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
<table>
<thead>
<tr>
<th><strong>US Pediatric Development Laws: PREA vs BPCA</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediatric Research Equity Act (PREA)</strong></td>
</tr>
<tr>
<td>• Drugs and biologics</td>
</tr>
<tr>
<td>• Studies must be labeled</td>
</tr>
<tr>
<td>• Mandatory (required)</td>
</tr>
<tr>
<td>• No financial incentive</td>
</tr>
<tr>
<td>• For indication under review</td>
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<tr>
<td>• Orphan indication exempted</td>
</tr>
<tr>
<td><strong>Best Pharmaceuticals for Children Act (BPCA)</strong></td>
</tr>
<tr>
<td>• Drugs and biologics</td>
</tr>
<tr>
<td>• Studies must be labeled</td>
</tr>
<tr>
<td>• Voluntary (written request)</td>
</tr>
<tr>
<td>• Financial incentive</td>
</tr>
<tr>
<td>• May expand to other indications</td>
</tr>
<tr>
<td>• May be requested in orphan indication</td>
</tr>
</tbody>
</table>

* FDA Regulatory Education for Industry (REdI) Pediatric Drug Development: Regulatory Expectations, Alyson Karesh, M.D.– Fall 2015
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: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. December 2014.

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)

**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 there a PD measurement that can be used to predict efficacy in children?**
  - [ ] No
  - [ ] Yes

- **Is the drug (or active metabolite) concentration measurable and predictive of clinical response?**
  - [ ] No
  - [ ] Yes

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

- **“No extrapolation”**
- **“Partial extrapolation”**

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

- **Conduct:**
  1. Adequate dose-ranging study in children to select dose(s) that achieve the target PD effect.
  2. Safety trials 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.
Example 1: Stepwise extrapolation proposal in a PSP to satisfy PREA requirement

Different extrapolation strategies may be adopted
3-level Bayesian Hierarchical Model

Level 3 of the hierarchy
- Overall Patient Population
  - Adults
    - Study 1A
      - Subject $y_1, \ldots, y_{n_1}$
  - Adolescents (Age 12-17)
    - Study 1B
      - Subject $y_1, \ldots, y_{n_2}$
  - Children (Age 5-11)
    - Study 3
      - Subject $y_1, \ldots, y_{n_3}$
  - Children (Age 2-4)
    - Study 2 (PK/PD)
    - Study 4 (PK/PD)

Level 2 of the hierarchy
- Study level

Level 1 of the hierarchy
- Subject level

- Study 1A
- Study 1B
- Study 3
- Study 2 (PK/PD)
- Study 4 (PK/PD)

- Subject $y_1, \ldots, y_{n_1}$
- Subject $y_1, \ldots, y_{n_2}$
- Subject $y_1, \ldots, y_{n_3}$
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
Example 2: Cinacalcet Bayesian Extrapolation Analysis Under BPCA Written Request

- 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.

http://www.sensiparhcp.com/secondary-hpt-therapies/#
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
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
3-level Bayesian Hierarchical Model – Primary Method for US submission

Overall Patient Populations

- Adults
  - Level 2:
    - Study 20000172
    - Study 20000183
  - Level 1:
    - $y_1, \ldots, y_{n1}$
    - $y_1, \ldots, y_{n2}$

- Pediatrics
  - Level 2:
    - Study 20000188
    - Study 20070208 (Age 6-17)
  - Level 1:
    - $y_1, \ldots, y_{n3}$
    - $y_1, \ldots, y_{n4}$
  - Study 20110100 cohort 1 (Age < 6)

- $y_1, \ldots, y_{n5}$
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).
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 $\geq 30\%$ reduction from baseline in mean $i$PTH)
  - $p_{pkc}$ 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
    \[ Y_{pkc}|p_{pkc} \sim \text{Binomial}(n_{pkc}, p_{pkc}) \]

- **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

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

\( \beta_{pc} \) is the population effect,

\( \gamma_{pkc} \) is the study level random effect,

\( \gamma_{pkc} \sim N(0, \sigma_{pc}^2) \), where \( \sigma_{pc}^2 \) accounts for the between-study variation.
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:
    \[ \beta_{pc} = \beta_c + \mu_{pc} \]
  - \( \beta_c \) is the treatment effect such that \( \expit(\beta_c) \) 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.
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

<table>
<thead>
<tr>
<th></th>
<th>Placebo Median (95% Crl)</th>
<th>Cinacalcet Median (95% Crl)</th>
<th>Difference (Δ) Median (95% Crl)</th>
<th>Δ &gt; 0%</th>
<th>Δ &gt; 10%</th>
<th>Δ &gt; 20%</th>
<th>Δ &gt; 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Pediatric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(28 days to &lt; 18 years)</td>
<td>21.5 (2.1, 86.6)</td>
<td>80.8 (27.4, 98.2)</td>
<td>53.2 (-19.9, 90)</td>
<td>92.4</td>
<td>87.9</td>
<td>81.9</td>
<td>74.2</td>
</tr>
<tr>
<td><strong>Pediatric patients</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(28 days to &lt; 18 years)</td>
<td>17.5 (2.6, 62)</td>
<td>69.3 (36.1, 90.2)</td>
<td>48.6 (-2.3, 79.7)</td>
<td>97.0</td>
<td>93.9</td>
<td>88.4</td>
<td>79.2</td>
</tr>
<tr>
<td>ESS/n_ped</td>
<td>21.0 / 21b</td>
<td>25.1 / 29c</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
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<td><strong>Pediatric patients</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(28 days to &lt; 6 years)</td>
<td>18.0 (1.2, 78.7)</td>
<td>93.1 (66.4, 99.5)</td>
<td>71.8 (10.7, 95.1)</td>
<td>99.0</td>
<td>97.6</td>
<td>95.5</td>
<td>92.5</td>
</tr>
<tr>
<td>ESS/n_100</td>
<td>- *</td>
<td>-0.6/7e</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*No extrapolation, fit 208 and 100 data only

*With extrapolation, fit adult and pediatric data together

*a, b, c, d, e represent different sources or calculations.
Observed Data and Posterior Estimates

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>Cinacalcet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult 172</td>
<td>21/205</td>
<td>128/205</td>
</tr>
<tr>
<td>Adult 183</td>
<td>17/165</td>
<td>112/166</td>
</tr>
<tr>
<td>Adult 188</td>
<td>9/101</td>
<td>173/294</td>
</tr>
<tr>
<td>Ped 208</td>
<td>4/21</td>
<td>12/22</td>
</tr>
<tr>
<td>Ped 100</td>
<td>-</td>
<td>7/7</td>
</tr>
</tbody>
</table>

- Extrapolate to overall Pediatric
- Extrapolate to younger age children

**Group**
- Placebo
- Cinacalcet

AMGEN
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