

# Extrapolation

Summary of selected publications

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### **Extrapolation – Framework**

- A Review of the New Antiepileptic Drugs for Focal-Onset Seizures in Pediatrics: Role of Extrapolation (Arzimanoglou et al., 2018)
- Challenges and Opportunities in the Development of Medical Therapies for Pediatric Populations and the Role of Extrapolation (Barrett et al., 2018)
- Extrapolation of Efficacy in Pediatric Drug Development and Evidence-based Medicine: Progress and Lessons Learned (Sun et al., 2018)
- Extrapolation in the development of paediatric medicines: examples from approvals for biological treatments for paediatric chronic immune-mediated inflammatory diseases (Stefanska et al., 2017)
- Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs (Dunne et al., 2011)

### **Modelling approaches for extrapolation**

- Unified approach for extrapolation and bridging of adult information in early-phase dose-finding paediatric studies (Petit et al., 2018)
- Extrapolation of a Brivaracetam Exposure–Response Model from Adults to Children with Focal Seizures (Schoemaker et al., 2018)
- Exposure Matching for Extrapolation of Efficacy in Pediatric Drug Development (Mulugeta et al., 2016)

### **Validation of extrapolation**

- Asymmetric inner wedge group sequential tests with applications to verifying whether effective drug concentrations are similar in adults and children (Hampson et al., 2017)

### **More approaches specific for extrapolation**

- Adaptive paediatric investigation plans, a small step to improve regulatory decision making in drug development for children? (Bauer et al., 2016)
- Evidence, eminence and extrapolation (Hlavin et al., 2016)

### **Link to historical controls & meta-analysis / meta-analytical prediction**

- Extrapolation of efficacy and other data to support the development of new medicines for children: A systematic review of methods (Wadsworth et al., 2018)
- How to use prior knowledge and still give new data a chance? (Weber et al., 2018)
- Statistical modeling for Bayesian extrapolation of adult clinical trial information in pediatric drug evaluation (Gamalo-Siebers et al., 2017)

### **Use of prior elicitation**

- Better decision making in drug development through adoption of formal prior elicitation (Dallow et al. 2018)
- Elicitation of Expert Prior Opinion: Application to the MYPAN Trial in Childhood Polyarteritis Nodosa (Hampson et al. 2015)

# Key publications

- Extrapolation framework
  - Extrapolation in the development of paediatric medicines: examples from approvals for biological treatments for paediatric chronic immune-mediated inflammatory diseases (Stefanska et al., 2017)
  - Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs (Dunne et al., 2011)
  - Challenges and Opportunities in the Development of Medical Therapies for Pediatric Populations and the Role of Extrapolation (Barrett et al., 2018)
  - A Review of the New Antiepileptic Drugs for Focal-Onset Seizures in Pediatrics: Role of Extrapolation (Arzimanoglou et al., 2018)
- Statistical methods utilizing extrapolation
  - Extrapolation of efficacy and other data to support the development of new medicines for children: A systematic review of methods (Wadsworth et al., 2018)
  - Statistical modeling for Bayesian extrapolation of adult clinical trial information in pediatric drug evaluation (Gamalo-Siebers et al., 2018)

# Extrapolation framework

- Article
  - Stefanska A M, Distlerová D, Musaus J, Olski T M, Dunder K, Salmonson T, Mentzer D, Müller-Berghaus J, Hemmings R, Veselý R
  - Extrapolation in the development of paediatric medicines: examples from approvals for biological treatments for paediatric chronic immune-mediated inflammatory diseases
  - Arch Dis Child 2017;102:952-957
- Description
  - Review of application of extrapolation for PK, PD, efficacy and safety in pediatric chronic immune-mediated inflammatory diseases and discussion of general issues.
  - The article presents several case studies for discussion extrapolation in pediatric development for chronic immune-mediated inflammatory diseases like juvenile idiopathic arthritis, psoriasis and inflammatory bowel disease. The article discusses mainly medical and pharmacological issues and gives guidance for development strategies based on feasible extrapolation.
- Classification
  - Pediatrics
- Reader level: Introduction
- Recommendation:
  - The article is well written and gives a good understanding in understanding about the level of evidences and prerequisites for extrapolation as well as resulting pediatric development strategies. This is illustrated on case studies. Although the case studies only deals with inflammatory diseases the knowledge can be translated to other diseases easily. Despite statistical topics are not discussed the article provided useful background knowledge required for statistical modelling and analysis.

# Extrapolation framework

- Article
  - Dunne J, Rodriguez W J, Murphy M D, Beasley B N, Burckart J, Filie J D, Lewis L L, Sachs H C, Sheridan P H, Starke P, Yao L P
  - Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs
  - Pediatrics 2011;128:e1242-e1249
- Description
  - A Review of pediatric studies submitted to the FDA between 1998 and 2008 in response to written requests is presented. In this review it is evaluated how and when extrapolation for efficacy from adult data or other data was used. An introduction to extrapolation is given. Rules and examples for full and partial extrapolation or when no extrapolation is feasible are provided. Cases and types of extrapolation for efficacy are identified. Appropriate pediatric development strategies resulting from type available data (adult, other pediatric age groups of populations etc.) and from required pediatric data to support extrapolation are described. In addition, it is determined whether the data was sufficient to result in new pediatric labeling.
- Classification
  - Pediatrics
- Reader level: Introduction
- Recommendation
  - The article is well written and gives a good introduction to extrapolation for pediatric development. It describes how extrapolation strategies will depend on the type of available data and provides an overview of the type of required pediatric data to support extrapolation. This gives basic guidance to reader in order select an optimal extrapolation strategy to optimize pediatric development.

# Extrapolation framework

- Article
  - Barrett J S, Bishai R, Bucci-Rechtweg C, Cheung A, Corriol-Rohou S, Haertter S, James A, Kovacs S J, Liu J, Potempa D, Strougo A, Vanevski K
  - Challenges and Opportunities in the Development of Medical Therapies for Pediatric Populations and the Role of Extrapolation
  - Clinical Pharmacology & Therapeutics 2018;103:419-433
- Description
  - Introduction to extrapolation practices including regulatory framework and requirements for extrapolation to be valid. Role of model-informed framework to support extrapolation is discussed and illustrated on case studies.
  - In the framework of regulatory requirements for extrapolation from adults to pediatrics, describes the different situations in which full/partial/no extrapolation can be used. A quantitative framework using modelling and simulation is proposed but no details are provided. Uses case studies in various disease areas to illustrate the validity of using extrapolation techniques
- Classification
  - Pediatrics
- Reader level: Introduction
- Recommendation
  - A comprehensive introduction to regulatory requirement for use of extrapolation in pediatric drug development is outlined focusing on relevant key elements. Application and limitations of model-informed methods as robust quantitative framework is discussed and illustrated on case studies. An outline of a model-informed strategy plan is introduced as tool for guiding these approaches. Statistical approaches for extrapolation are not discussed.

# Extrapolation framework

- Article
  - Arzimanoglou A, D'Cruz O'N, Nordli D, Shinnar S, Holmes G L
  - A Review of the New Antiepileptic Drugs for Focal-Onset Seizures in Pediatrics: Role of Extrapolation
  - Pediatric Drugs 2018;20:249-264
- Description
  - Introduction to extrapolation framework and application of PK-PD modelling to support extrapolation.
  - Basic introduction of extrapolation and case examples on how extrapolation can be applied for development of antiepileptic drugs for focal-onset seizures. In particular, the applicability of PK-PD modelling to support extrapolation is outlined and discussed.
- Classification
  - Small population, Pediatrics
- Reader level: Advanced
- Recommendation
  - The case examples provide a good introduction to extrapolation and important points to consider. In addition, they illustrate how the benefit in joining expertise of different discipline like pharmacometrics and statistics.

# Statistical methods utilizing extrapolation

- Article
  - Wadsworth I, Hampson L V and Jaki T
  - Extrapolation of efficacy and other data to support the development of new medicines for children: A systematic review of methods
  - Statistical Methods in Medical Research 2018;27:398-413
- Description
  - Literature review of statistical methods for extrapolation in pediatric development
  - Review of statistical methods for extrapolation: Covers Bayesian and frequentist methods. Bayesian methods: Extrapolation via informative prior (adaptive down weighting: adaptive power priors, commensurable priors, robust MAP derived priors. Non-adaptive down weighting: power priors, variance enlargement for normal priors), Assessing consistency between source and target population. Frequentist: weights combination of data, assessing consistency between source and target data.
- Classification
  - (Small population), Pediatrics, General
- Reader level: Introduction
- Recommendation
  - An introduction to extrapolation and its context in pediatric development is provided which will be of benefit when entering this topic. An overview of statistical methods is presented structured by statistical approach, Bayes or frequentist and by way how extrapolation is done, e.g. combining target and source data, methods for down-weighting, consistency evaluation between source and target population. The methods presented are of general nature and can be applied e.g. on small populations as well. However, the focus off application lies on pediatric development.



# Statistical methods utilizing extrapolation

- Article
  - Gamalo-Siebers M, Savic J, Basu C, Zhao X, Gopalakrishnan M, Gao A, Song G, Baygani S, Thompson L, Xia H A, Price K, Tiwari R and Carlin B P
  - Statistical modeling for Bayesian extrapolation of adult clinical trial information in pediatric drug evaluation
  - Pharmaceutical Statistics 2017;16:232-249
- Description
  - Review of Bayesian methods for extrapolation of adult information in pediatric drug development
  - Introduction to pediatric development including opportunity for Bayesian methods is given. Bayesian statistics for extrapolation using a two-step approach [deriving posterior information from adults which is used as prior in analysis of pediatric trial], e.g. using the meta-analytical prediction approach and robust prior is presented. Further, Bayesian method for a combined approach using power priors and commensurate priors is discussed. In addition, methods for partial extrapolation are described. Examples with application of these approaches are presented for extrapolation of treatment comparison and exposure response are presented.
- Classification: (Small population), Pediatrics, General
- Recommendation: High, Introduction level
  - The article is well written, introducing an introduction to pediatric development and role of extrapolation. Core is an overview of state-of-the art general Bayesian methods suitable for extrapolation in pediatric development. Further application of these methods on real application is demonstrated and discussed.