# Quantitative challenges of extrapolation

Michael Looby, Frank Bretz (Novartis)

EMA workshop on extrapolation of efficacy and safety in medicine development across age groups May 17-18, 2016



### Extrapolation from adult to pediatric population Quote from Reflection Paper

Quantitative approaches that summarise the prior information whilst integrating expert judgement could be considered as part of the extrapolation exercise, although methods to do this are still in the early stages of development

- Extrapolation from adult to pediatric population often not straightforward
- Analytical approaches must be tailored to the amount and types of data and the clinical setting

**NOVARTIS** 

# Qualitative extrapolation

First step in building quantitative case





# Choosing the development path

Need principles and knowledge of available data to inform the path

- Clinical pharmacology considerations inform the development path
- Foundation for data, study designs and analytical strategy
- Extrapolation opens possibility to use supplementary evidence beyond traditional pediatric trials.
  - Implementation will challenge traditional approaches to design and analysis of pediatric programmes.



(Manolis, Pons 2009)

# Quantitative extrapolation

Calibrating treatment and filling the gaps in pediatric development

#### Adult



#### Children

#### Extrapolation occurs at 3 levels

#### 1. Treatment Calibration

• 'Calibrate' treatment for age/size/... based on appropriate signal (exposure, biomarker or response)

#### 2. Information Augmentation

• Augment pediatric data with relevant data from adults or (other) children

#### 3. Level of direct evidence

 Given successful treatment in adults, *appropriately* adjust level of information in children required to confirm overall benefit/risk

#### EMA Extrapolation workshop | Bretz & Looby | Quantitative challenges of extrapolation

#### Good analytical practices and principles Rigor in using models

- Address the right questions with the right methodologies to
  - Learn in a manner that provides confidence in subsequent decisions
  - Confirm in a manner that underwrites decisions while facilitating the necessary learning



# Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

EFPIA MID3 Workgroup: SF Marshall<sup>1</sup>\*, R Burghaus<sup>2</sup>, V Cosson<sup>3</sup>, SYA Cheung<sup>4</sup>, M Chenel<sup>5</sup>, O DellaPasqua<sup>6</sup>, N Frey<sup>3</sup>, B Hamrén<sup>7</sup>, L Harnisch<sup>1</sup>, F Ivanow<sup>8</sup>, T Kerbusch<sup>9</sup>, J Lippert<sup>2</sup>, PA Milligan<sup>1</sup>, S Rohou<sup>10</sup>, A Staab<sup>11</sup>, JL Steimer<sup>12</sup>, C Tornøe<sup>13</sup> and SAG Visser<sup>14</sup>

# **Statistics and Pharmacometrics**

Learning from each other to facilitate better drug development

 "Pharmacology and statistics are the two threads that run right through drug development.
I hope that our two communities can increase our collaboration in the future, learn from each other, and help spread to others in drug development what we have learned."

#### Pharmaceutical statistics

 "pragmatic in purpose, empirical in method, and skeptical and pessimistic in attitude. Its approach to modelling is biologically innocent and its view of causality is 'voluntary'."

#### Pharmacometrics

 "explanatory in purpose, theory based, and optimistic in attitude. Its approach to modelling is biologically knowledgeable and its view of causality is mechanistic".

Senn (2010)

#### Data, information, knowledge & decisions It is not about modeling vs statistics, but the best analytical approach





# Extrapolation in transplant medicine

Available data drives the analysis design

- In liver transplantation, rich PKPD information on similar immunosuppressive treatments in adults and children allowed
  extrapolation on exposure response and could account for differences in timing of co-medications
- In kidney transplantation, extrapolation on response using a meta-analytical approach was necessary to account for differences in immunosuppressive treatments

(see presentation from T Dumortier in Session 4 for details)





# Extrapolation: Working definition

Quote from Concept Paper (repeated in Reflection Paper)

Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related products, to make inferences for another subgroup of the population (target population), or condition or product

- Prediction outside the range of observed data (e.g. outside the age range)
  - ... to support dosing decisions, design, etc.
- Transferring conclusions from source to target population

**NOVARTIS** 

• ... to reduce the need to generate additional information

10 | EMA Extrapolation workshop | Bretz & Looby | Quantitative challenges of extrapolation

## Extrapolation: Statistical considerations Points to consider

- Summary of available information in the clinical setting
  - For example, formal meta-analysis resulting in point estimates and confidence intervals, forest plots, ...
- Different uses of the (meta-analysis) summary results are possible, depending on the amount and types of data
  - Use summary results as prior information in a Bayesian analysis
    - For example, update prior information in children with new pediatric trial results
  - Meta-analytic prediction-validation approach
    - For example, assess similarity of predictions from adult data with new pediatric trial results

**NOVARTIS** 

- Specification of level of evidence
  - For example, relax the significance level for new pediatric trial(s)

# Meta-analysis of available clinical information

#### Identify sources of information

- Data gathering can be time-consuming, requires cross-functional expertise, and may not lead to a unique set of trials
- Systematic reviews methodology (e.g. Cochrane Handbook, 2011)
- Assessing similarity of trial data (e.g. Pocock's criteria, 1976)

## Statistical modeling

- Identify a common statistical measure that is shared among trials
- Uses a statistical model for all quantities involved
  - Account for between-trial heterogeneity
  - Include covariates on trial level
- Many approaches are conceptually and mathematically similar, resulting in a weighted average of that common measure

# **Bayesian analysis**

 Bayesian paradigm: Take prior knowledge and add observed evidence to obtain updated knowledge prior × data < posterior</li>



- When applied repeatedly, posterior from previous step becomes prior for next step → Bayesian adaptive design
  - see presentation from M Bacchi in Session 4 for an example

# **Prediction-validation approach**

#### Prediction step

 Bayesian meta-analysis using adult study level data to derive posterior predictive distributions and predict outcomes of study designs matching the ones in the available paediatric studies

## Validation step to confirm the predicted degree of similarity

 If the adult and paediatric population are similar, the outcome of the paediatric studies should be in the range of the posterior predictive distribution derived from prediction step

# Specification of level of evidence

- Under the assumptions that
  - the drug is approved for adults (based on pivotal trials) and
  - results from adult trials can be extrapolated to a certain extent to children

can we relax the standard significance level for pivotal trials in children?

- Our confidence in approving the drug for children should not be less than our confidence in approving it for adults
- If yes, how to choose the relaxed significance level?
  - Proposals are emerging in the literature (e.g. Hlavin et al., 2016)
  - Methods on the previous slides implicitely aim at similar objective

# Other considerations

- Be mindful about making assumptions
  - Whenever making assumptions, they should be stated explicitly
  - Validate assumptions through model diagnostics, sensitivity analyses, ...
  - Inferences should be robust with respect to (moderate) deviations of assumptions
- Challenges in practical implementation, such as:
  - Need for novel reporting structures as part of an Extrapolation Study Report
  - Lack of familiarity and comfort with novel / advanced methodologies
- Use of pediatric registry data (and other observational data)?
  - Need to rely on very different methods (e.g. causal inference approaches)

- Implementation of an adaptive extrapolation framework?
  - Need to reflect continuous learning as we cumulate information when progressing through an adult and pediatric development program

# Quantitative challenges of extrapolation ...

- are best addressed by a collaborative effort of Pharmacometrics, Statistics, and Clinical
- Icok at the scientific problems

It will require not only new tools ... but a radical change in the structure of pharmaceutical clinical R&D units: A reorientation of thinking cannot be accomplished without a reorientation of process. (Sheiner, 1997)

Finding the question is often more important than finding the answer ... Neither exploratory nor confirmatory is sufficient alone. We need them both. (Tukey, 1980)

# Acknowledgements

- M Bacchi (Actelion)
- C Gerlinger (Bayer)
- P Bauer (Medical U Vienna)
- F Koenig (Medical U Vienna)

- S Ballerstedt (Novartis)
- B Bornkamp (Novartis)
- T Dumortier (Novartis)
- R Fisch (Novartis)
- O Sander (Novartis)
- H Schmidli (Novartis)
- JL Steimer (Novartis)

# References

- Higgins, Green (eds) (2011) Cochrane handbook for systematic reviews of interventions, version 5.1.0. March 2011, www.cochrane-handbook.org
- Hlavin, Koenig, Male, Posch, Bauer (2016) Evidence, eminence and extrapolation. Statistics in Medicine 35, 2117-2132
- Manolis, Pons (2009) Proposals for model-based paediatric medicinal development within the current European Union regulatory framework. Br J Clin Pharmacol 68, 493– 501
- Pocock (1976) The combination of randomized and historical controls in clinical trials. Journal of Chronic Diseases 29, 175-188
- Senn (2010) Statisticians and pharmacokineticists: what they can still learn from each other. Clinical Pharmacology & Therapeutics 2010 88:328-34
- Sheiner (1997) Learning versus confirming in clinical drug development. Clinical Pharmacology & Therapeutics 61, 275-291
- Tukey (1980) We need both exploratory and confirmatory. The American Statistician 34, 23-25

**NOVARTIS**