ICH E11A: Pediatric Extrapolation

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Disclosure Statement

- I have no financial relationships to disclose relating to this presentation

- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

Pediatric Extrapolation

- 1994: Final Regulation: Pediatric Labeling Rule
- "A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted"
- Efficacy may be extrapolated from adequate and well-controlled studies in adults to pediatric patients if:
  - The course of the disease is sufficiently similar
  - The response to therapy is sufficiently similar
- Dosing cannot be fully extrapolated
- Safety cannot be fully extrapolated

Brief History of Pediatric Drug Development

1994
- Pediatric Labeling Rule
- Introduces concept of Pediatric Extrapolation

1997
- First incentives laws for pediatric drug development passed
- Becomes Best Pharmaceuticals for Children Act (BPCA) in 2002

1998
- First requirement for pediatric drug development promulgated by FDA
- Becomes Pediatric Research Equity Act in 2003

2000
- ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population published

ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population published

Guideline topics

- Pediatric Formulations
- Timing of Pediatric Studies
- Types of Studies
- Age Classification of Pediatric Patients
- Ethical Issues in Pediatric Studies

Pediatric patients should have access to products that have been appropriately evaluated

Product development programs should include pediatric studies when pediatric use is anticipated

In 2000:

- BPCA enacted in 2002 and PREA enacted in 2003
- Only 52 Pediatric Labeling Changes in U.S.
- No Pediatric Regulation in EU
- Limited experience with pediatric drug development

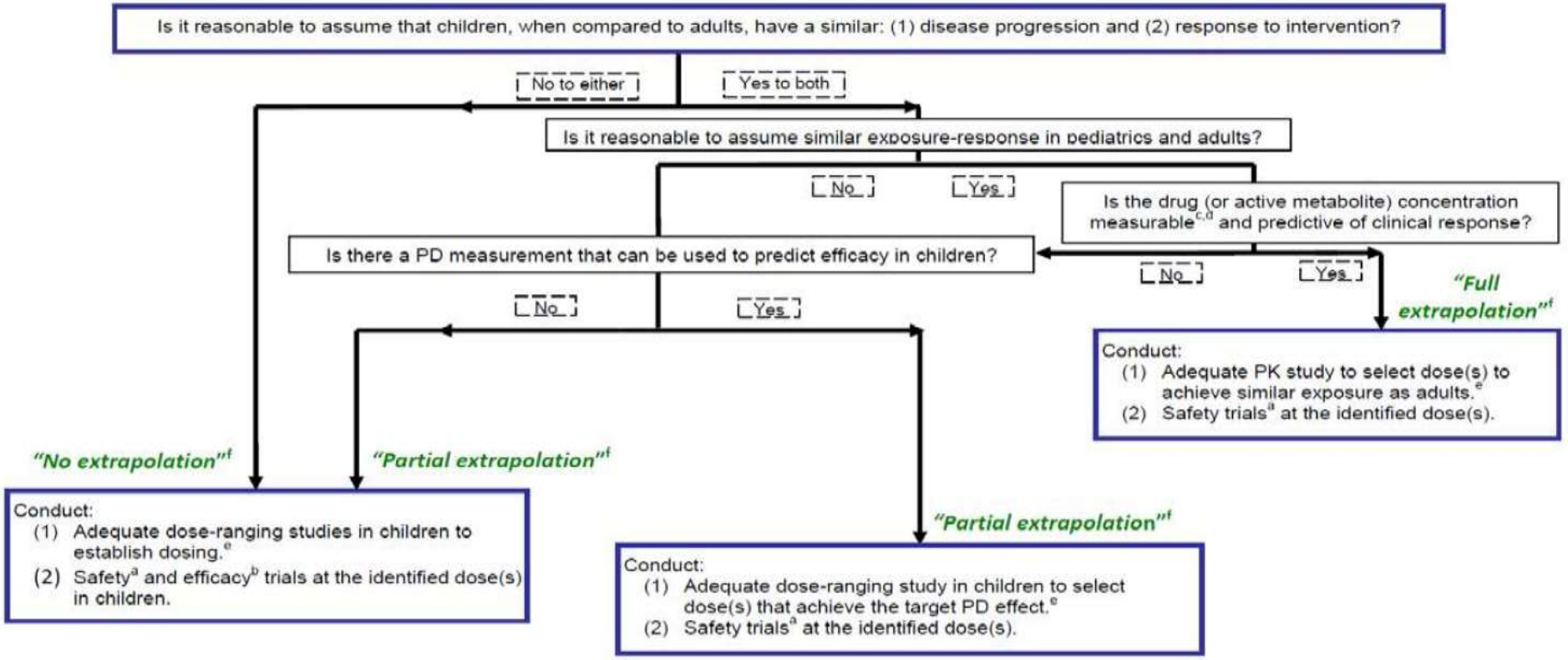
Global Pediatric Product Development

- Advances in understanding of pediatric product development
  - Advancements in scientific and clinical knowledge of pediatric diseases and therapeutics
  - Increased understanding in design and conduct of pediatric clinical trials
  - Changes in regulatory requirements for pediatric product development
  - Better understanding of complexities related to pediatric product development
- E11(R1) intended to complement and provide clarification and current regulatory perspective on topics in pediatric drug development
- Understood that a separate guidance would be needed in the future to provide more detailed guidance on Pediatric Extrapolation

Brief History of Pediatric Drug Development

2000	• ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population published
2007	• Pediatric Regulation Enacted in European Union
2014	• ICH E11(R1) Expert Working Group (EWG) established
2017	• ICHE11(R1): Addendum published
2017	• ICH E11A Pediatric Extrapolation EWG established

Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

FDA Draft Guidance: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, December 2014

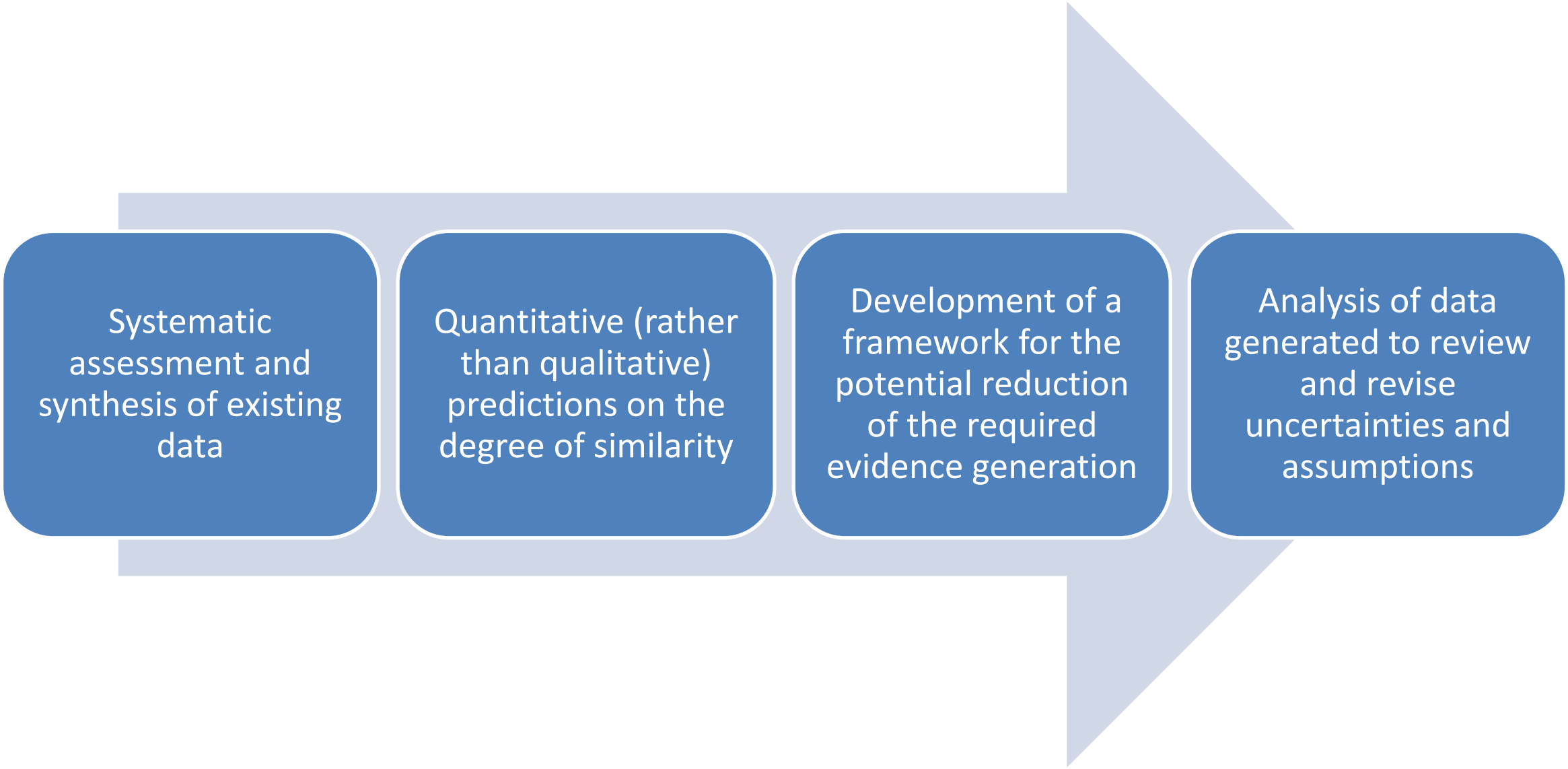
EMA Reflection Paper

- Published as draft in October 2017 and Finalized October 2018
- Addresses the use of quantitative methods to help assess the relevance of existing information in a source population to one or more target population(s)
  - Extrapolation Concept
  - Intended to identify gaps in knowledge
  - Strength of evidence available
- Address gaps in knowledge and assumptions, so that the totality of available evidence can address the scientific questions of interest for marketing authorisation in the target population
  - Extrapolation Plan
  - Studies to be conducted/Information to be collected to address gaps in knowledge
- Validation of the Extrapolation Concept and Mitigation of Risks associated with Extrapolation
- Does not discuss “categories” of extrapolation (i.e., full or partial extrapolation)

ICH E11(A): Pediatric Extrapolation

- E11(R1) Addendum recognized the need for more detailed ICH guidance on Pediatric Extrapolation
- Concept Paper finalized in October 2017
- Expert Working Group assembled
  - Global Regulatory Authorities and Drug Development Organizations
- Align terminology
- Systematic approach to use pediatric extrapolation
- Study designs, statistical methodologies, and Modeling and Simulation strategies that can be considered

Systematic Approach to Use of Pediatric Extrapolation



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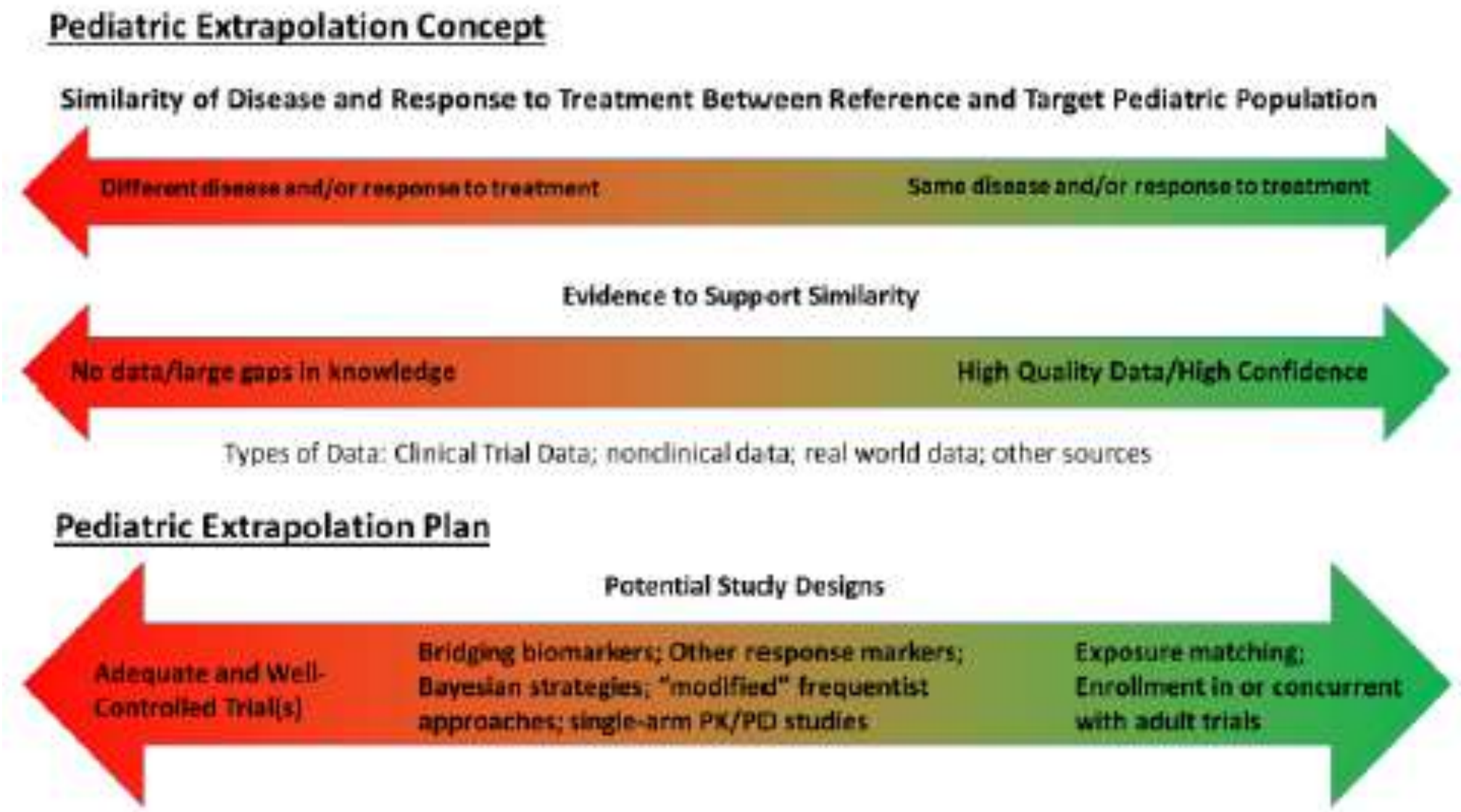
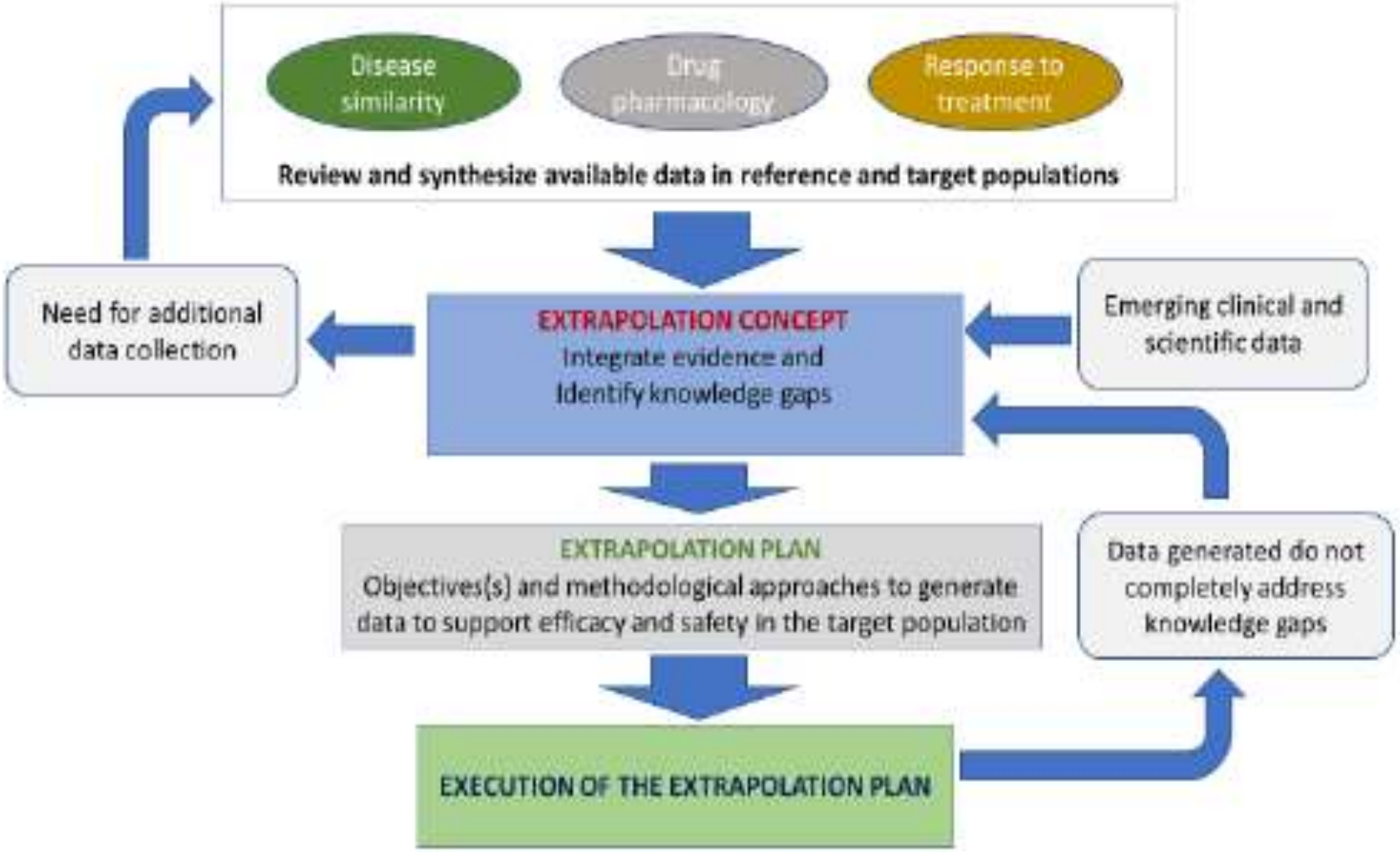


Pediatric Extrapolation Framework



Extrapolation Plan

- Model-Informed Approaches
  - Tools that can be used as to inform both the concept and plan
  - Assess data on similarity of disease and response to treatment
  - Inform study designs, and dosing strategies
- Efficacy Studies
  - Describes different study designs that can be used as part of an extrapolation plan
  - Considerations for the incorporation of external data and quantifying the impact of use of reference data
  - Presentation and Justification for the Pediatric Trial
  - Analysis, Reporting, and Interpretation

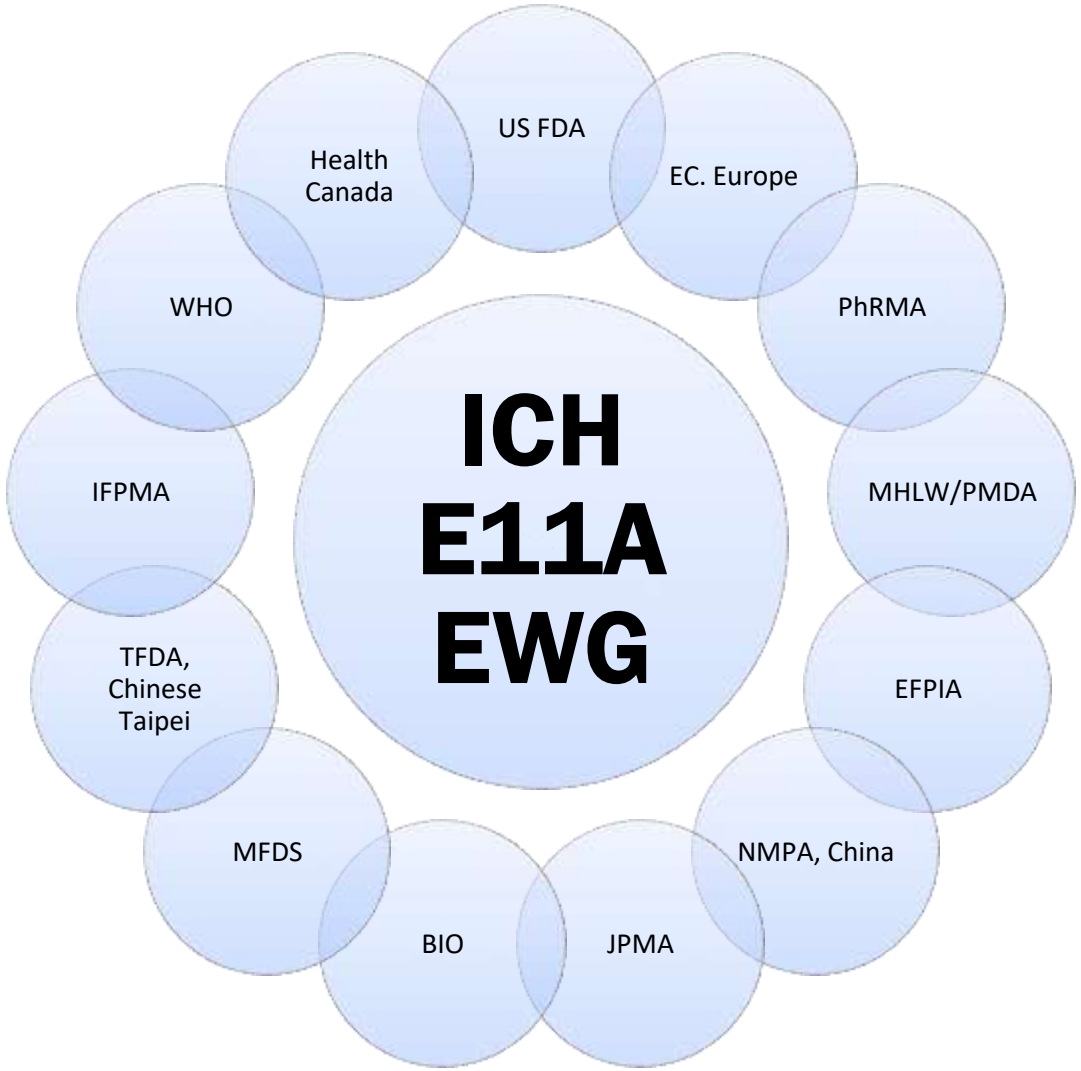
Current Status and Next Steps

- ICH E11A endorsed by the ICH Assembly on 4 April 2022 (Step 2b)
- Current Status: Step 3
- Public consultation dates:
  - EC, Europe - Deadline for comments by 6 August 2022
  - NMPA, China - Deadline for comments by 30 July 2022
  - TFDA, Chinese Taipei - Deadline for comments by 31 July 2022
- Other regions pending translation and/or clearance
- All regions expected to have comments returned by end of 2022
- ***Training material case example being developed for posting during public consultation period***

Summary

- Pediatric extrapolation can be used to maximize the efficiency of pediatric product development while maintaining important regulatory standards for approval
- Pediatric extrapolation has matured over the last 20 years
- ICH E11A intended to provide systematic framework for utilization of pediatric extrapolation
  - Not intended to be standard, harmonized regulatory “recipe book”
- Use of well-conceived and well-designed models and statistical methodologies can greatly aid in addressing gaps in knowledge in pediatric extrapolation approaches
  - Early discussions with regulatory authorities encouraged

Acknowledgements



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Thank you