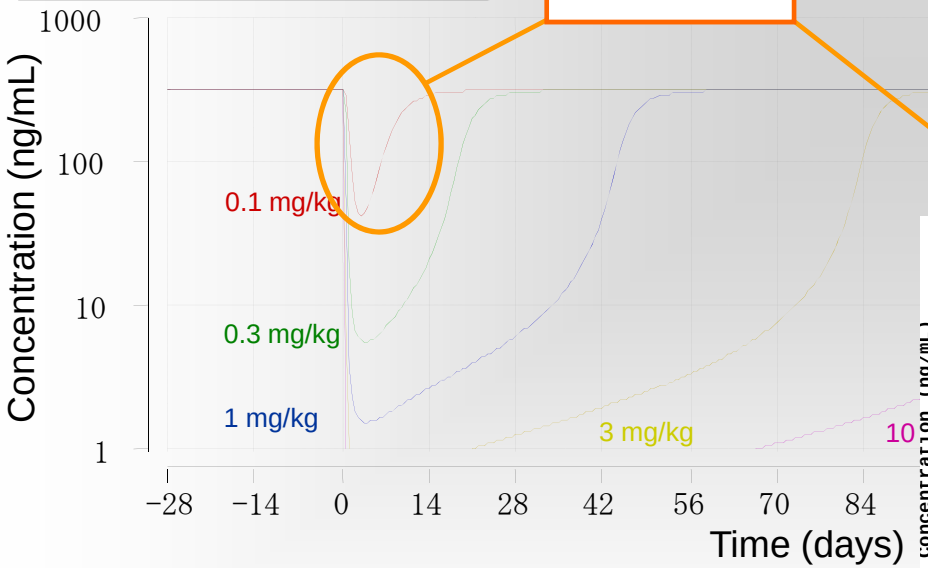
Example 4: target suppression in safety assessment

predicted effect in man **soluble ligand**

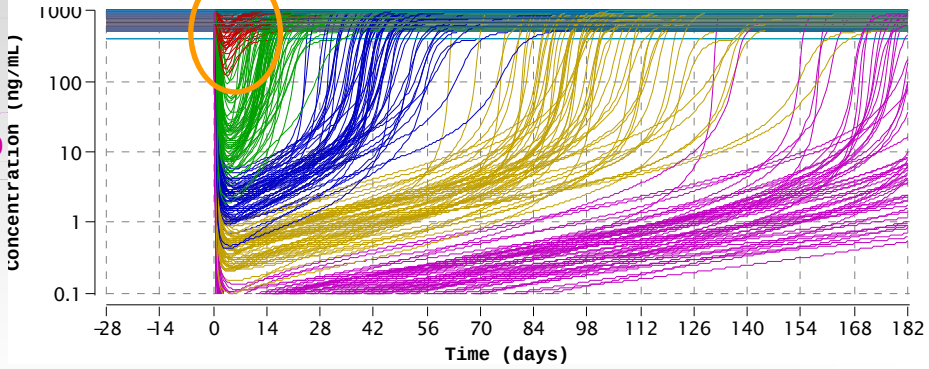


- pre-clin exposure data adjusted to man
- binding affinity in PK-PD model adjusted to man

MABEL



Monte-Carlo simulation



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**

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

Toxicology (exposure)

[1] NOAEL 100 mg/kg

[2/3] HED 100 mg/kg

- adjust for anticipated **exposure** in man?

[4] Apply ≥10-fold safety factor

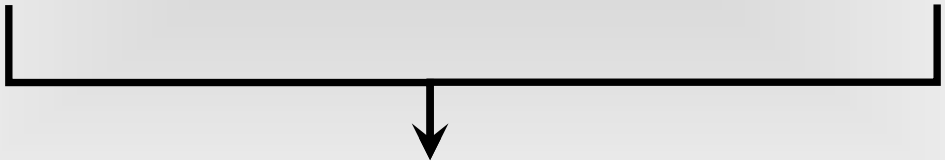
10 mg/kg *

Pharmacology (response)

[5] PAD / MABEL

- **justify based on pharmacology**
- (demonstration of max pharmacology in pre-clinical species)
- adjust for anticipated **exposure** in man
- include anticipated duration of effect
- adjust for **inter-species differences in affinity / potency**

1 mg/kg *



"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