Pediatric Extrapolation

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Disclosure Statement

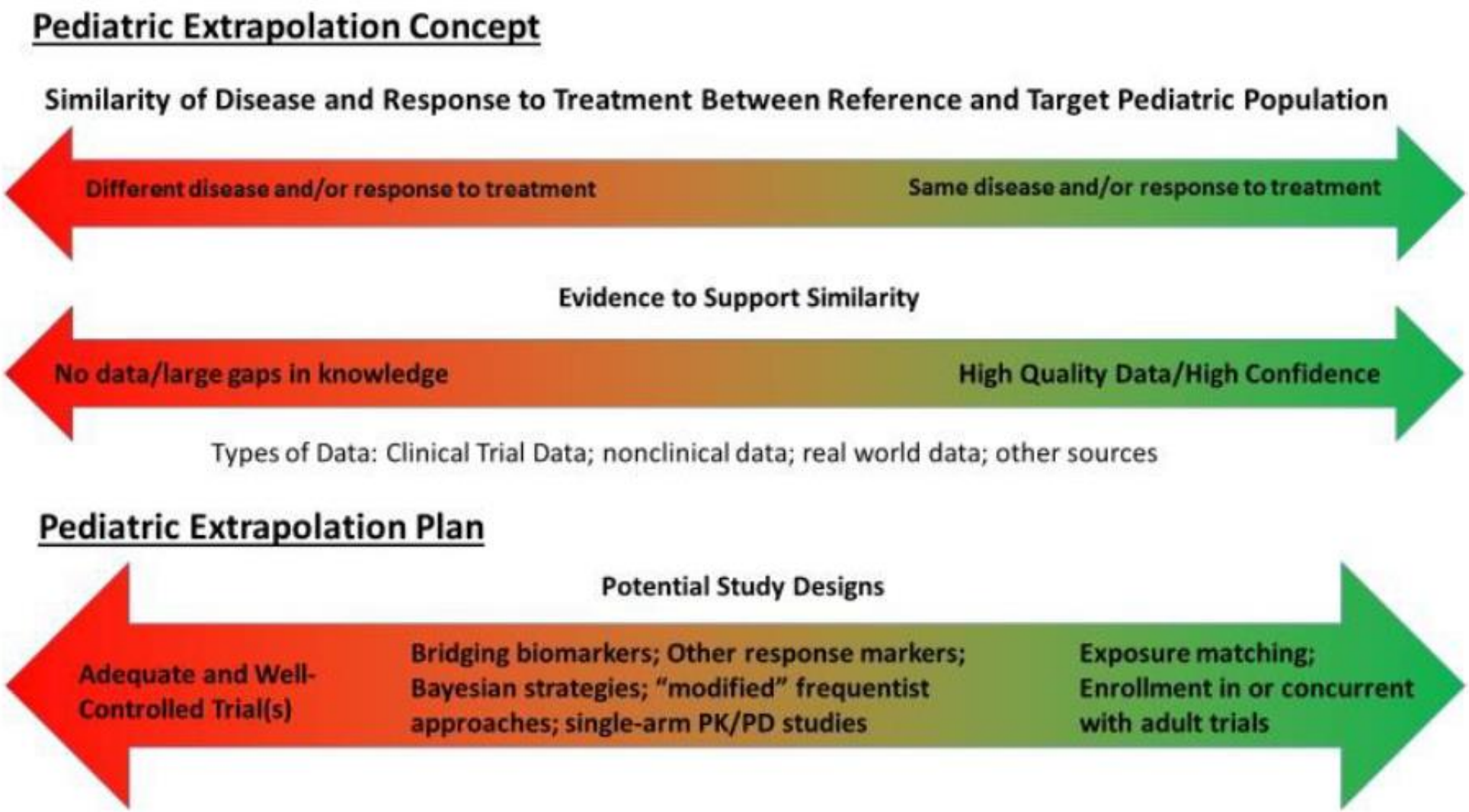
- I have no financial relationships to disclose relating to this presentation

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

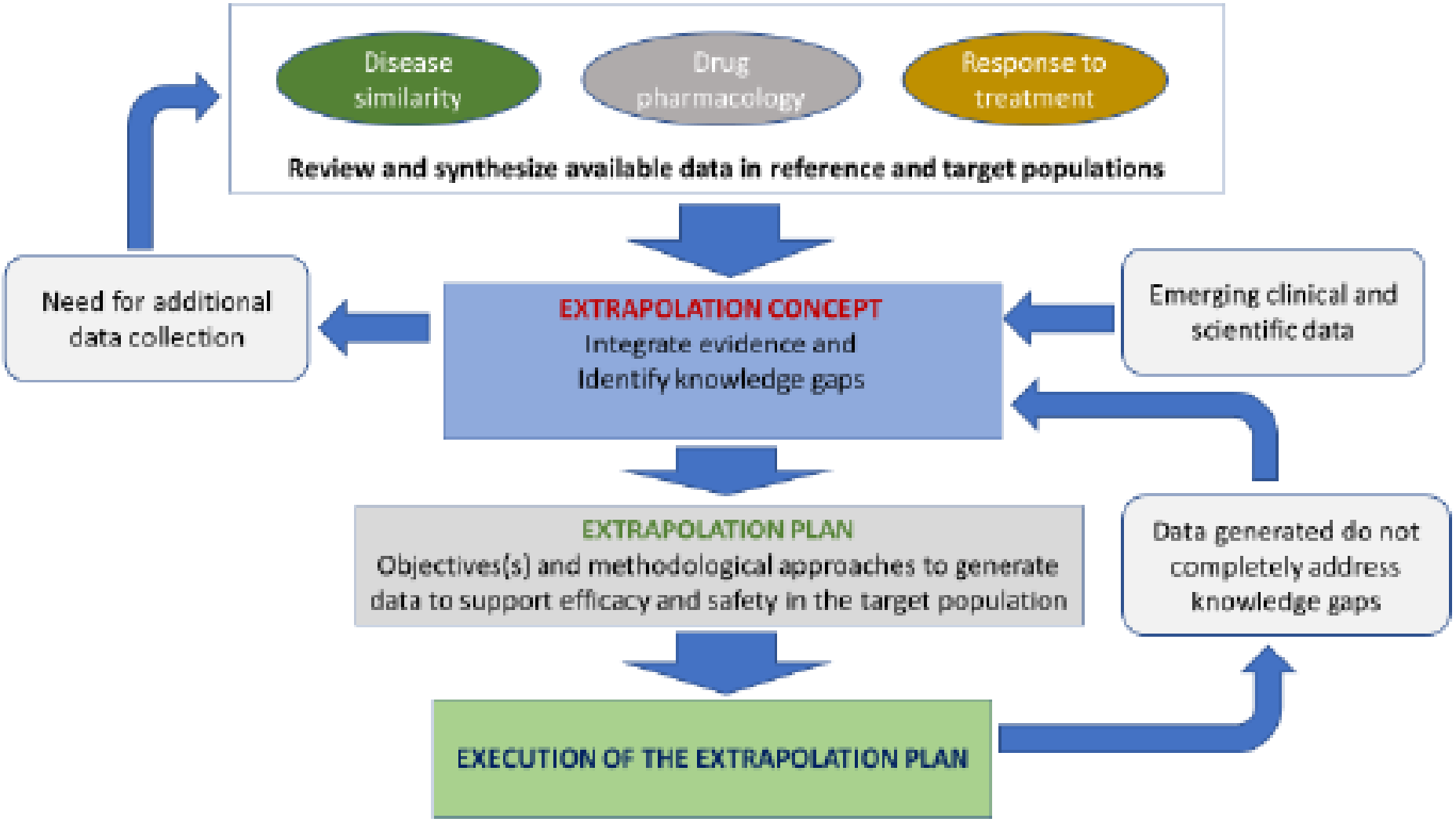
Pediatric Extrapolation

- ICH E11(R1): Guideline on clinical investigation of medicinal products in the pediatric population
  - Adopted by ICH August 2017
- "Pediatric extrapolation" is defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population.
- ICH E11A Pediatric Extrapolation Draft Guideline
  - Published by FDA on August 25, 2022
  - Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11a-pediatric-extrapolation

Pediatric Extrapolation Concept and Plan



Pediatric Extrapolation Framework



Use of Existing Data

- Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults)

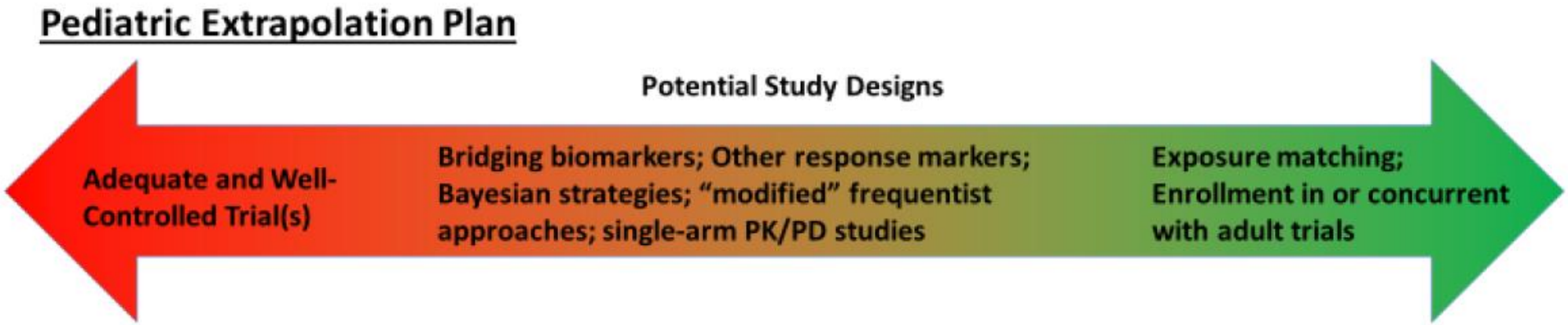
Sources of Data	Types of Data
Clinical data	PK, PK/PD, E-R, and clinical data in the same condition for a drug or drugs in the same class
	PK, PK/PD, E-R, and clinical data in other related conditions for a drug or drugs in the same class
	PK, PK/PD, E-R, and clinical data in the same condition for a drug or drugs in a different class
Nonclinical data	ADME Data from animal models
	In silico, in vitro, and in vivo data (e.g., disease-response, PK, PK/PD, semi-mechanistic, and mechanistic)
	Juvenile nonclinical toxicology data
Real World Data	Data including but not limited to disease registries (regional, national, and international), electronic health records, health claims databases
Other sources	Systematic reviews or meta-analyses including those that can be used to evaluate suitable biomarkers Professional organization guidelines/Clinical practice guidelines/Consensus documents
	Published models/simulations (e.g., PK/PD, mechanistic)
	Expert opinion
	Standard of care/practice of medicine

Development of a Pediatric Extrapolation Concept

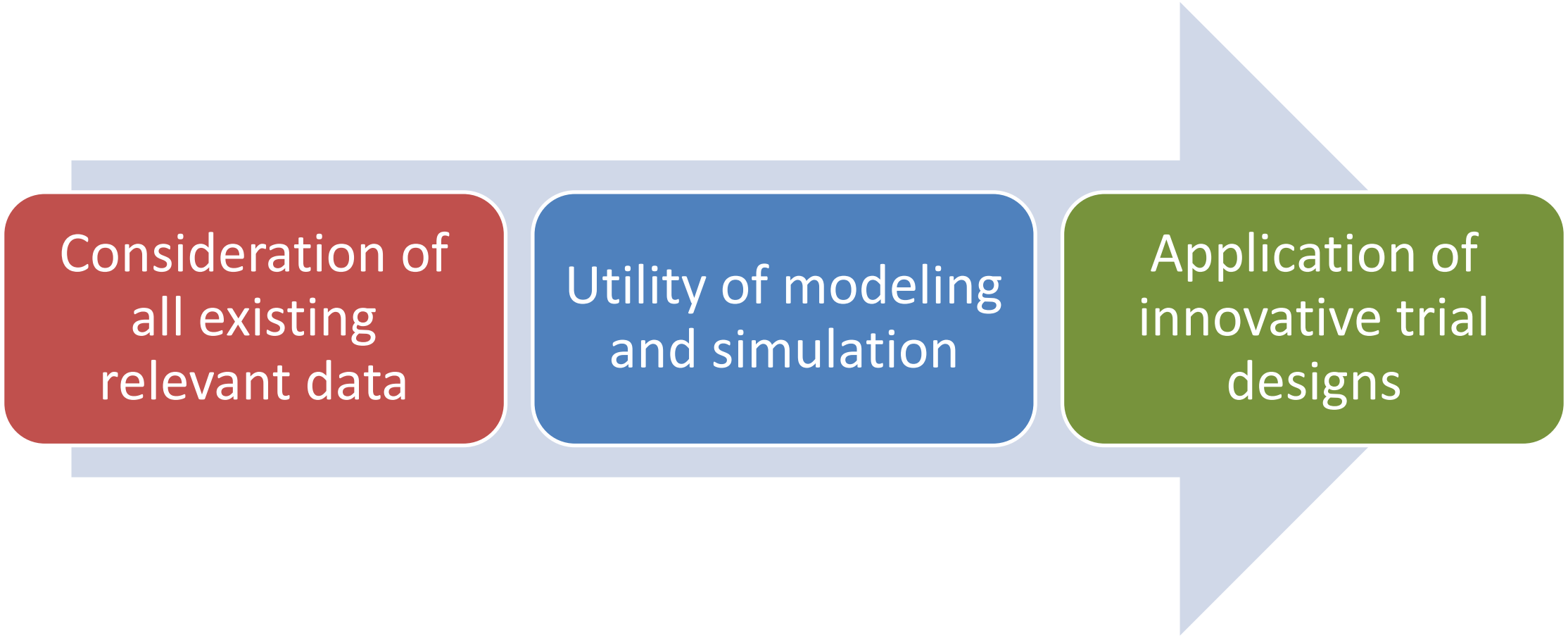
- Evaluate the body of evidence and clinical relevancy of the similarities and differences between the reference and target population
  - Disease, drug pharmacology, response to treatment
- Consider the types and sources of data that have been identified
  - How consistent are the findings across the types and sources of data
  - What are the uncertainties in the data
  - What are the limitations of the data
- What are the existing knowledge gaps that need to be filled
  - Both efficacy and safety

Development of a Pediatric Extrapolation Plan

- The Pediatric Extrapolation Plan should be developed to answer the knowledge gaps identified in the pediatric extrapolation concept
- Model-Informed Approaches
  - 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



Advances in the Application of Pediatric Extrapolation



Examples of Advances in Use of Pediatric Extrapolation

Disease	Treatment	Innovation
Heart Failure	Sacubitril/Valsartan (Entresto)	Use of a bridging biomarker
Systemic Lupus Erythematosus	Belimumab (Benlysta)	Use of a post-hoc Bayesian Analysis*
Schizophrenia	Atypical Antipsychotics	Review of available data on exposure-response
Covid-19	Tocilizumab (Actemra)	Extrapolation of adult COVID-19 data with dosing and safety from other approved pediatric conditions

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
- The use of pediatric extrapolation may be limited in certain situations
  - Rare pediatric or "pediatric-only" diseases
  - Diseases specific to neonates
- Can Pediatric Extrapolation be applied to Pediatric Major Depressive Disorder?