Modeling and Simulation to Support Pediatric Clinical Trials

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Acknowledgements

• PKPD – Xin (Cindy) Zhang
• PBPK – Maria Posada
• QSP – Jason Chan
• Statistics – Meg Gamalo
• Medical – Robert Hoffman, A.J. Allen, Mary Short
Outline

• Motivation
• Example
• Conclusions
Should we all be treated the same?
Should we all be treated the same?

Not pharmaceutically!
Motivation

- See back-ups
- It takes too long for information on treating pediatric populations to be available (~9 years on average)
- Many potentially effective products in pediatrics have no label information (~half)
- Many pediatric studies fail to demonstrate efficacy (42%)
Why is it so hard?

- Smaller population
- More mandated pediatric clinical trials
- Vulnerable population
- Unwillingness to expose to placebo or ineffective doses
- Access to treatments via approved adult indications
Example

• NME
• Adult Phase 3 is complete
• Pediatric patients tend to have more severe disease
• There is a biomarker that correlates well with the disease severity
• This biomarker is along the pathway of drug mechanism
Background

- Drug X: oral
- Pharmacokinetics:
  - 30% by kidney
  - 70% by liver metabolism (CYP3A4)
- Pharmacodynamics:
  - Biomarker of target engagement measurable in plasma
  - Biomarker of disease severity measurable in plasma
- Pediatric studies in this population have suffered from poor enrollment
- Disease and exposure-response may differ between adults and pediatrics
  - These can be modeled
What we can do

Adult Results

![Bar chart showing response levels for Pbo, 50mg, and 100mg doses](chart.png)
What we can do

**Adult Results**

- Pbo
- 50mg
- 100mg

**Pediatric Prior**

9/8/2017
What we can do

Adult Results

Different disease progression
Different exposure-response

Pediatric Prior
What we can do

Adult Results

- Different disease progression
- Different exposure-response

Pediatric Prior

9/8/2017
What we can do

Adult Results

- Pbo
- 50mg
- 100mg

Different disease progression
Different exposure-response

Pediatric Prior

Adult PKPD

Pediatric PKPD???
What we can do

Adult Results

- Pbo
- 50mg
- 100mg

Adult PKPD

- Response vs Dose
- Concentration vs Dose

Pediatric Prior

- Different disease progression
- Different exposure-response

Pediatric PKPD???

Models!
What we can do

### Adult Results

<table>
<thead>
<tr>
<th></th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pbo</td>
<td><img src="image" alt="Pbo" /></td>
</tr>
<tr>
<td>50mg</td>
<td><img src="image" alt="50mg" /></td>
</tr>
<tr>
<td>100mg</td>
<td><img src="image" alt="100mg" /></td>
</tr>
</tbody>
</table>

* Different disease progression
  Different exposure-response

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### Adult PKPD

- **Response**
  - 0.30
  - 0.35
  - 0.40
  - 0.45
  - 0.50

- **Dose**
  - 0
  - 50
  - 100

- **Concentration**
  - 2809
  - 5618

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### Pediatric Prior

Simulate!

---

### Pediatric PKPD???

Models!
Pediatric Plan

• Use PBPK model to adjust for pediatric age-related renal and hepatic function differences
• Use QSP model to bridge pediatric exposure-response relationship from adult exposure-response relationship
• Simulate priors for Bayesian extrapolation from QSP model at doses yielding target exposures for pediatric patients
Physiologically-Based PK Modeling

Drug parameters:
- LogP, pKa, fraction unbound, B:P

Physiological parameters:
- Blood flows
- Organ weights and volumes
- Enzyme amounts
- Plasma protein concentrations
- Hematocrit
- Tissue compositions
- Lipids

Population parameters:
- Age, weight, gender, and enzyme phenotype.
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PBPK Model

- Model parameters can be interpreted physiologically

- Assumptions can be made about how parameters will change to predict PK in pediatric subjects
  - Renal clearance dependent on GFR
  - Hepatic CL dependent on CYP abundance and activity

**Kidney**

**Liver**

**GFR vs. Age**

**Enzyme Maturation Function**

\[
\begin{align*}
CL_{NR,3.44} &= \frac{CL_{NR,Adult} \times 0.76 \times Age^{0.83}}{0.31 \times Age^{0.83}} \\
CL_{NR,1.42} &= \frac{CL_{NR,Adult} \times 0.16 \times Age^{1.41}}{1.13 + Age^{1.41}} \\
CL_{NR,2C9} &= \left( CL_{NR,Adult} \times 0.06 \times \frac{0.79 \times Age}{0.01 + Age} + 0.21 \right)
\end{align*}
\]

Johnson et al. Clin Pharmacokinet 2006;45
Predicted PK Parameters

- CL/F
- Cmax
- AUC

Age groups: 2-6, 6-12, 12-18

9/8/2017
Predicted PK Profiles in Children Compared to Adult
Quantitative Systems Pharmacology

A mathematical representation of biology, including disease states, that incorporates various data types (preclinical, clinical, PK/PD) into a common dynamic framework and is used to understand the impact of perturbation via drugs or other interventions.
QSP model used to estimate effect of differences in pathophysiology

Patients can be stratified to adult and pediatric populations based on known differences in biology.
QSP model can be used to adjust pediatric dosing

QSP model integrates differences in PK and underlying physiology between adult and pediatric populations to estimate dose/response relationship in pediatric population.

<table>
<thead>
<tr>
<th>Dose</th>
<th>A</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK</td>
<td>Adult</td>
<td>Pediatric</td>
<td>Pediatric</td>
</tr>
<tr>
<td>Biomarker</td>
<td>Adult</td>
<td>Pediatric</td>
<td>Pediatric</td>
</tr>
</tbody>
</table>
Results of Modeling

**Adult Results**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Response</th>
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<tbody>
<tr>
<td>Pbo</td>
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</tr>
<tr>
<td>50mg</td>
<td></td>
</tr>
<tr>
<td>100mg</td>
<td>*</td>
</tr>
</tbody>
</table>

**Pediatric Target E-R**

**Adult PKPD**

Response vs. Dose

**Pediatric PKPD**

Response vs. Concentration
Simulated Pediatric Study

Ages 12-18
Pbo
Low Dose
High Dose

Ages 6-12

Ages 2-6

Response

0.0 0.2 0.4 0.6

50mg
100mg

35mg
70mg

17mg
35mg
Bayesian Sample Size

• Borrow information from other data sources (e.g. adult studies) – “prior”
• Can lead to more efficient study
• Depends on consistency between prior and new data
• Amount of borrowing should be based on biology and pharmacology - not just how similar the data looks
Bayesian Approach

Prior = $\epsilon \cdot \text{(Informative Prior)} + (1-\epsilon) \cdot \text{(Non-informative Prior)}$

- Use the prior data
- Let new data speak for itself
Bayesian Approach

Prior = $\epsilon \cdot \text{(Informative Prior)} + (1-\epsilon) \cdot \text{(Non-informative Prior)}$

- Use the prior data
- Let new data speak for itself

Weights

9/8/2017
Bayesian Approach

Prior = $\epsilon*(\text{Informative Prior}) + (1-\epsilon)\text{*(Non-informative Prior)}$

- Use the prior data
- Let new data speak for itself

Weights

- Could be Adult Data
- Here, we will use QSP Simulated Pediatric Data
Bayesian Approach

Prior = \( \epsilon \) * (Informative Prior) + (1-\( \epsilon \)) * (Non-informative Prior)

- Could be Adult Data
- Here, we will use QSP Simulated Pediatric Data

Use the prior data

Let new data speak for itself

Posterior Probability of Pediatric Response

Group
- Dose 1
- Dose 2

prior
- Non-informative
- Informative
Use of “Prior” QSP Model results in a more efficient study
Gives feasible options for study designs
Conclusions

• Due to ethical, feasibility, and scientific challenges, extrapolation is often necessary to guide pediatric treatments

• Even when disease progression or exposure-response are expected to differ between adults and pediatrics, modeling and simulation can be used to bridge data gaps

• Efficient clinical studies should be run when possible to confirm models
Thank you!
Back-ups
### Time Lapse: Adult NDA Date to First Ped Label

#### Average Time Lapse (in years)

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<tbody>
<tr>
<td>2001 &amp; Earlier</td>
<td>7.03</td>
<td>9.84</td>
<td>7.06</td>
<td>9.68</td>
</tr>
<tr>
<td>N=17</td>
<td>N=35</td>
<td>N=34</td>
<td>N=28</td>
<td></td>
</tr>
</tbody>
</table>

*Source: Simpkins, P.L., 2017. Analysis was completed using data from Evaluate Pharma, [Drugs@FDA.gov](https://Drugs@FDA.gov) (label) and FDA New Pediatric Labeling Information Database (pediatric label changes). Accessed February 2017. Sample size N = 114 pediatric labels. Rx products only (excludes OTC products).*

- On average, it takes 9 years from the time of a product’s approval for use in adults until the label is updated to include pediatric data.
- Off-label use occurs during this time period.
Pediatric Information

Pediatric RCTs, 2008-2010, ClinicalTrials.gov

- Completed, 81%
- Discontinued, 19%
- Other, 63%
- Patient Accrual, 37%

1 Pica N. and Bourgeois F., Discontinuation and Nonpublication of Randomized Clinical Trials Conducted in Children, Pediatrics, on-line, Aug. 4, 2016

Physicians Desk Reference

- 1975
  - No Ped Info, 78%
  - Ped Info, 22%
- 2009
  - No Ped Info, 44%
  - Ped Info, 56%

2 FDA OPT and Pediatric and Maternal Health Staff, More drug labels include pediatric information, but work remains, AAP News 2012;33;12
Pediatric Labeling

US NMEs, 2002-2008

- No Potential Ped Use, 26%
- Potential Ped Use, 74%
- No Pediatric Labeling, 59%
- Pediatric Labeling, 41%

Written Requests, 1998-2012

- Efficacy Not Demonstrated, 42%
- Efficacy Demonstrated, 58%

1FDA OPT and Pediatric and Maternal Health Staff, More drug labels include pediatric information, but work remains, AAP News 2012;33;12
2Wharton G. et al., Impact of Pediatric Exclusivity on Drug Labeling and Demonstrations of Efficacy, Pediatrics, 2014;134;e512