Application of Bayesian Extrapolation in Pediatric Drug Development Program

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Outline

- **Pediatric Development Laws and Regulatory Guidelines**

- **Pediatric Extrapolation**

- **Statistical Extrapolation – Bayesian Methods**

- **Example 1 – a pediatric extrapolation proposal**

- **Example 2 – a statistical extrapolation analysis**

- **Summary**

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US Pediatric Development Laws: PREA vs BPCA

- **Pediatric Research Equity Act (PREA)**
  - Drugs and biologics

  - Studies must be labeled

  - Mandatory (required)

  - No financial incentive

  - For indication under review

  - Orphan indication exempted

- **Best Pharmaceuticals for Children Act (BPCA)**
  - Drugs and biologics

  - Studies must be labeled

  - Voluntary (written request)

  - Financial incentive

  - May expand to other indications

  - May be requested in orphan indication

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Recent Regulatory Guidelines

- **ICH. E11(R1**): Addendum: Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population. Step 2b; 12 October 2016.

- **FDA**. Guidance for Industry: Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices. June 2016.

- **FDA**. Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans. March 2016.

- **FDA**. Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. December 2014.

- **EMA**. Reflection Paper on Extrapolation of Efficacy and Safety in Pediatric Medicine Development, EMA/199678/2016.

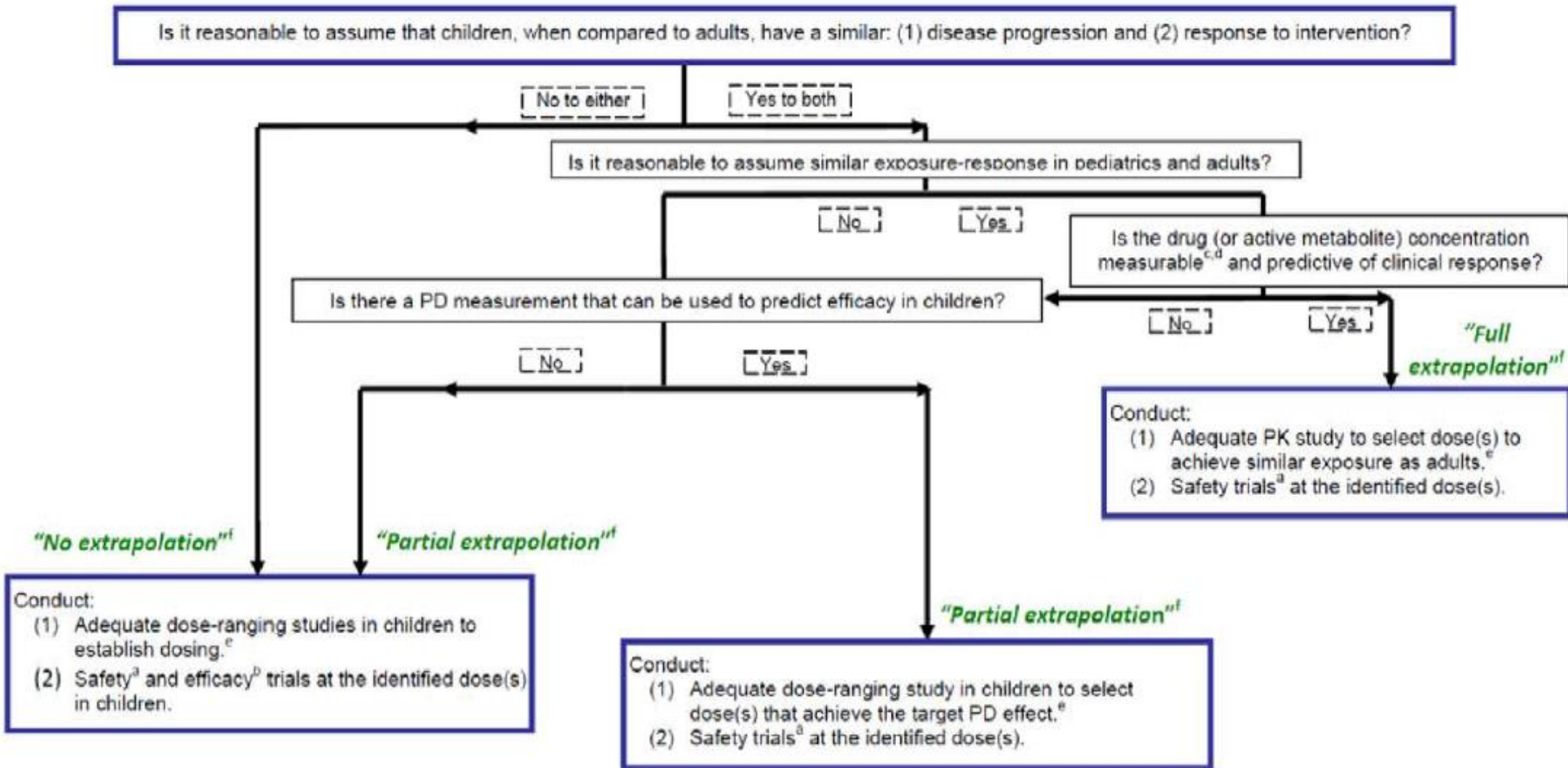**AMGEN**

Pediatric Study Plan Contents*
Required per Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA)

1. OVERVIEW OF THE DISEASE IN THE PEDIATRIC POPULATION (1-3 pages)

2. OVERVIEW OF THE DRUG OR BIOLOGICAL PRODUCT (1-3 pages)

3. **OVERVIEW OF PLANNED EXTRAPOLATION OF EFFECTIVENESS TO SPECIFIC PEDIATRIC POPULATIONS (1-3 pages)**

4. PLANNED REQUEST FOR DRUG-SPECIFIC WAIVER(S) (1-3 pages)

5. PLAN TO REQUEST DEFERRAL OF PEDIATRIC STUDIES (1-3 pages)

6. TABULAR SUMMARY OF PLANNED NONCLINICAL AND CLINICAL STUDIES

7. AGE-APPROPRIATE FORMULATION DEVELOPMENT (1-3 pages)

8. NONCLINICAL STUDIES (1-3 pages)

9. CLINICAL DATA TO SUPPORT DESIGN AND/OR INITIATION OF STUDIES IN PEDIATRIC PATIENTS (1-5 pages)

10. PLANNED PEDIATRIC CLINICAL STUDIES

    10.1 Pediatric Pharmacokinetic Studies (1-10 pages)

    10.2 Clinical Effectiveness and Safety Studies (1-10 pages)

11. TIMELINE OF THE PEDIATRIC DEVELOPMENT PLAN (1 page)

12. AGREEMENTS FOR PEDIATRIC STUDIES WITH OTHER REGULATORY AUTHORITIES (1-3 pages)

* FDA. Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans. March 2016.

Pediatric Study Planning and Extrapolation Algorithm

Is it reasonable to assume that children, when compared to adults, have a similar: (1) disease progression and (2) response to intervention?

No to either — Yes to both

Is it reasonable to assume similar exposure-response in pediatrics and adults?

No — Yes

Is the drug (or active metabolite) concentration measurable[c,d] and predictive of clinical response?

Is there a PD measurement that can be used to predict efficacy in children?

No — Yes

No — Yes

"Full extrapolation"[f]

Conduct:
(1) Adequate PK study to select dose(s) to achieve similar exposure as adults.[e]
(2) Safety trials[a] at the identified dose(s).

"No extrapolation"[f]

"Partial extrapolation"[f]

Conduct:
(1) Adequate dose-ranging studies in children to establish dosing.[e]
(2) Safety[a] and efficacy[b] trials at the identified dose(s) in children.

"Partial extrapolation"[f]

Conduct:
(1) Adequate dose-ranging study in children to select dose(s) that achieve the target PD effect.[e]
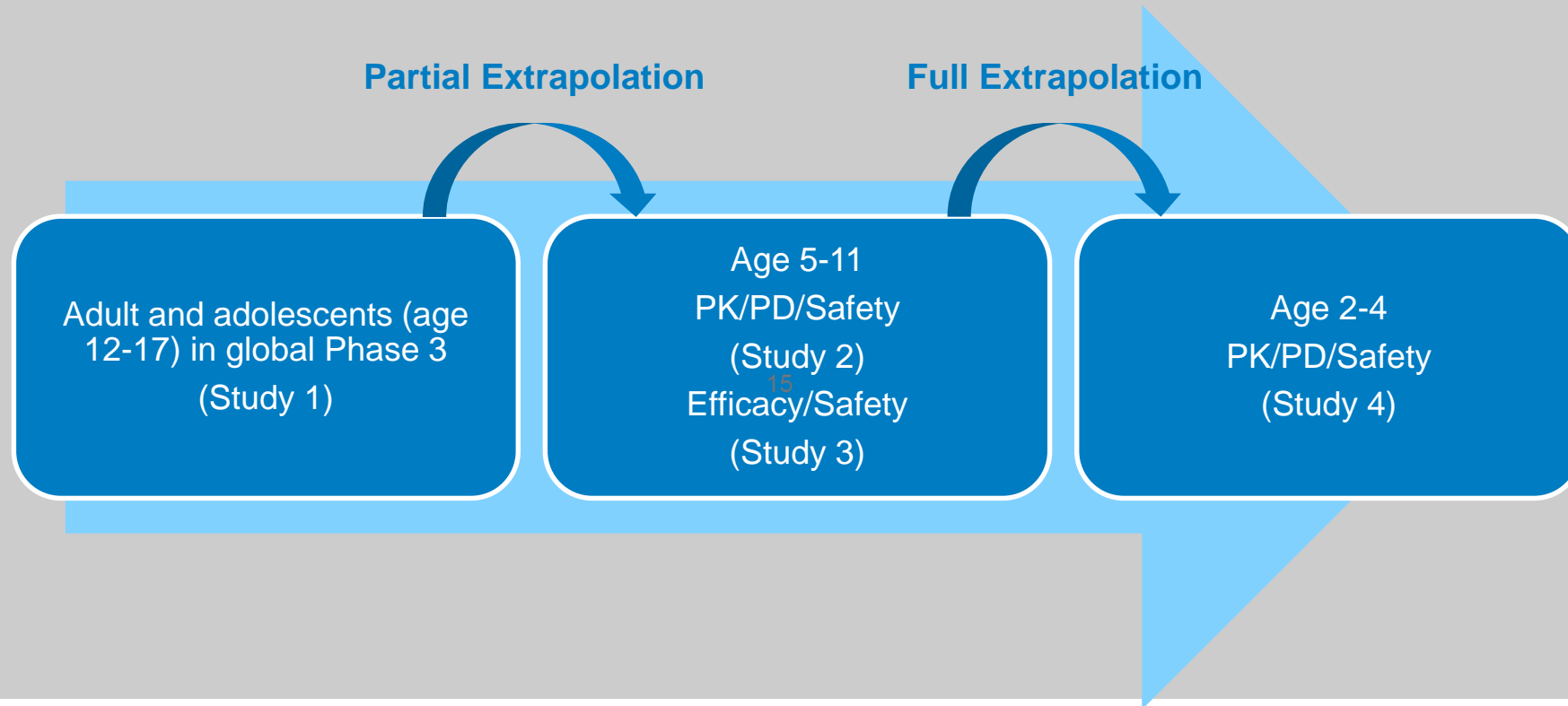(2) Safety trials[a] at the identified dose(s).

Extrapolation framework

- Extrapolation concept
  - Define source and target population
  - Form predictions and hypotheses

- Extrapolation plan
  - Prospective; including study planning and sample size

- Confirmation & extrapolation
  - Confirm consistency between prediction and observed target data
  - Iterative process of predicting and confirming
  - Conclusion based on confirmed concept

- Mitigating uncertainty and risk

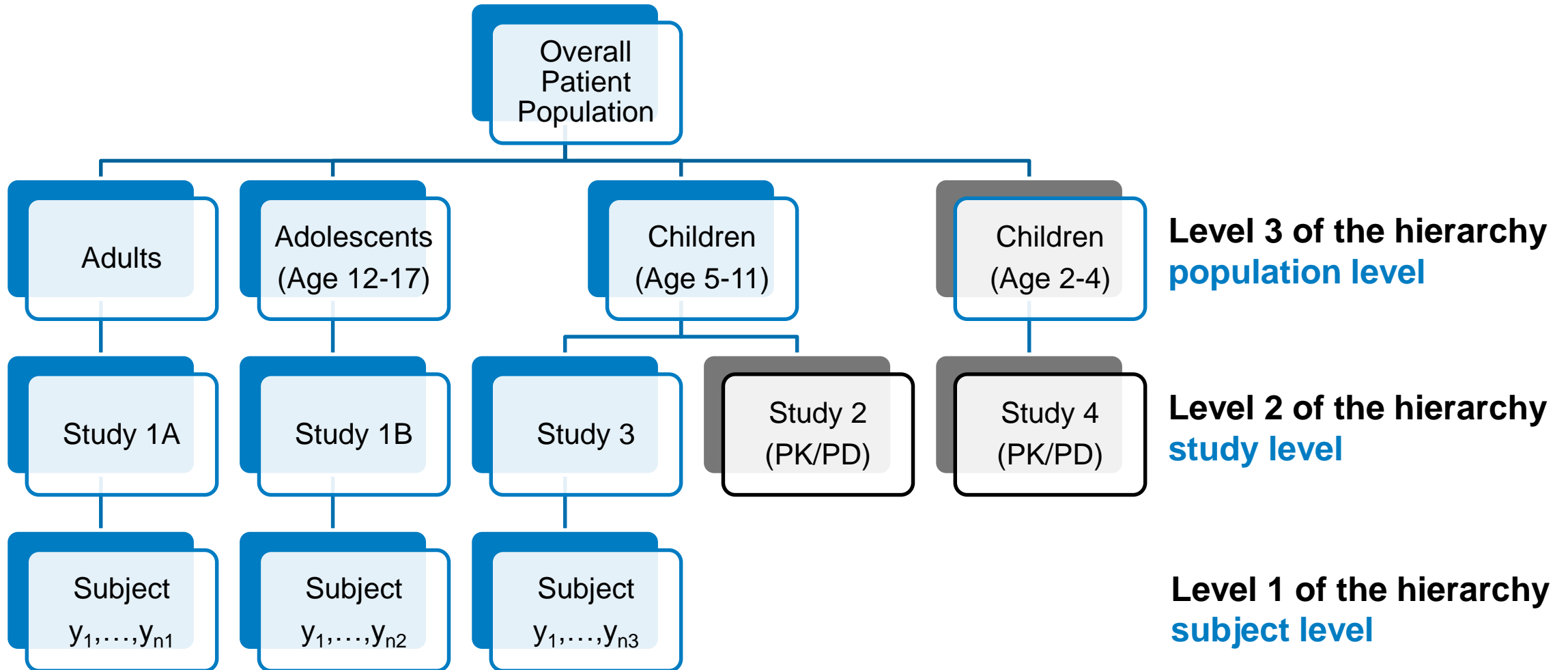# Bayesian Methods for Pediatric Extrapolation

- Bayesian methods are a natural choice for quantitatively extrapolating information from source to target population in a **partial extrapolation** setting (ICH, 2014; US FDA, 2016).

- Bayesian methods to consider:
  - Use the posterior from source as the prior for target population
  - Power prior (Ibrahim and Chen, 2000)
  - Bayesian hierarchical modeling

- FDA's "Guidance for Industry and Food and Drug Administration Staff: Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices" (US FDA, 2016) recommended **Bayesian Hierarchical Model** as an appropriate method for extrapolation.

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Example 1: Stepwise extrapolation proposal in a PSP to satisfy PREA requirement

Partial Extrapolation

Full Extrapolation

Adult and adolescents (age 12-17) in global Phase 3
(Study 1)

Age 5-11
PK/PD/Safety
(Study 2)
Efficacy/Safety
(Study 3)

Age 2-4
PK/PD/Safety
(Study 4)

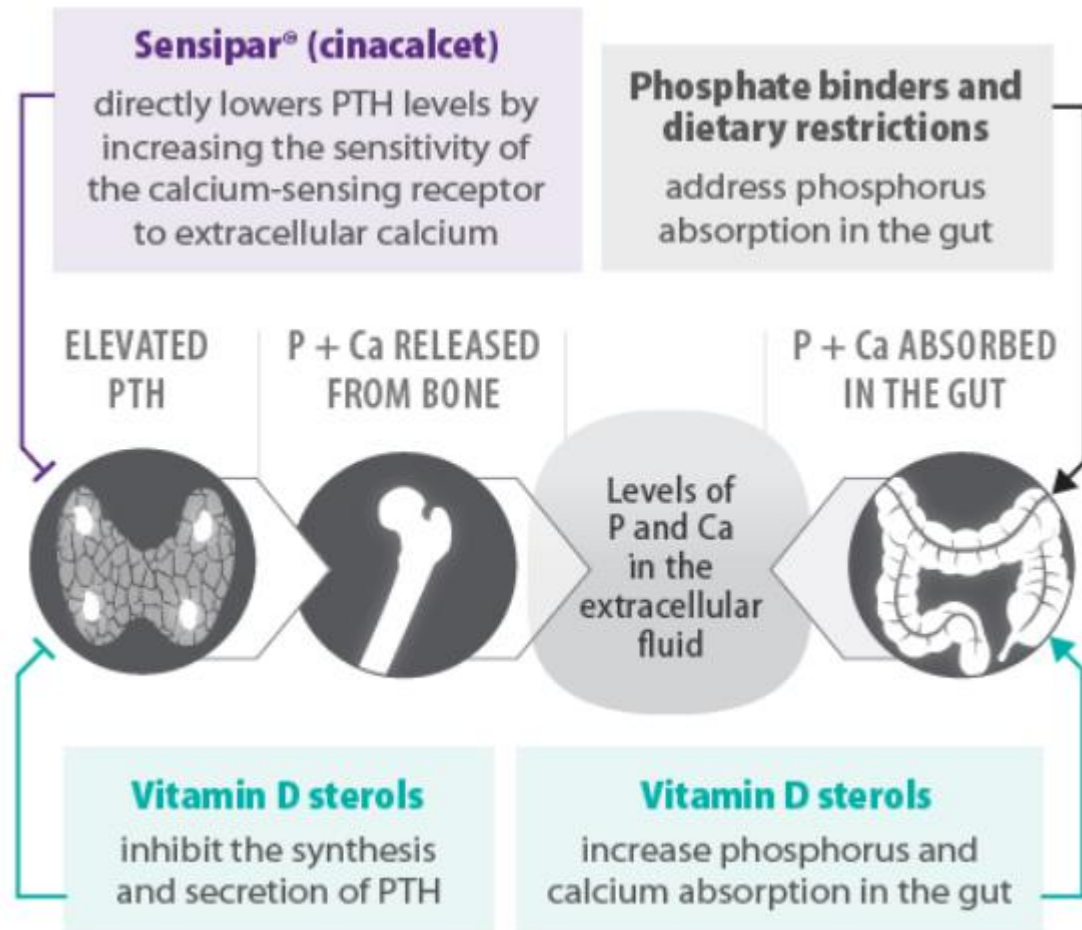**Different extrapolation strategies may be adopted**

3-level Bayesian Hierarchical Model

Extrapolation Reduced Proposed Sample Size

- PSP sample size justification for Study 3 (children 5-11 years)

  - Source data can be extrapolated

    - Adult, adolescent data from Study 1

    - Placebo data from other pediatric (age 5-11) program

  - Extrapolation can save up to 50% of subjects in trial 3 assuming extrapolated information cannot exceed that are observed in the target population

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Example 2: Cinacalcet Bayesian Extrapolation Analysis Under BPCA Written Request

Sensipar® (cinacalcet)
directly lowers PTH levels by increasing the sensitivity of the calcium-sensing receptor to extracellular calcium

Phosphate binders and dietary restrictions
address phosphorus absorption in the gut

ELEVATED PTH | P + Ca RELEASED FROM BONE | P + Ca ABSORBED IN THE GUT

Levels of P and Ca in the extracellular fluid

Vitamin D sterols
inhibit the synthesis and secretion of PTH

Vitamin D sterols
increase phosphorus and calcium absorption in the gut

http://www.sensiparhcp.com/secondary-hpt-therapies/#

- Cinacalcet is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease receiving dialysis

- Cinacalcet is a calcimimetic agent which acts as a modulator of the calcium-sensing receptor (CaR) and regulates PTH secretion

- Pediatric, orphan indication
    - < 1000 pediatric patients on dialysis will develop secondary HPT. Of these, approximately 300 patients are estimated to be 0 to 5 years of age

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Rationale for the Pediatric Extrapolation Strategy

- The adult and pediatric populations are similar in the following aspects according to ICH E11 (ICH, 2000):
    - Pediatric population in which cinacalcet has been studied are similar to those of the approved population in adults (i.e., patients with secondary HPT treated with dialysis).
    - The pathophysiology and course of the disease process (secondary HPT) is similar in adult and pediatric populations with CKD receiving dialysis.
   - The outcome of therapy is likely to be comparable.

Pediatric Extrapolation Strategy by Age Category

- Partial extrapolation for age 6 – 17

  - Sample sizes of pediatric studies were too small to have adequate power

  - Adult data were borrowed to estimate treatment effect

- Full extrapolation for age younger than 6

  - Younger age study focused on safety rather than efficacy

  - No control arm in younger age study, and relative treatment effect in younger age cannot be directly estimated

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Bayesian Statistical Models for Extrapolation

- ## Bayesian hierarchical model
  - Assumes exchangeability at population level, study level and subject level
  - Objective amount of borrowing depending on the consistency of evidence across information sources: more borrowing if results are more similar, less borrowing if results are less similar
  - **Recommended in FDA guidance (2016); primary method in FDA filing**

- ## Power prior
  - Discount adult data by the power prior parameter
  - Pre-specified power prior parameter: subjective amount of borrowing
  - Relation to hierarchical models: power prior parameter connects to the variance parameters in hierarchical models

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3-level Bayesian Hierarchical Model – Primary Method for US submission
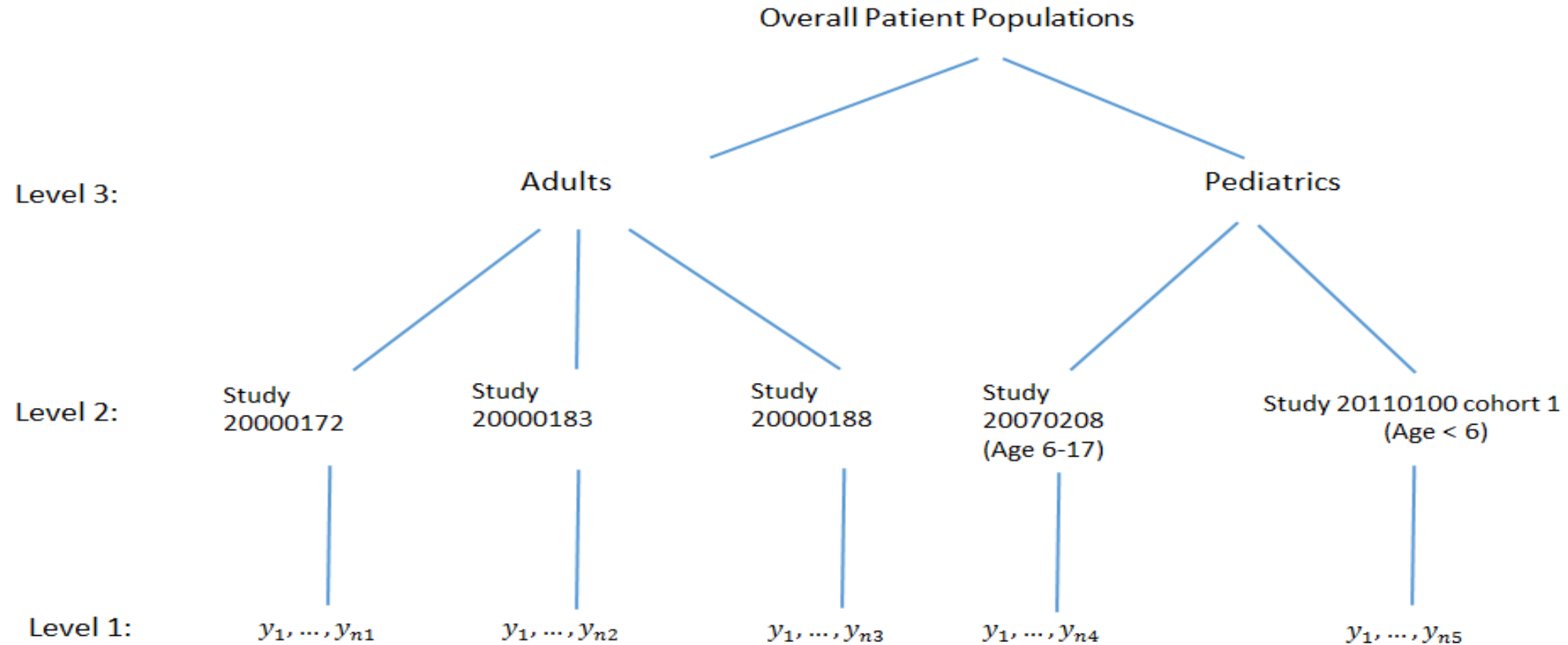
Bayesian Hierarchical Model Requires Exchangeability

- The model assumes exchangeability at each hierarchical level

  - subjects within a study are exchangeable (at Level 1)

  - studies within a patient population are exchangeable (at Level 2)

  - patient populations are exchangeable (at Level 3)

- Exchangeable means there is nothing known a priori that would imply one (subject, study, or population) would be better or worse in the outcome of interest than another (US FDA, 2016).

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3-level Bayesian Hierarchical Model

- **Notations**
  - treatment group *c*
    - *c* = 0 for placebo
    - *c* = 1 for cinacalcet
  - patient population *p*
    - *p* = 0 for pediatric
    - *p* = 1 for adult
  - study *k*
    - when *p* = 0: *k* = 1 for Study 20070208; *k* = 2 for Study 20110100 cohort 1
    - when *p* = 1: *k* = 1 for adult Study 20000172; *k* = 2 for adult Study 20000183; *k* = 3 for adult Study 20000188
  - n_{pkc} be the number of subjects for population *p*, study *k* and treatment group *c*
  - Y_{pkc} be the number of responders (number of subjects achieving ≥ 30% reduction from baseline in mean iPTH)
  - p_{pkc} be the proportion of responders (response rate)

3-level Bayesian Hierarchical Model

- ## Level 1 of the hierarchy – subject level

  - Assuming binomial distribution for Y_{pkc}, that is
$$Y_{pkc} | p_{pkc} \sim Binomial(n_{pkc}, p_{pkc})$$

- ## Level 2 of the hierarchy – study level

  - Study level random effects are introduced to account for the between-study variabilities:
$$logit(p_{pkc}) = \beta_{pc} + \gamma_{pkc}$$

where

$$logit(x) = log\left(\frac{x}{1-x}\right),$$

β_{pc} is the population effect,

γ_{pkc} is the study level random effect,

$\gamma_{pkc} \sim N(0, \sigma_{pc}^2)$, where σ_{pc}^2 accounts for the between-study variation.

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3-level Bayesian Hierarchical Model

- ## Level 3 of the hierarchy – population level

  - Pediatric and adult population parameters are assumed to be random samples from an overall patient population, that is:

  $$\beta_{pc} = \beta_c + \mu_{pc}$$

  - β_c is the treatment effect such that $\text{expit}(\beta_c)$ is the overall response rate for treatment group c across all age groups and $\mu_{pc} \sim N(0, \sigma_c^2)$ which captures the between-population variability

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Effective Sample Size

- The information borrowed from the source population can be quantified using effective sample size (ESS) calculated based on variance reduction

- ESS was selected using a grid search method following the FDA Guidance (US FDA, 2010) that the ESS could not exceed the observed sample size in the target population.

- The restriction was implemented to prevent the adult data from being too informative and dominate the limited pediatric data.

3-level Bayesian Hierarchical Model

	Placebo Median (95% CrI)	Cinacalcet Median (95% CrI)	Difference (Δ) Median (95% CrI)	Posterior Exceedance Probability			
				Δ > 0%	Δ > 10%	Δ > 20%	Δ > 30%
No extrapolation, fit 208 and 100 data only							
Overall Pediatric (28 days to < 18 years) response rates (%)	21.5 (2.1, 86.6)	80.8 (27.4, 98.2)	53.2 (-19.9, 90)	92.4	87.9	81.9	74.2
With extrapolation, fit adult and pediatric data together							
Pediatric patients 28 days to < 18 years response rates (%)[a]	17.5 (2.6, 62)	69.3 (36.1, 90.2)	48.6 (-2.3, 79.7)	97.0	93.9	88.4	79.2
ESS /n_ped	21.0 / 21[b]	25.1 / 29[c]	-	-	-	-	-
Pediatric patients 28 days to < 6 years response rates (%)[d]	18.0 (1.2, 78.7)	93.1 (66.4, 99.5)	71.8 (10.7, 95.1)	99.0	97.6	95.5	92.5
ESS/n_100	-*	-0.6/7[e]	-	-	-	-	-

Observed Data and Posterior Estimates
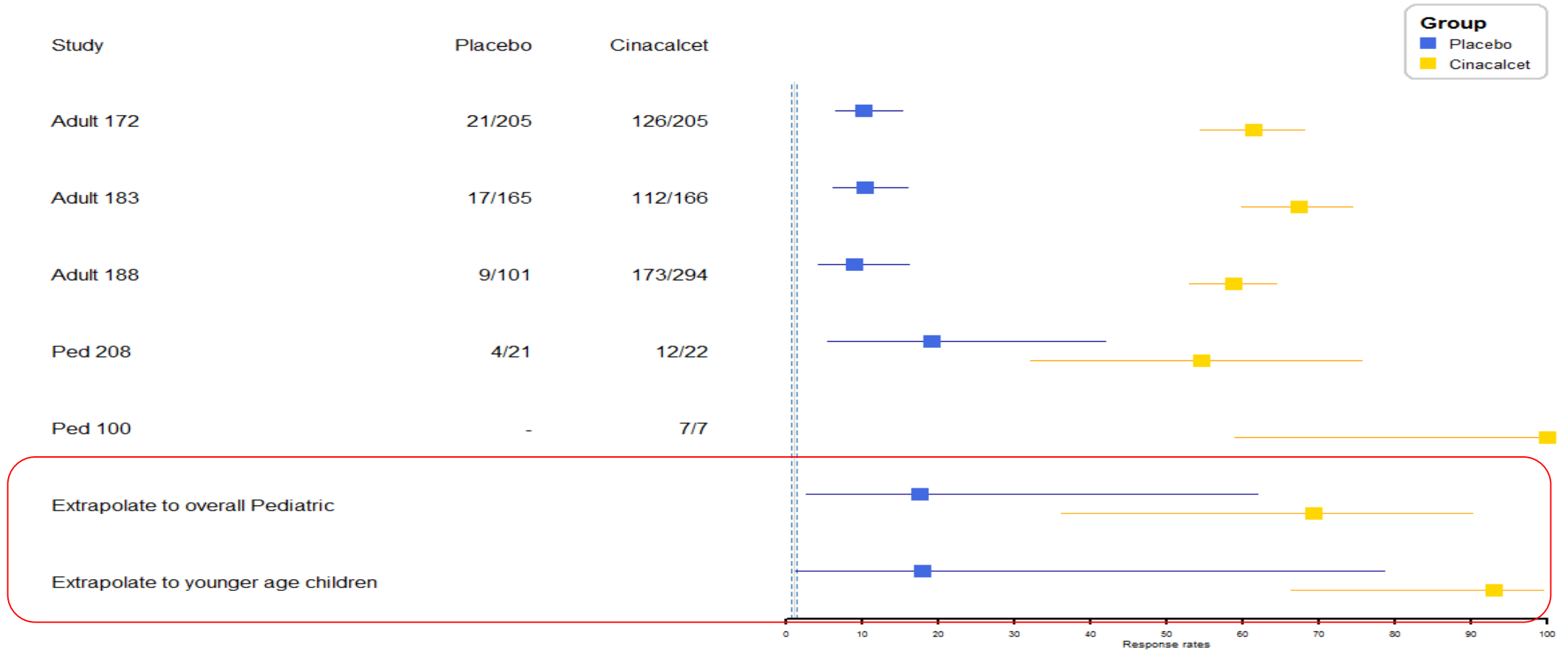
Summary

- **Partial or full extrapolation are supported by HA to reduce the need to run large pediatric trials given similarities in disease progression and response to intervention**
  - Justifications for extrapolation need to be carefully examined
  - Collaborative work with PK/PD and Clinical teams

- **Bayesian extrapolation has broad applications to help with sample size limitations and missing control arms in pediatric setting**
  - Extrapolation from one population to another population
  - Extrapolation from historical data to current studies

- **The usefulness of sensitivity analysis using different statistical methods**
  - Power parameter in the power prior method
  - Commensurate prior method

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