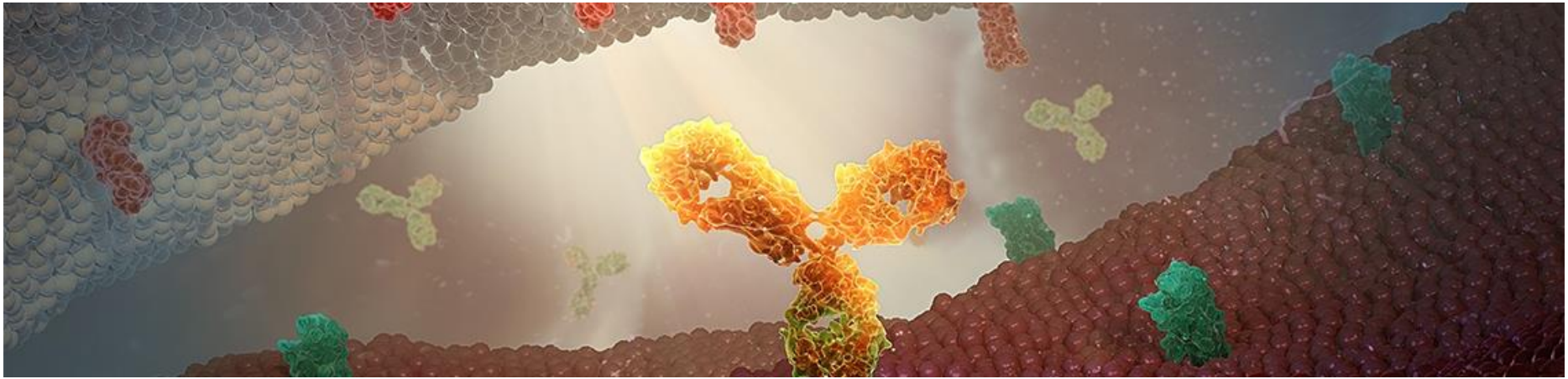
An Industry Perspective on Utilizing MIDD for Pediatric Studies Requiring Integration on Ontogeny

Solange Corriol-Rohou, M.D.

FDA/MCERSI WORKSHOP
Pediatric Ontogeny: Ready for incorporation into Modeling in Pediatric Development? 16 May 2019



Agenda

1. Pediatric development: the regulatory framework
2. ICH and pediatric drug development
3. Ontogeny and pediatric drug development
4. Utilizing MIDD for Pediatric Studies Requiring Integration on Ontogeny – some examples

A Brief History of Pediatric Drug Development

1977 — AAP Committee on Drugs publishes statement calling for drugs to be tested in children if used in children

1979 — FDA issues first pediatric labeling requirement

Dec,1994 — Final rule: Revisions to Pediatric labeling; Extrapolation concept first described

1997 — FDAMA: first incentive provisions

Dec1998 — Pediatric Rule: first requirements for pediatric studies

2000 — ICH E11 published

Jan 2002 — BPCA signed into law

Oct 17, 2002 — Pediatric Rule struck down

Dec, 2003 — PREA signed into law

Jan 2007 — **Pediatric Regulation enacted in EU**

Sept 2007 — FDAAA reauthorizes BPCA and PREA; PeRC created; Pediatric cluster initiated

July 2012 — FDASIA permanently reauthorizes BPCA & PREA

EC 5 Year Report 2013

2014 — ICH E11 Addendum EWG established

Sept. 2017 — ICH E11(R1) Addendum finalised

Oct. 2017 — **EC 10 Year Report**

Mid. Aug. 2020 — RACE for Children ACT

End 2020 — ICH E11A1 Step 2

As of 2020, end of the exemption for cancer drugs with orphan designations if the molecular target of the drug is relevant

Ref: Modified from L. Yao, FDA

ICH and pediatric drug development

- **ICH S11** – Nonclinical Safety testing in support of development of Paediatric Medicines – Step 4: Nov. 2019

- **Potential future topic:** MIDD (Model Informed Drug Development)

ICH E11A – Paediatric Extrapolation

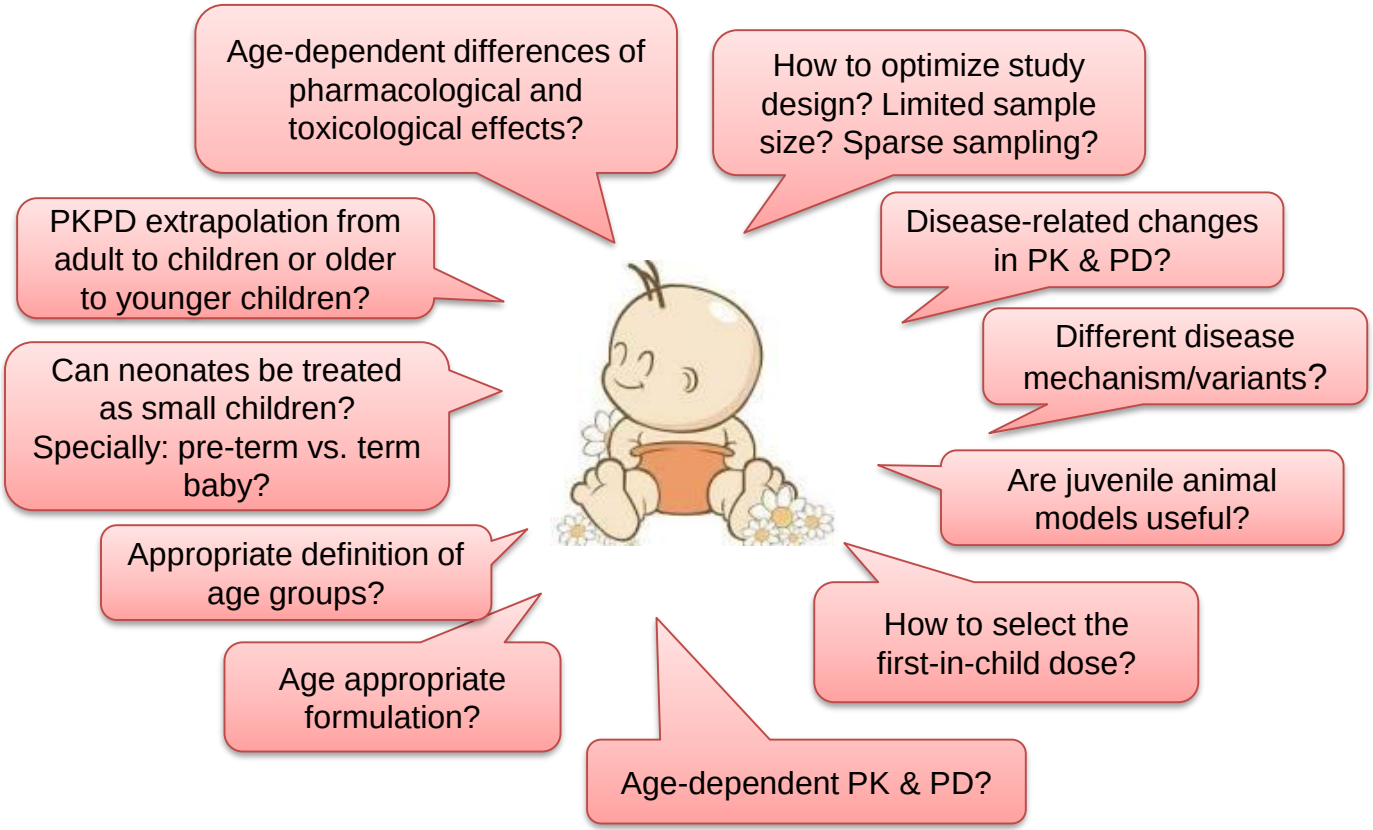
- **Disease similarity & similarity of response to therapy**
  - Prior knowledge?
  - Factors to consider? … maturation of the target

- **Biostatistics**
  - Dose findings
  - Interpretation of source data in the context of design
  - Choice of endpoint
  - Analysis
  - Interpretation
  - Reporting

- **M&S**
  - Decision tool – similar disease progression, response to intervention, D-E-R, PD measurement to predict efficacy?
  - Use of prior information
  - Study optimisation
  - Data analysis & interpretation
  - Documentation and Reporting

Challenges in pediatric drug development:

- potential factors in trial success/failure



Challenges in pediatric drug development:
- when considering Extrapolation – ICHE11(R1)

1. What evidence supports a common pathophysiology of disease, natural history, and similarity of the disease course between the reference and pediatric population(s)?

2. What is the strength of the evidence of efficacy in the reference populations?

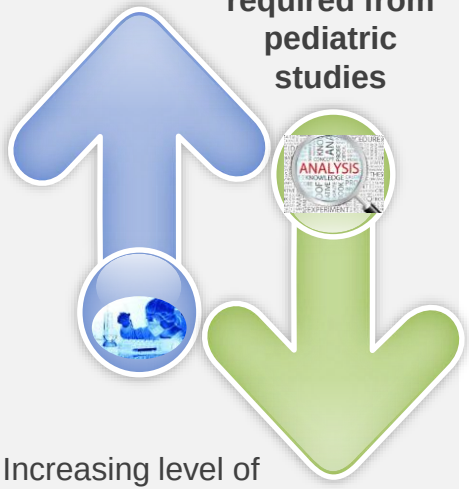
3. Is there a biomarker or surrogate endpoint in the reference populations that is relevant in the pediatric population (s)?

5. What uncertainties and/or limitations do the existing data (e.g., clinical or historical data and published literature) have, and what uncertainties about the pediatric population remain?

6. If uncertainties remain, what additional information should be generated (e.g., information from M&S, animal, adult, pediatric subgroup studies) in order to inform the acceptability of the extrapolation approach?

4. What evidence supports a similar exposure-response between the reference and intended populations?

Extrapolation approaches in pediatric programs



~60% Pediatric Programs
require at least 1 adequate, well-controlled efficacy trial (clinical or surrogate endpoint) – 1998-2009

Extrapolation approach	Disease area examples where such approach was successful
1 or more adequate-well controlled studies powered on a clinically meaningful endpoint	Bipolar disorder, systemic juvenile idiopathic arthritis, major depression, migraine, poly-articular JIA, bronchopulmonary dysplasia, ADHD, nausea/vomiting, partial onset seizures respiratory syncytial virus, prophylaxis of venous thromboembolism, atopic dermatitis, etc.
1 or more adequate-well controlled studies powered on a surrogate endpoint	Diabetes, anemia, idiopathic thrombocytopenia, treatment of venous thromboembolism, hypertension, hypercholesterolemia, asthma, etc.
Controlled study without formal statistical power	Community acquired pneumonia, nosocomial infections, skin and skin structure infections, etc.
Descriptive efficacy study without concurrent control	Plaque psoriasis, Neurogenic detrusor over-activity, pJIA (NSAIDs), etc
Small dose-ranging studies (randomization to multiple dose levels)	Sedation, ulcerative colitis, Crohn's, etc.
Small PK/PD studies (single dose level matching adult exposures)	HIV, erosive esophagitis (infants), anesthetics, pulmonary arterial hypertension
PK /safety only (single dose level matching adult exposures)	gastroesophageal reflux disease, bacterial sinusitis, herpes simplex, analgesics/anesthetics (well known MOAs; over 2 y/o), imaging products, melanoma (adolescents)

From Dr L. Yao - List partially adapted from Dunne et al. *Pediatrics* 2011

With scientific knowledge gained

- 2011 FDA pediatric extrapolation publication with new pediatric labeling between January 1998 and February 2009*
- 2017 FDA analysis of products with new pediatric labeling between January 2009 and December 2014**
- **Possible reasons for pattern shifting**
  - Failures when a single adequate and well-controlled trial was thought to be sufficient
  - Inability to identify an exposure-response relationship in the overall pediatric population or in an age subgroup

Extrapolation Category	Current Data Numbers of Products (%)	Dunne's Reference Numbers of Products (%)
Complete	53 (34)	24 (14)
Partial	46 (29)	113 (68)
No	58 (37)	29 (18)

Dunne et al. Pediatrics 2011
**Sun et al. TIRS 2017*

FDA Commissioner: "Cures Act provides FDA with tools aimed at modernizing our regulatory programs"

FDA identified MIDD as an important pathway for lowering drug attrition and dealing with regulatory uncertainty

How FDA Plans to Help Consumers Capitalize on Advances in Science

Posted on July 7, 2017 by FDA Voice

By: Scott Gottlieb, M.D.

We're at a point in science where new medical technologies hold out the promise of better treatments for a widening number of vexing conditions. Over the last few decades, science has enabled fundamental advances in our understanding of the genetic and protein bases of human disease. These developments are already being translated into new medicines. In more cases, these treatments target the underlying mechanisms that drive different diseases. These advances hold out the promise of arresting and even curing a growing number of diseases.

To build upon such opportunities, FDA will soon unveil a comprehensive Innovation Initiative. It will be aimed at making sure our regulatory processes are modern and efficient, so that safe and effective new technologies can reach patients in a timely fashion. We need to make sure that our regulatory principles are efficient and informed by the most up to date science. We don't want to present regulatory barriers to beneficial new medical innovations that add to the time, cost, and uncertainty of bringing these technologies forward if they don't add to our understanding of the product's safety and benefits.

"I want to highlight one example of these steps, which we're investing in, and will be expanding on, as part of our broader Innovation Initiative. ***It's the use of in silico tools in clinical trials for improving drug development and making regulation more efficient.***

FDA's Center for Drug Evaluation and Research (CDER) is ***currently using modeling and simulation*** *to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms."*

Some definitions

- **Ontogeny:** the development, or course of development, of an individual organism

- **MID3:** quantitative framework for prediction and extrapolation, centered on knowledge and inference generated from integrated models of compound, mechanism and disease level data and aimed at improving the quality, efficiency and cost effectiveness of decision making
  (EFPIA MID3 WG; CPT PSP 2016)

- **MIDD:** refers to the application of a wide range of quantitative models in drug development to facilitate the decision making process
  (Wang et al. CPT PSP 2019)

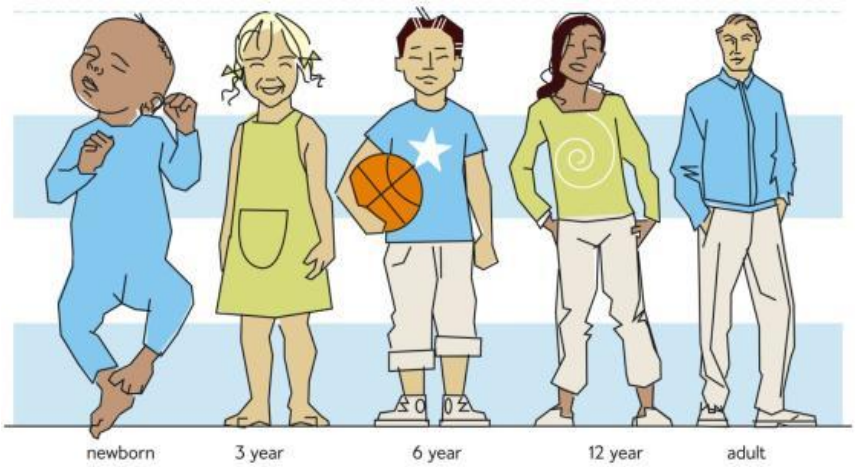
Dose selection is key in pediatric development

Huge diversity in the pediatric population: understanding appropriate scaling methods is crucial

Premature neonates to less than 18:

- Different needs with regard to formulations
- Differences in opportunities for PK/PD samplings
- Differences in availabilities for inclusion, exclusion criteria in studies
- Differences in size
- Differences in status of maturation
- Differences in relevance of clinical efficacy and safety endpoints
- Differences in disease progression due to age

Extrapolating the Dose from Adults to Children: Which knowledge can pediatric PK predictions be based on?



- Growth and maturation, can be described using models incorporating size (typically weight) and maturation (typically age) assuming linear approximation

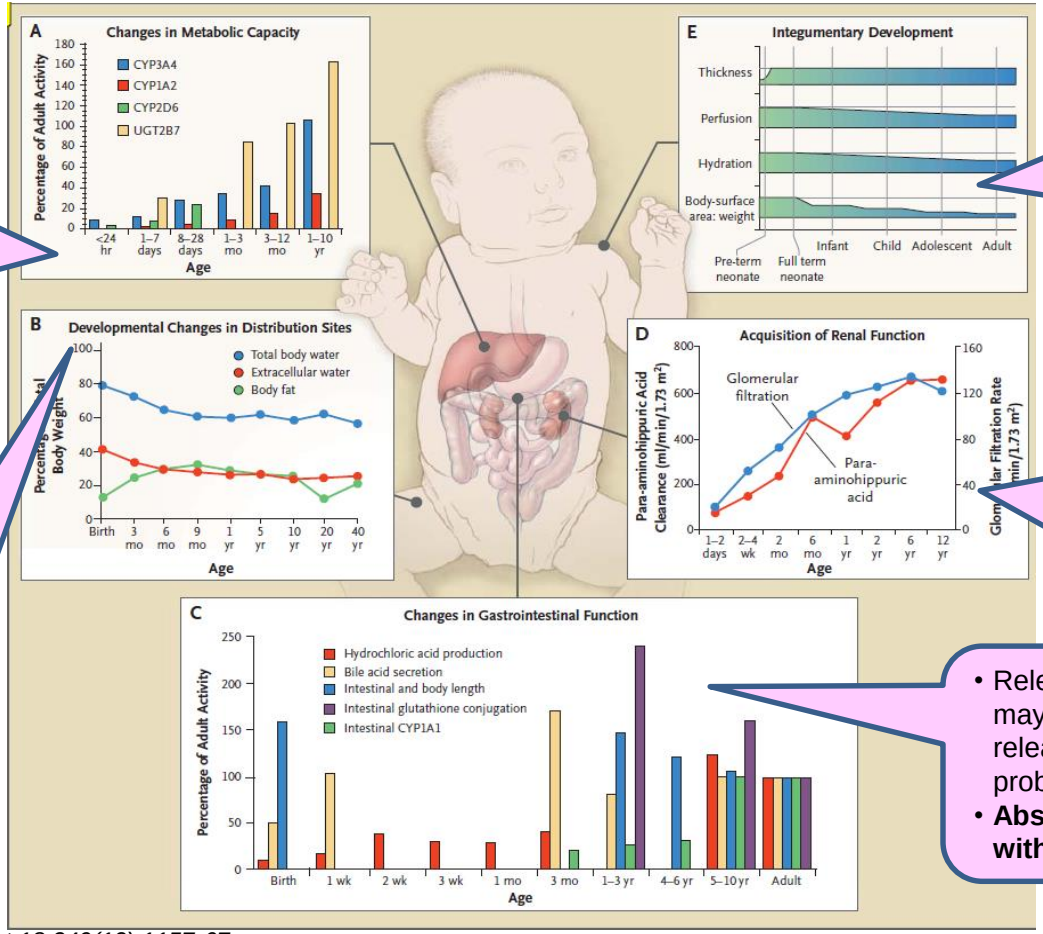
- Is it reasonable to expect linearity in
  - Liver size, kidney function, body fat ...
  - ... ADME ....
  - ... PK?

  No… they follow non-linear processes, and we need to account for system specific parameters

Overview of Developmental Changes of ADME

Determining appropriate dosing regimes is complex owing to the physiological and anatomical changes that occur during childhood

- **Drug-metabolising enzymes show age-dependent changes** in activity
- **Time of maturation** is enzyme-specific



Higher percutaneous absorption; higher BSA/WT and thus mg/kg dose

Body composition depends on age – so does drug distribution: Low plasma protein concentrations and a higher body water composition
Absorption can be affected by differences in gastric pH and stomach emptying time

Renal excretion is reduced in neonates due to immature GFR, tubular secretion and reabsorption
GFR approx. 90% of adult value at age of 1 year

- Release from **formulation** may be modified (extended release and enteric coating problematic)
- **Absorption will change with age**

Kearns et al., N Engl J Med. 2003 Sept.18;349(12):1157-67

Approaches to age-related dosing regimens

Optimising study design to collect the right information

- Clinical studies with innovative approaches that reduce the burden on paediatric patients are preferred
  - Small number of patients, ethically acceptable
  - Sequential design, Bayesian approach, adaptive or withdrawal design

- Age-appropriate formulation
  - Should be ideally bioequivalent to adult formulation

- Blood sampling
  - Blood loss should not exceed 39% of the total blood volume during a period of 4 weeks, and 1% at any single time
  - In a new-born (estimated total blood volume: 80-90ml/kg^{-1} body weight)
    - 1%-> 3ml, and 9ml over a period of 4 weeks
  - Alternative options, e.g., dried blood spots to avoid venepuncture

PD process considerations - some examples

- Limited information about how human growth and development and their intersection with disease impact PD

- Clinically, there are some well described examples of age-dependent differences in PD:
  - Higher incidence of valproic acid–associated hepatotoxicity in young infants,
  - Greater frequency of paradoxical CNS reactions to diphenhydramine in infants,
  - Higher incidence of weight gain with the use of atypical antipsychotic agents in adolescents,
  - Altered concentration vs. effect profiles for warfarin in children with congenital heart disease

- Neurodevelopmental animal models have revealed temporal differences in the maturation of neurotransmitters (e.g. norepinephrine, serotonin) and receptors (e.g. GABA receptors)
  - Paradoxical seizures experienced by infants after exposure to benzodiazepines
  - Increased sensitivity of neonates to morphine – increased postnatal expression of the μ-opioid receptor

- Enhanced sensitivity to drug response associated with development
  - Altered concentration vs. effect profile for CsA in young infants
  - Higher sensitivity towards QTc prolongation in neonates as compared to older children

Van den Ancker et al. Journal of Clinical Pharmacology 2018

PD process considerations - some examples

- How to measure drug effect?

- Indirect assessment of developmental changes in PD by functional biomarkers with desired characteristics, used to
  - describe disease progression or response – exhaled nitric oxide for asthma
  - predict systemic drug exposure or effect – CYP2D6 for codeine response
  - describe PD - esophageal pH monitoring for gastroesophageal reflux

- Infrared pupillometry to assess the PD of opiate analgesics – predictive association between mean pupillary constriction velocity and opiate dose in children aged 8-17 for pain control

Van den Ancker et al. Journal of Clinical Pharmacology 2018

Approaches to age-related dosing regimens

- **Approaches**
  - Simple dosage formulas (normalised by body weight or Body Surface Area) and allometric scaling
  - Pop-PK approach with covariate analysis e.g. age, body weight, clearance
  - Pop-PKPD model if clinical response data are available
  - PBPK models developed to predict PK in children
    - Combine the development physiological processes of the child with adult PK data
    - Require drug-specific information (adult PK data) and system-specific information on the ontogeny of anatomical, physiological, and biochemical variables from birth to age 18
    - Use of prior knowledge is critical

- **For children below 2**
  - It is more complex due to the fast changes in physiology
  - Multiple approaches may be needed to optimize the age-related dose regimens

We need a general strategy

- To ensure use of all relevant available information

- To ensure appropriate use of available methodology

Adapted from Ine Skottheim-Rusten – EMA/EFPIA D-E-R Workshop 2014

Collect & synthetize prior information

Define D-E-R in animals, adults, children

Predictions for the selected pediatric age subsets

Study design optimization

Collect and systemize drug and system data
- *In vitro* drug data
- Non clinical drug data
- Adult drug data
- Paediatric drug data
- Adult and paediatric drug data on similar (model) substances, indications etc
- Adult and paediatric system data (such as relevant physiological, pathophysiological and PK and PD

Define D-E-R and estimate relevant parameters and variability based on available data
- PK parameters and variability
- PD parameters and variability
- Efficacy and safety parameters and variability
- Establish covariate relationships
- Qualify the models for the existing data at the key interim and final stages

Scale available predictions to the relevant pediatric population
- Address major assumptions and potential impact of violating assumptions
- Uncertainty quantification such as sensitivity analysis of the important/main parameters (worst/best case scenarios)
- Evaluate if there are assumptions that mandate a conservative approach (titration from lower doses etc.) or if there are opportunities for interpolation or partial extrapolation

Determine type of study(ies) needed
- Separate PK study, separate PK/PD study, micro-dosing study, confirmation of PK/PD within an E&S study in an adaptive manner etc
- Determine the need for several doses in order to further inform on the D-E-R relationship also in paediatric patients
- Optimization of number of patients and sampling scheme for the PK and PD parameters

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Potential methods:
- Population PK/PD/response /safety models
- PBPK/PBPD
- system pharmacology models
- Bayesian methods

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- Allometric scaling
- Organ function
- Maturation function
- Covariate structure

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Potential methods:
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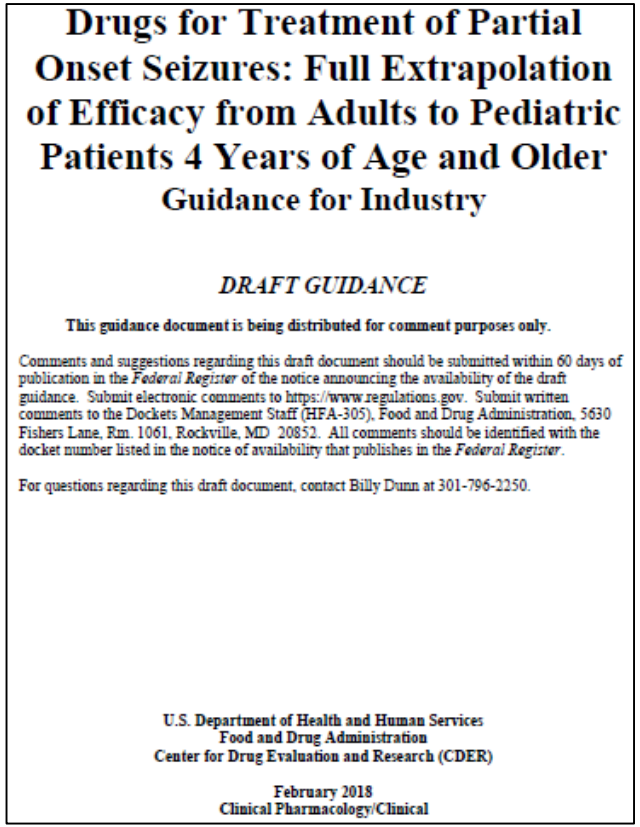
Learn & confirm paradigm - updating and refining the models with new information

Some examples

Partial Onset Seizures – Pediatric Extrapolation



Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 4 Years of Age and Older

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Billy Dunn at 301-796-2250.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2018
Clinical Pharmacology/Clinical

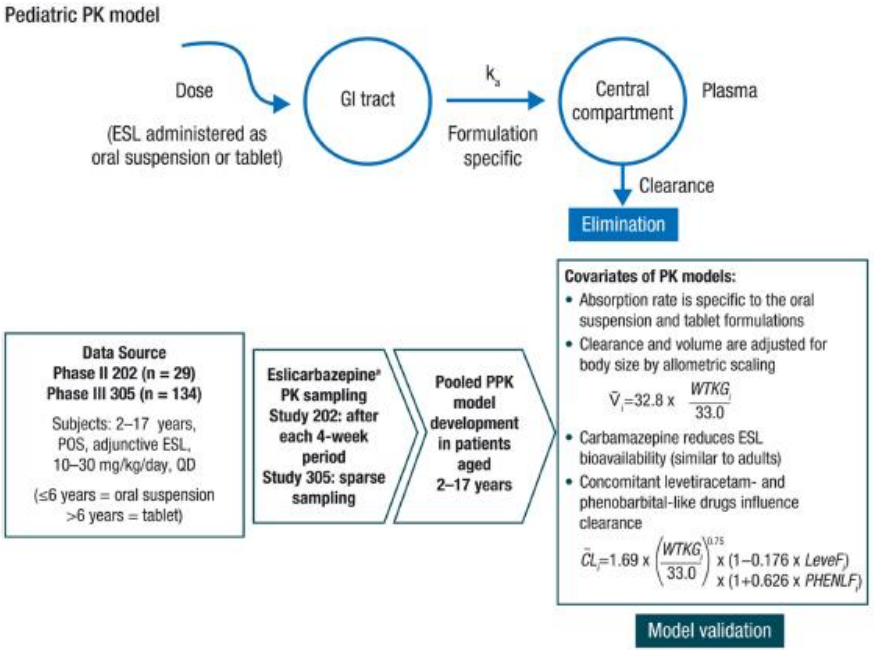
As a result of the PEACE Consortium work

Pellock et al. Epilepsia 2017

- **An approved indication for the treatment of POS in adults**
- **A PK analysis to allow selection of dosing regimens for pediatrics aged 4-17 years that provide drug exposure similar to that known to be effective in adults**
- **An open label 6 month safety study; 100 children with POS**

Also acceptable in the EU

M&S to support dose selection for eslicarbazepine acetate (ESL) therapy in pediatric patients with POS



A Pediatric Model was developed using Nonmen & KIWI:

- Exploratory analysis of existing data
- Application/refinement of the one compartment model previously developed in adults
- Evaluation of covariates on clearance and distribution volume - age; eGFR; height; race and sex

Evaluation of the final model ➔ concomitant use

- with carbamazepine or phenobarbital-like AEDs would decrease the exposure of ESL
- with levetiracetam would increase the exposure of ESL

Sunkaraneni et al. Journal of Pharmacokinetics and Pharmacodynamics. 2018

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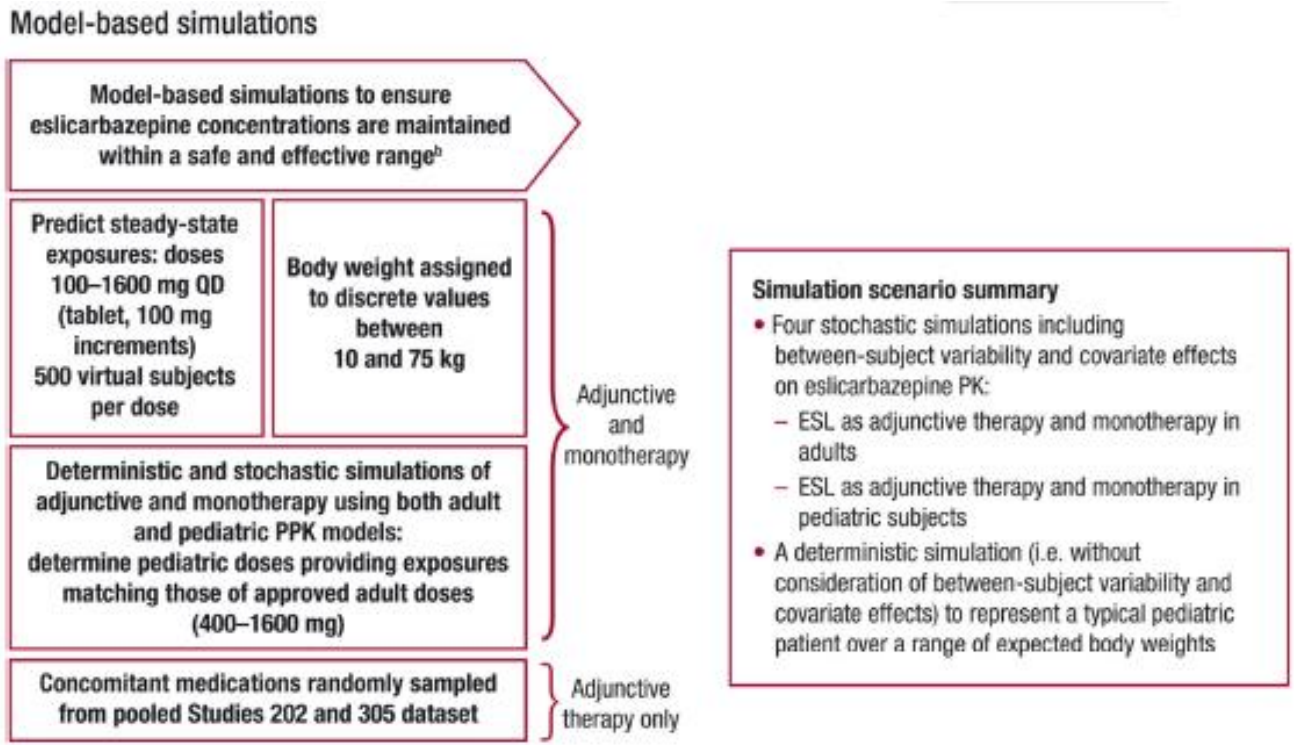


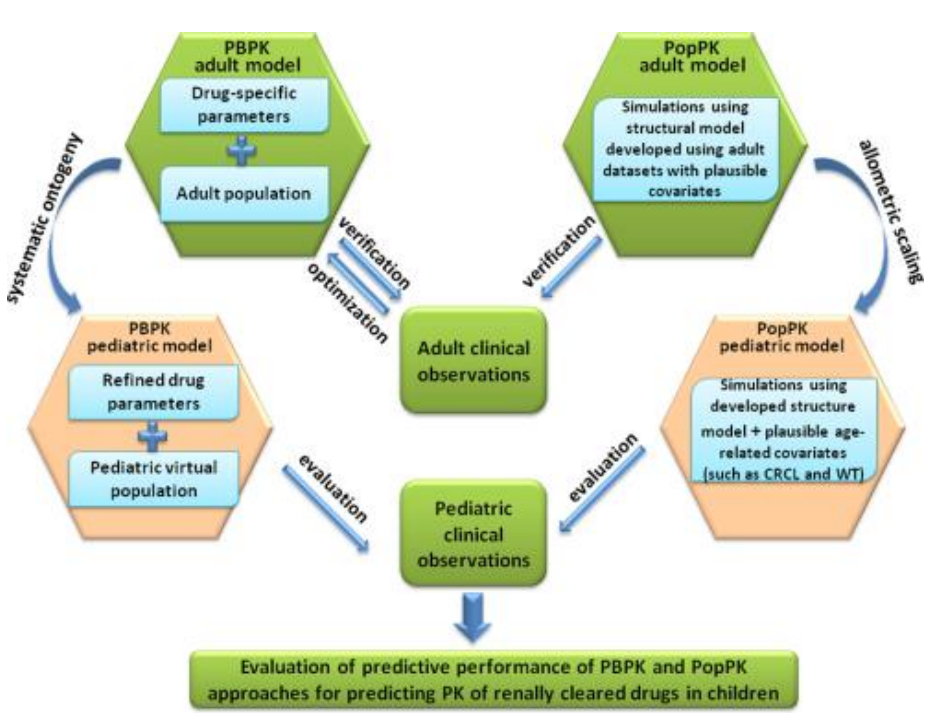
Model based simulation were performed to apply target exposure matching of selected ESL doses for pediatric subjects to attain ESL exposures associated with effective and well-tolerated ESL doses in adults

➔ ESL dose selection to be used in children above 4 – mono & adjunctive therapy

➔ Without the need for a specific clinical trial

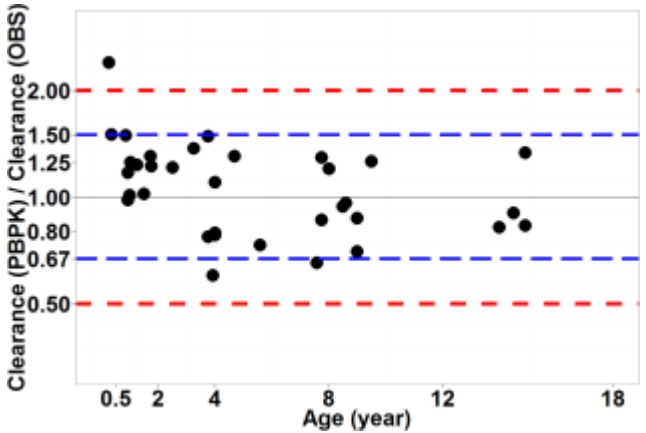
Sunkaraneni et al. Journal of Pharmacokinetics and Pharmacodynamics. 2018

Predictive Performance of PBPK and Pop-PK Modeling of Renally Cleared Drugs in Children



Workflow of the development of PBPK and Pop-PK models and prediction of PK in pediatrics for (34) drugs eliminated by the kidneys

PBPK and Pop-PK adult models (developed in Simcyp and Nonmem), after verification with additional adult PK studies and incorporation of known ontogeny of renal filtration, can reasonably predict exposure of renally eliminated drugs in children 1 month and older



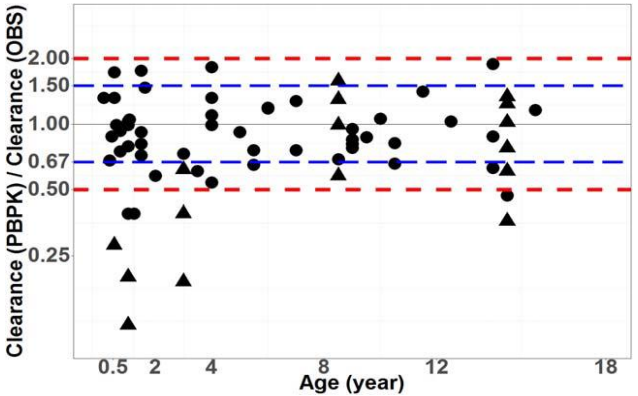
OVERALL PREDICTIVITY of PBPK MODELS: Filled circles represent mean ratios of PBPK predicted clearance over observed clearance of all drugs in children 1 month to 18 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and twofold error.

Zhou et al. CPT PSP 2016; 5:475-83

Predictive Performance of PBPK Modeling of Drugs Extensively Metabolized by Major Cytochrome P450s in Children

- PBPK modeling is a useful tool for extrapolation of PK profiles in children with only adult clinical trial results and is exceptionally valuable to guide selection of doses in first-in-pediatric studies
- A total of 67 clinical studies from 10 CYP-metabolized drugs were available across all pediatric age groups (1 month to <18 years)
- Predictive performance of PBPK modeling approach was evaluated using 10 drugs extensively metabolized by major CYP enzymes - desloratadine, diclofenac, itraconazole, lansoprazole, montelukast, ondansetron, sufentanil, theophylline and tramadol

PBPK models can reasonably predict exposure in children 1 month and older for an array of predominantly CYP metabolized drugs. The default ontogeny functions within Simcyp should be applied for all CYP enzymes except for CYP2C8, where the function proposed by Upreti and Wahlstrom should be used



OVERALL PREDICTIVITY of PBPK MODELS: Filled circles represent mean ratios of PBPK predicted clearance over observed clearance of all drugs (except esomeprazole, presented as filled triangles) in children 1 month to 18 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and 2-fold error.

Zhou et al. CPT PSP 2017

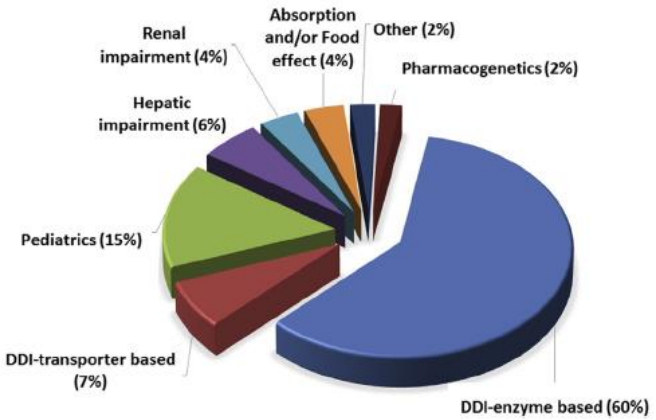
PBPK model applications in drug development

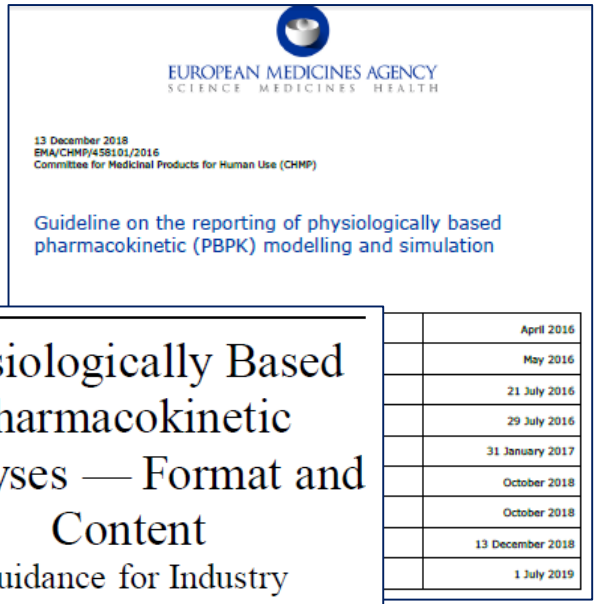
Increased regulatory acceptance over the years

Number of NDA Submissions Per Year Containing PBPK Analyses and Respective Areas of Application, in the Period of 2008 to 2017

Area of Application	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Total Submissions	1	3	1	5	5	11	13	11	17	27	94
DDI total	1	3	0	3	3	7	9	5	15	26	72
DDI-enzyme based	1	3	0	2	3	5	9	5	12	11	52
DDI-P-gp transporter	0	0	0	1	0	1	0	0	1	9	12
DDI-transporter based	0	0	0	0	0	1	0	0	2	6	8
Specific populations											
Pediatrics	0	0	0	2	1	2	1	1	2	3	12
Hepatic impairment	0	0	1	0	0	1	2	1	1	2	8
Renal impairment	0	0	0	0	0	0	0	1	2	1	4
Oral absorption	0	0	0	0	1	3	1	2	1	0	8
Biologics	0	0	0	0	0	0	1	0	0	1	2
Others	0	0	0	0	0	1	0	1	1	1	4
Total intended applications[a]	–	–	–	–	–	–	–	–	–	–	110

[a] The total number of intended PBPK applications exceeds the number of NDA submissions containing PBPK analyses as each submission might contain more than 1 area of application.

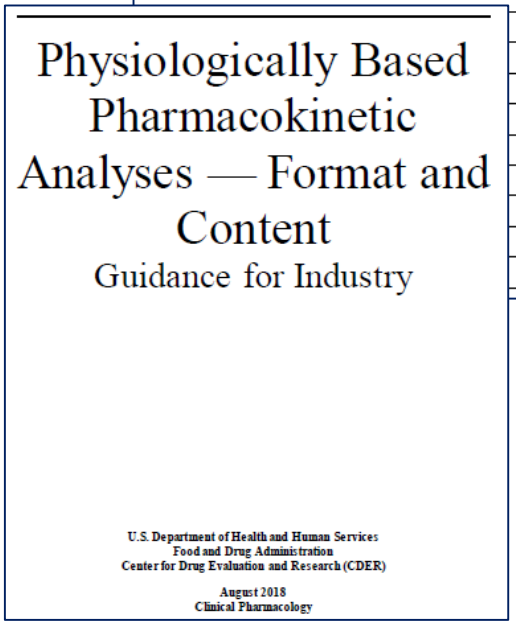



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

	April 2016
	May 2016
	21 July 2016
	29 July 2016
	31 January 2017
	October 2018
	October 2018
	13 December 2018
	1 July 2019


Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2018
Clinical Pharmacology

Grimstein et al. J Pharm Sci 2019

In summary

- Progress has been made in pediatric drug development
- The dosing regimen for adults cannot be simply or linearly extrapolated to children, particularly in neonates and infants
- Effects of ontogeny such as maturation of the GI, hepatic and renal systems, or potential quantitative changes in the contribution of the various elimination pathways with involved enzymes and transporters or receptor system sensitivity in pediatric age subsets, should be addressed
- PBPK is a powerful tool to propose starting dose for pediatric clinical trials
- The ICH E11A Expert Work Group expects to deliver a useful guideline

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