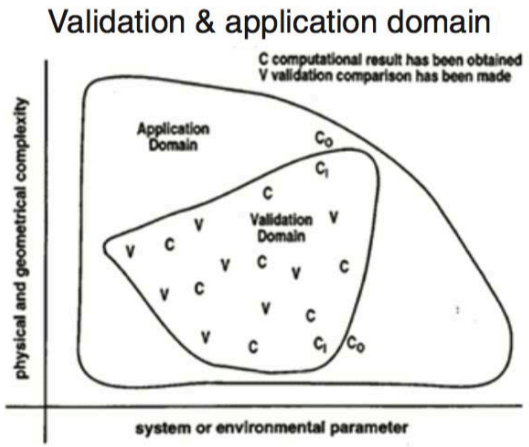
Decision making, revisited

Model informed decision making calls for evaluation of the confidence in the model predictions

- The quality and explored domain of the existing evidence
- The fit of the model with this evidence
- Determining the validation domain versus the application domain
- Consider all assumptions- MID3 framework
- Quantifying the impact of uncertainty
- Fit for purpose- impact level



The decision making should be accompanied by a risk assessment- Expert opinion needed

Model informed evaluation of uncertainty

Fit for purpose models

- Different levels of precision can be accepted depending of the use
- Different levels of characterisation of impact of biologic variability, inclusion of relevant pathways and assumptions can be accepted

Address what-if scenarios - best and worst case - to inform risk assessment and decision making

- Assessment of the consistency, robustness and distribution of the source data
- Expert informed scenario analysis to inform the boundaries for uncertainty quantification (UQ)
- Quantify impact of input, parameter and assumption uncertainty in the resulting predictions

Model informed evaluation of uncertainty

Can we implement systematic use of Uncertainty Quantitation and sensitivity analyses?

- Do we have fit for purpose UQ methodologies for models of varying complexity? Should we request it?
- Do we have fit for purpose methods for supporting the expert decision making based on uncertainty risk assessment?
- How should we quantify the performance of extrapolation strategies?

Iterative loops of learn, plan and confirm to investigate and (in)validate assumptions in the extrapolation concept

Objectives

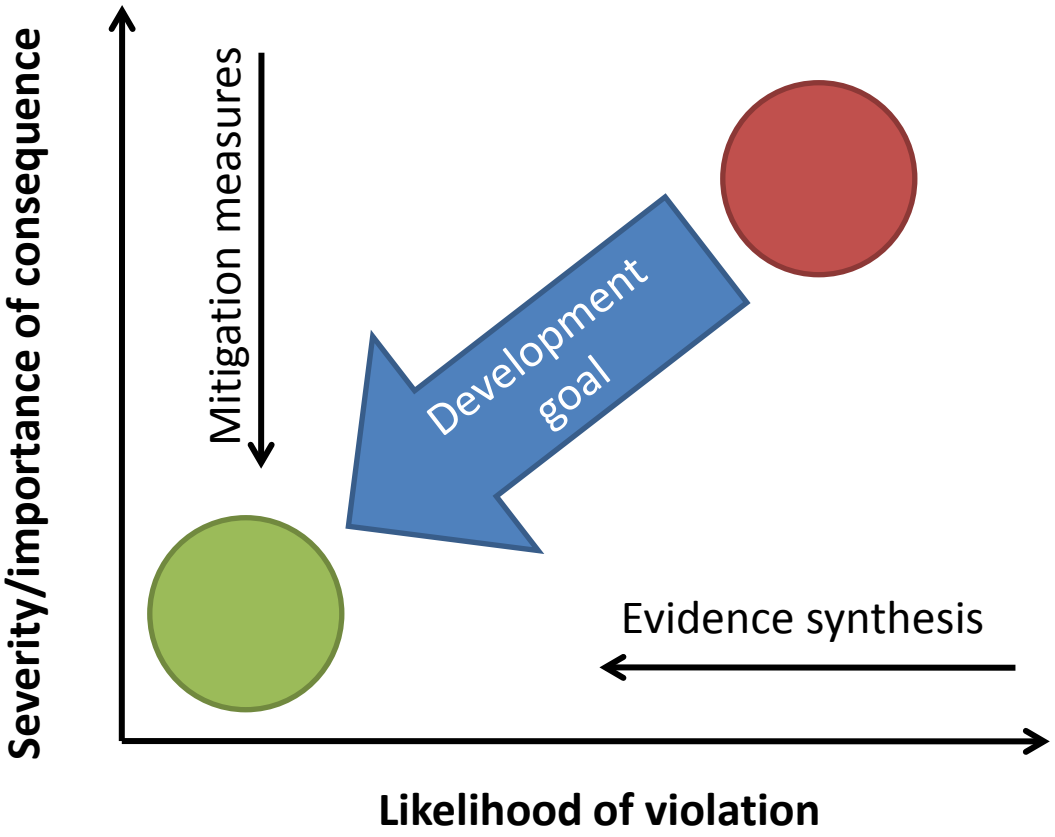
- Understand the tools we have to confirm the stat, PMX approach to extrapolation
- Clarify the handling of the uncertainties across the extrapolation life cycle
- Clarify the decision making at the end of the exercise
- Clarify the risks taken with each approach and how likely will be to get additional data to mitigate these
- Role of post marketing data

Points to consider for the panel

- Do we need confirmatory statistics to apply to extrapolation models and study designs?
  - The decision makers needs it, but the learning on the way to the confirmatory evidence provision is often more difficult to get to
- Can we make principled decision regarding the reduced (stand-alone) efficacy requirements (e.g. scepticism factors)
  - No conclusive answer
- How do we document and report the conclusions from the exercise and the associated uncertainties?
  - MID3 /DDMoRe
- If efficacy data is not collected in the target population, do we have an opportunity to evaluate the extrapolation concept in the post-marketing setting?
  - Least preferable option (unbiased evidence provision unlikely), adaptive licensing

Impact of Assumptions

Evidence vs. Inference



How to evaluate and quantify the impact of uncertainties and assumptions, i.e. the probability of violating assumptions and the clinical consequences?

Assumption Impact & Consequence

Assumption	Probability to violate (uncertainty)	Consequence	Potential M&S impact
	Based on biological/ pharmacological/clinical prior understanding	Needs to adjust for environmental condition	Generally depends on density of available data
AUC_{ped} = AUC_{adult} (assuming allometric scaling)	**likely (at design stage)**	**major (equal exposure assumption in stats analysis)**	**… allows regrouping … PKPD-model to define EC90**
AUC_{ped} ~ AUC_{adult}	**unlikely (post readout)**	**moderate**	**… quantifies confounding factors**
CPX_{ped} ~ CPX_{adult} (clinic. meaningful effect size)	**moderate**	**moderate**	**… allows bridging only in conjunction with HDs**
$(CPX\sim HD)_{ped}$ = $(CPX\sim HD)_{adult}$	**unlikely**	**major**	**… qualifies bridging of CPX~HD EPs between populations**
DP_{ped} = Dp_{adults}	unlikely	moderate	… justifies design in SP
$HD\text{-}ER_{ped}$ = $HD\text{-}ER_{adults}$	unlikely	major	… justifies dose in children
$HD\text{-}ER_{<7y/non\text{-}able}$ = $HD\text{-}ER_{>7y/able}$	unlikely	major	… justifies dose in younger/non-able children
$HD\text{-}ER_{strata}$ = $HD\text{-}ER_{major\text{-}group}$	moderate	moderate	… quantifies dose for strata
$CPX\text{-}ER_{<7y/non\text{-}able}$ = $CPX\text{-}ER_{>7y/able}$	very likely	major	No existing data, → future research

Assumption setting, evaluation, impact assessment and documentation: Paediatrics

Important assumptions	Justification	New/ established	Testable/ not-testable	Test/approach to assess impact	Evaluation
Pharmacological **The PK/PD relationship of Tocilizumab is independent of body weight and the lower efficacy in BW<30kg is due to a lower PK exposure**	No evidence that the IL-6 signalling pathway and the IL6-R expression would differ in low body weight kids	New	Testable	Test in phase III a higher dose selected by using a PK/PD modelling approach.	Using phase III data
Physiological assumption: **Renal clearance via GFR**	Population assumed to be the same as that used to develop the equation: $GFR = \left(\left(\frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}} \cdot (1 - GFR_{premat}) \right) + GFR_{premat} \right) \cdot Volume_{Kidney} \cdot GFR_{mat}$	Established from literature	Non-testable	NA	NA
Disease assumption: **(CPX~HD)paed= (CPX~HD)adult** **HD: hemodynamic endpoint** **CPX: cardio pulmonary exercise**	Linkage between HD changes and exercise capacity assumed to be the same as adults	New	Testable	Comparison of existing adult and paediatric data	The relationship is similar, HD can be used for dose selection Justify bridging of CPX~HD EPs between populations
Mathematical and/or statistical assumption **Similar variability in clearance between adults and children**	Physiological and PK knowledge	New	Not testable at the stage of predictions but can be evaluated with data from children	Sensitivity analysis on the variance value of clearance	If variance is 2-fold, children would be still with the highest dose in the safety range established for adults? ➔ Suggested dosing can be used in Children

Additional points …

- What's the regulatory risk taking a wrong decision?
  - Is M&S->MID3 generally reducing the risk? Yes, -> High impact
- What's the patient's/parent's/societies' risk taking a wrong decision?
  - M&S->MID3: Medium impact as informative to practitioners (only?)
- Learning vs confirmatory evidence synthesis generation and interpretation – how to cycle …
  - Providing unclear guidance to decision makers with limited evidence is still worst case
  - Fall back position of an intuitive pragmatic approach ("one must take decision anyway") shouldn't be acceptable
  - "In case data are available, preference is given to data (and not to expert opinion)"
    - Expert opinion need to be listen to, but should not overrule when evidence **could have been provided** through MID3 – **but that needs to be asked for**

- Why?
  - No doubt after this WS …
- What? … is being applied to an ongoing program
  - Is down to … negotiation around the strength of evidence interpretation and it's future likelihood of being generated or it's informativeness
- How?
  - Extensive solutions available …