Population PK/PD in paediatrics; a perspective on the way forward

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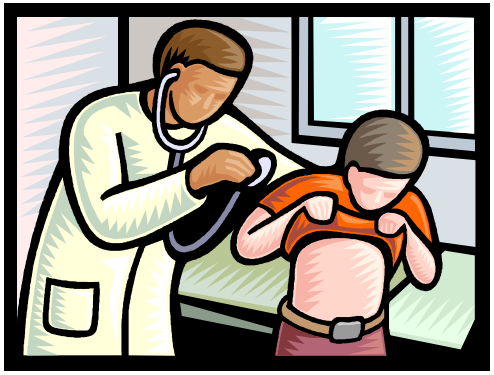


Overview

- Model based drug development;
  - Disease models.
- PK/PD/Disease models in paediatrics.
- Modelling and simulation in paediatrics today.
- The way forward.
- Summary.

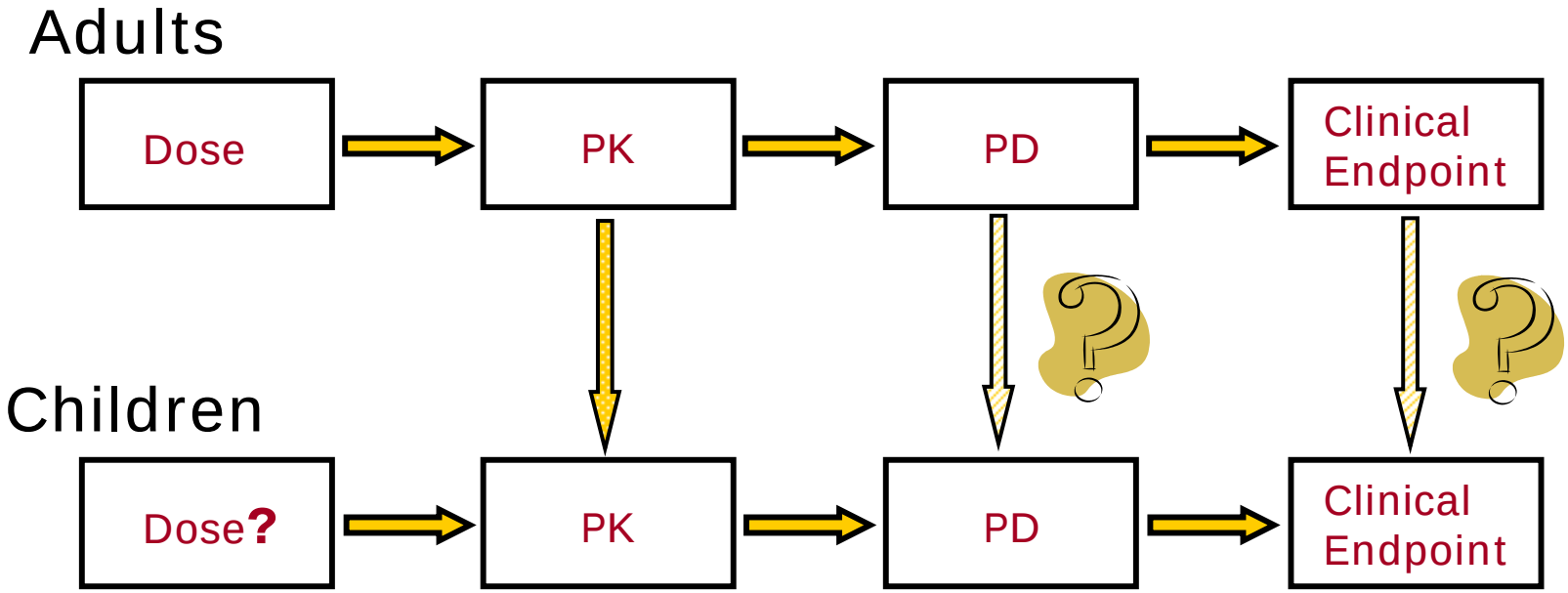
Model based drug development

- Models are built to answer specific questions.
- A model based project is a success when it supports a decision.
  - What starting dose to use, for the different age groups, in paediatrics?
  - How to adjust the dose (if necessary)?

Model based drug development

- Adult drug development rests on volume, both in the numbers of subjects and the amount of information available for each subject.
  - This is not possible in paediatrics, therefore we need to be more efficient with the information/subjects we do have; model based drug development is one way to be more efficient.
- Model based drug development;
  - PK/PD model.
  - Disease model.
  - Adherence/Compliance model.
  - Drop out model.

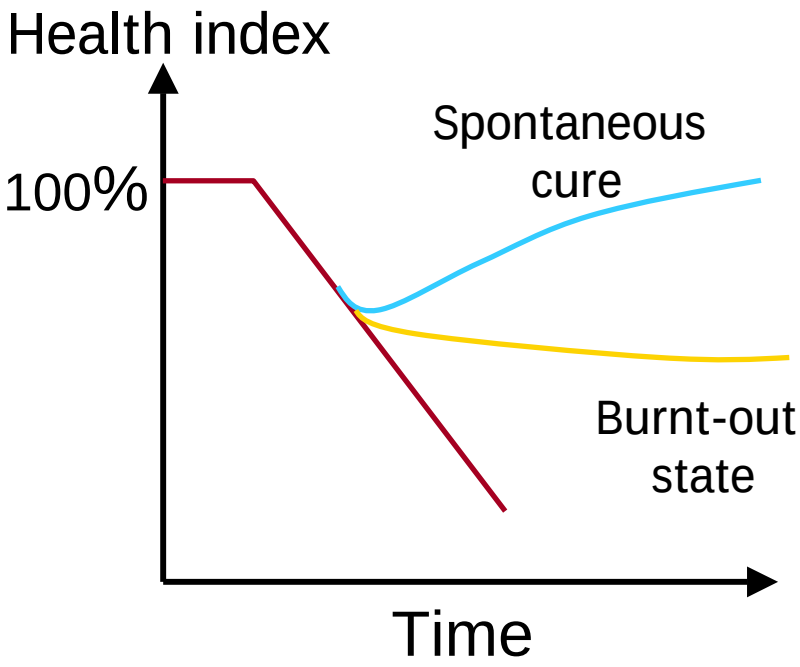
Model based drug development in paediatrics

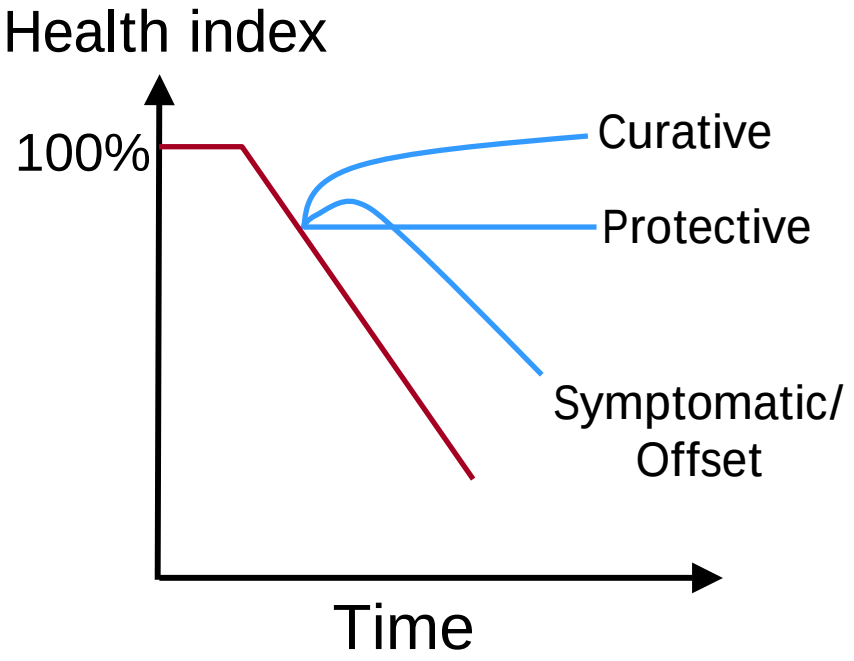


Disease models

- Visualization of the time course of disease in individual patients under treated and untreated conditions.
- Growing amount of literature about disease progression models and drug effects upon them.
- Use of disease progression models allows characterisation of drug effects as symptomatic, protective or curative.

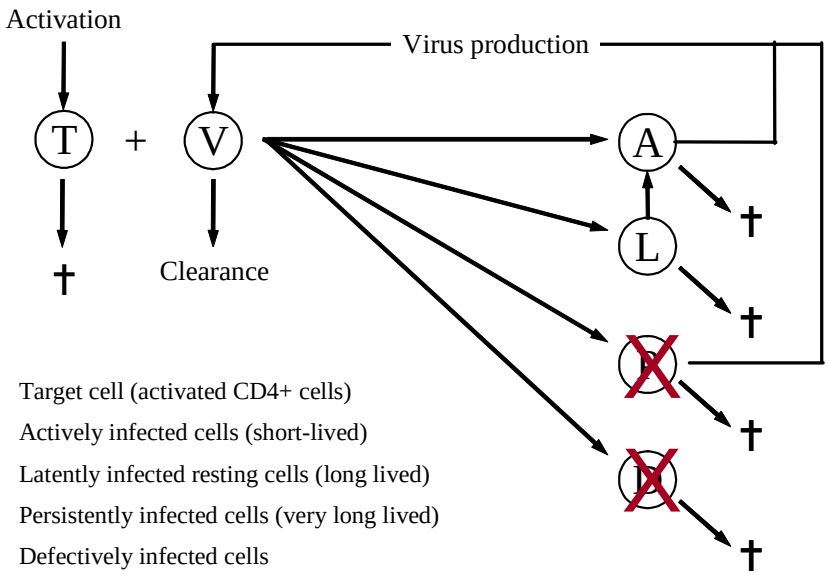
Disease models





- Relapsing
- Cyclic
- Complex viral models
  - HIV
  - HCV

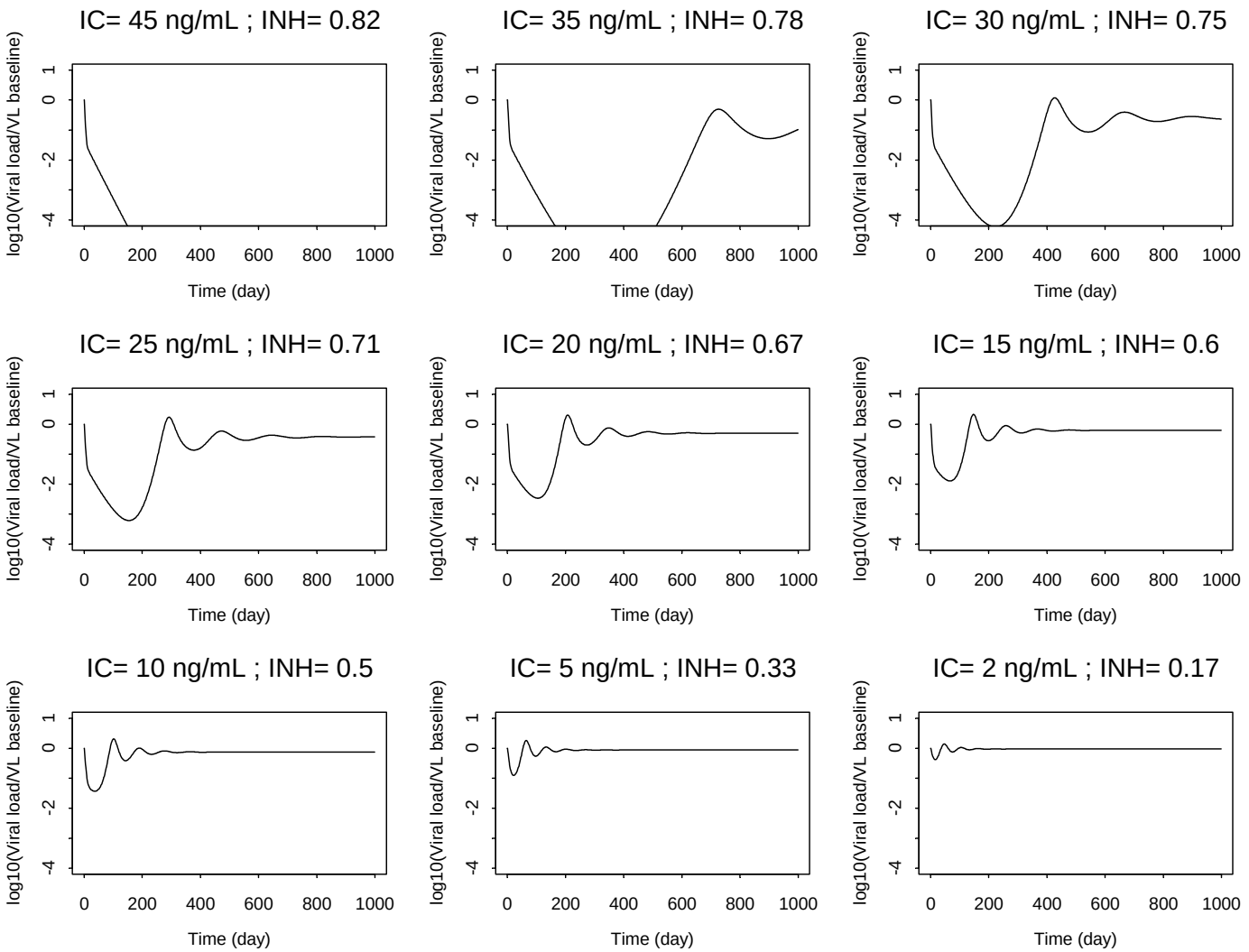
HIV disease model



T	Target cell (activated CD4+ cells)
A	Actively infected cells (short-lived)
L	Latently infected resting cells (long lived)
P	Persistently infected cells (very long lived)
D	Defectively infected cells
V	Infectious virus(copies HIV-1 RNA)

Jacqmin *et al.*, PAGE 2008

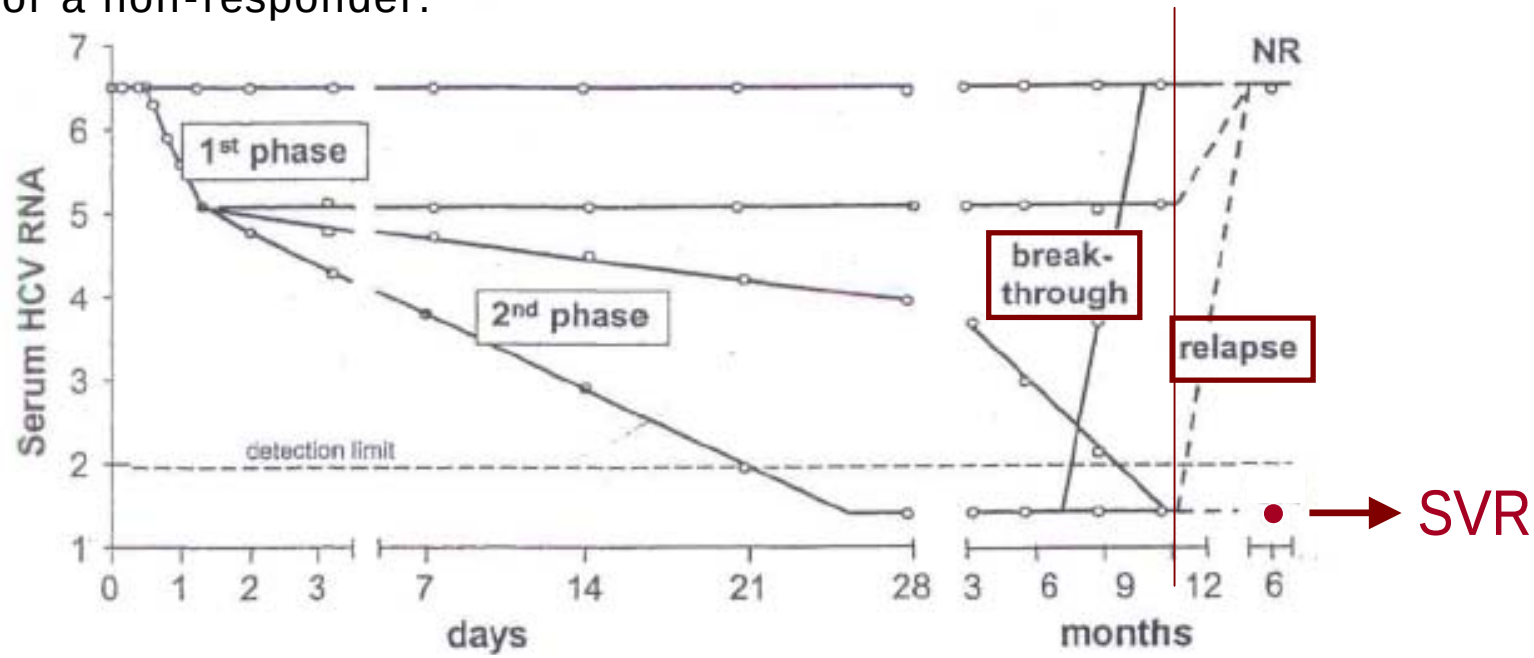
HIV disease model



Jacqmin *et al.*, PAGE 2008

HCV disease model

HCV RNA profiles during and after treatment differ largely between chronic hepatitis C patients resulting in a sustained virological response or a non-responder.

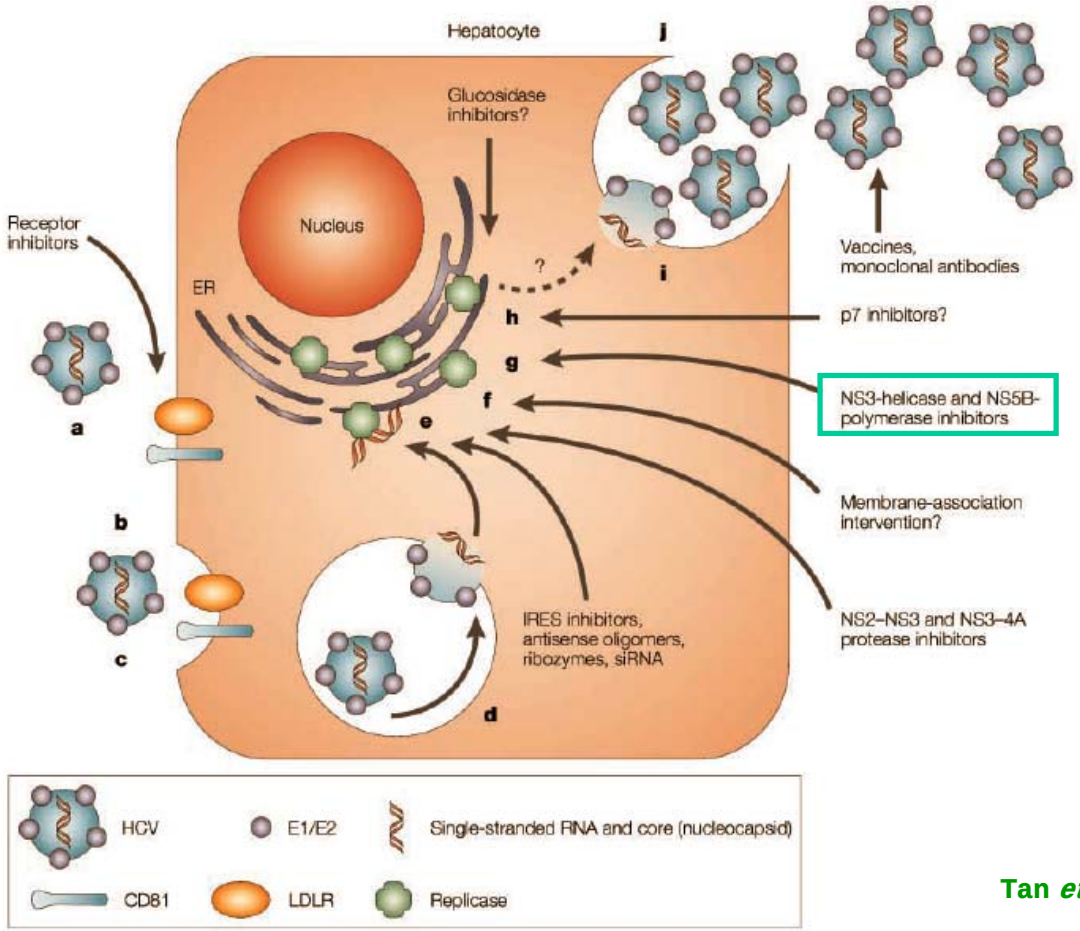


The currently developed HCV viral kinetic model can:

- Describe all these different profiles
- Provide an explanation for phenomena such as a break-through and a relapse
- Be used for initial exploratory simulations of alternative dosing schemes

Zeuzem *et al.*, Clin Liver Dis 2001

An HCV viral kinetic model developed based on data of a treatment with IFN combined with ribavirin might be updated to incorporate the antiviral efficacy of drugs with a new mechanism of action:



An updated model incorporating the effects of drugs with a new mechanism of action, might be used to perform simulations aiding in optimizing the design of clinical trials with these new drugs

Tan *et al.*, Nature Revievs/Drug Discovery 2002

Figure 2 | **Proposed replicative cycle of HCV and potential sites of therapeutic intervention.** The life cycle of the hepatitis C virus (HCV) has several specific steps, many of which are targets for antiviral drugs: **a** | attachment; **b** | endocytosis; **c** | virion– membrane fusion; **d** | uncoating; **e** | translation and polyprotein processing; **f** | replicase assembly; **g** | RNA replication; **h** | viral assembly and ER budding; **i** | vesicle transport and glycoprotein maturation; **j** | vesicle fusion and virion release. ER, endoplasmic reticulum; IRES, internal ribosome-entry site; LDLR, low-density lipoprotein receptor; NS, non-structural protein; siRNA, small interfering RNA.

Paediatric disease models

- Unlikely to have sufficient data to develop ‘pure’ paediatric disease models.
- Adult disease models could be used to extrapolate/bridge to the paediatric situation.
  - Careful consideration of factors that might be different in the paediatric situation.
    - Children’s immune systems, particularly very young children, are quite different from adults.
- Disease not present in adults will mean developing a paediatric disease model from scratch.
  - Is this possible?

Paediatric specific PK/PD/Disease models - Challenges

- Few subjects.
- Sparse pharmacokinetic sampling.
- Sparse pharmacodynamic sampling.
- Acceptability of population PK/PD/Disease modelling.

Modelling & Simulation in paediatrics today

- Literature has many examples saying PK/PD and M&S should be done in the paediatric situation but there are few actual examples.
  - Why is there so little?
  - What can be done to drive this?

Company regulatory departments

- PK/PD and M&S done but not submitted.
  - Staff in the regulatory departments don't fully understand/trust this methodology so it isn't included in submitted documentation.
    - For example, an NCE, for which it's advantage over existing therapy was declared as being better PK/PD properties, had only an ANCOVA with AUC and C_{max} in the submitted documentation, despite beautiful mechanistic PK/PD analyses being available.
- Even in adult context modelling and simulation content is generally watered down in submission and briefing documents.

The way forward

- The science exists.
- The tools exist.
- The pharmacometricians who can apply the science and tools exist.
- The pharmacometricians have been presenting the uses and applications of population PK/PD linked to modelling and simulation for paediatric drug development for many, many, years!

The way forward

- Political pressure is also needed.
- Regulatory agencies are uniquely positioned to supply this pressure.

The way forward – paediatric disease models

- There is very little information with which to develop paediatric disease models.
- Here the regulatory authorities could play a BIG role since they are in control of the largest repository of information available and which could be used to build paediatric disease models.
  - Build the disease models themselves.
  - Initiate collaborations with academic or other external parties to develop these models.

The way forward – paediatric disease models

- The existence of paediatric specific PK/PD/Disease models will facilitate putting changes in paediatric pharmacokinetics into perspective.
  - Drug drug interaction studies not repeated in paediatric populations. Paediatric PK/PD/Disease models could be used to simulate expected outcomes based on drug drug interactions observed in adults.

The way forward – paediatric PK/PD guideline

- Yes please!
- Overcome resistance within companies regulatory departments for submitting this kind of data.
- A guideline can drive implementation;
    - CWRES and shrinkage now increasingly done because of the EMEA ‘Reporting the results of population pharmacokinetic analyses’ guideline.
- A guideline will demonstrate that EU regulators expect, and can assess, these types of analyses.
    - Overcome remaining resistance to submitting this type of data.

PK/PD in paediatrics – publications of regulatory examples

- The FDA has done an enormous amount in driving the implementation of model based drug development by publishing papers that give an overview of submitted examples.
- The EU could add to this momentum by doing something similar for paediatric PK/PD work that has been submitted.
  - How the modelling work contributed (or not) to the regulatory assessment.
  - How the modelling work contributed (or not) to supporting labelling for paediatrics.

The way forward - PK/PD in paediatrics

- More EU regulators will be needed who can assess these types of analyses.
- The EMEA and the National agencies will need to further develop competence to evaluate the PK/PD modelling submissions they receive, both on short and long term.
  - Training of staff at the national level?
  - Position pharmacometric expertise in the various national agencies, or, linked to the paediatric secretariat at EMEA?

The way forward - summary

- The science, technology and pharmacometricians exist.
- More political/regulatory pressure will hugely facilitate the adoption of model based drug development for paediatrics.
  - The EU could take the initiative to require, demand or initiate model based drug development within paediatrics.
    - A paediatric PK/PD guideline or other publications would assist this process.
  - The EU could facilitate the development of paediatric disease models.