DEALING WITH RISK AND UNCERTAINTIES

Session 2:

Structure, methods and decision criteria for extrapolation

Extrapolation workshop; 30/9-2015

Anna Nordmark and Norbert Benda

Uncertainty in M&S used for extrapolation

- At which levels in M&S can uncertainty occur?
 - Input data
 - Physiological data
 - Structural model
 - Parameter estimates, statistical models
 - Assumptions (ADME, PD etc.)
 - Co-correlations

•

>> Outcome from the model



Learn and confirm paradigm in M&S



Can M&S help in addressing uncertainty?

- Quantify impact of input, parameter and assumption uncertainty in the resulting predictions
- Address worst case scenarios or what-if scenarios (= Risk assessment)
- To assess the consistency, robustness and distribution of the source data
- To quantify the impact of uncertainty in input data and the extrapolation assumptions on predictions

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

Controlling of uncertainty in M&S?

Important to remember that modelling is an iterative process of learning and confirming during the development process

- Uncertain assumptions or parameters can be confirmed
- Use of alternative sources of information to support assumptions or other vice reduce uncertainty (system data, other drug developments...)
- To integrate pharmacological, clinical and statistical expert judgment to identify uncertainty and associated risks
- To quantify the impact of uncertainty (UQ) in input data and the extrapolation assumptions on predictions

Decision making

- Model predictions appropriately evaluated should inform decision making
- Different levels of uncertainty in predictions may be acceptable depending on the type of risk and whether or not they can be mitigated
- Expert judgement needed for decision making, need tools to support the uncertainty risk assessment of predictions

Uncertainty of the method

- extrapolation exercise to generate a decision
 - drug /dose effective in children ?
 - estimation of treatment effect size, dose response, etc.
- extrapolation stragegy may lead to wrong decisions
 - how often do you get a wrong decision ?
 - how precise would you estimate what you wish to estimate ?
- extrapolation strategy more complex than a simple
 - statistical test
 - estimation function
- evaluation of the extrapolation strategy by
 - simulating data under different assumptions
 - application of the extrapolation strategy to the different simulations
 - challenging evaluation task to quantify method uncertainty would be required

Example of an extrapolation strategy



Evaluate extrapolation method

Set of different extrapolation strategies

Extrapolation Extrapolation strategy k strategy 1 Clinical Scenario Evaluation (CSE) Repeated simulations of an extrapolation exercise: Simulation of adult trials and paediatric data according to the different assumptions Apply different extrapolation strategies Conclusion/result for a specific simulation Summarize simulation results, e.g.

probability of a false positive decision

conclusion of a positive/relevant effect in children
if assumption x implies no effect in children

Assumption set on

- adult data
- paediatric data
- link

Assumption 1
Assumption 2
Assumption r
Assumption r

cse framework described in

Benda et al (2010) Aspects of modernizing drug development ... DIJ 44

Friede et al (2010) Refinement of the clinical scenario evaluation framework ... DIJ 44

Questions for discussion

- How to ensure implementation of M&S?
- How to systematically ensure communication between groups of expertice to identify sources of uncertainty?
- How to implement systematic use of Uncertainty Quantification and global sensitivity analyses?
- What are optimal methodology for Uncertainty Quantification for various models?
- What are good methods for supporting the expert decision making based on uncertainty risk assessment?
- How to quantify the performance of extrapolation strategies?
- Other aspects to improve the handling of uncertainty/risk?