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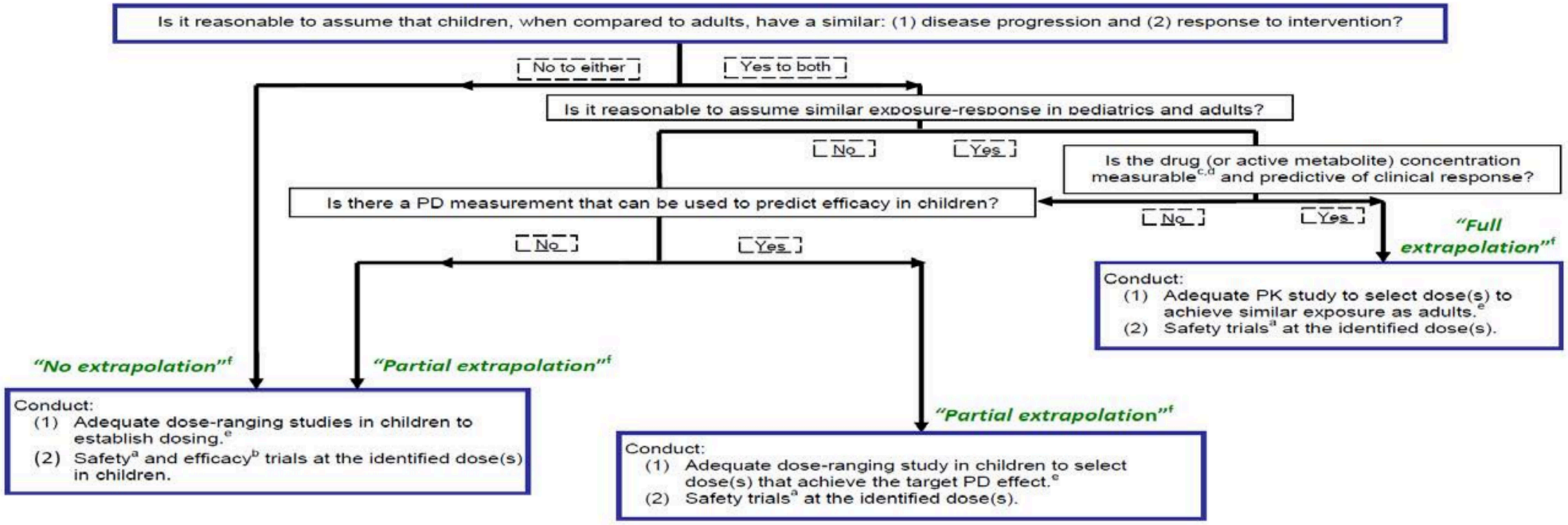
Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

The Confusion

Study design vs. Pediatric Study Waiver

Definitions

- **Allometric Models**
  - Correlation of body-size with key PK parameters using an exponent.
- **Maturation Models**
  - Correlation of age-metric with key PK parameters.
- **PBPK**
  - Whole-body physiologically based models.

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ELSEVIER

International Journal of Antimicrobial Agents 30 (2007) 320–324

INTERNATIONAL JOURNAL OF
Antimicrobial
Agents

www.ischemo.org

Optimising piperacillin/tazobactam dosing in paediatrics

Christoffer W. Tornøe [a,*], Jeffrey J. Tworzyanski [a], Menfo A. Imoisili [b], John J. Alexander [b], Joan M. Korth-Bradley [c], Jogarao V.S. Gobburu [a]

[a] *Office of Clinical Pharmacology, Center for Drug Evaluation and Research, FDA, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA*
[b] *Office of New Drugs, Center for Drug Evaluation and Research, FDA, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA*
[c] *Early Development and Clinical Pharmacology, Wyeth Research, Collegeville, PA 19426, USA*

Data summary

Table 1
Tested piperacillin clearance (CL) covariate models

Model description	Parameter	Estimate (SE)	Interindividual variability (CV)	Residual sum of squares
1. $CL = \alpha \cdot \exp(\eta)$	α	61.1 (7.81) mL/min	94.0%	46.9
2. $CL = \alpha \cdot WT \cdot \exp(\eta)$	α	4.77 (0.25) mL/min/kg	38.1%	7.69
3. $CL = \alpha \cdot WT^{\beta} \cdot \exp(\eta)$	α β	2.67 (0.48) mL/min/kg 1.23 (0.07)	34.9%	6.34
4. $CL = \alpha \cdot WT \cdot \frac{Age}{Age+A_{50}} \cdot \exp(\eta)$	α A_{50}	5.64 (0.34) mL/min/kg 0.18 (0.05) years	32.4%	5.47

SE, standard error; CV, coefficient of variation; α and β, slope and exponent of the CL–covariate relationship, respectively; η, interindividual random-effects parameter; WT, body weight; A_{50}, age required for 50% maturation of clearance.

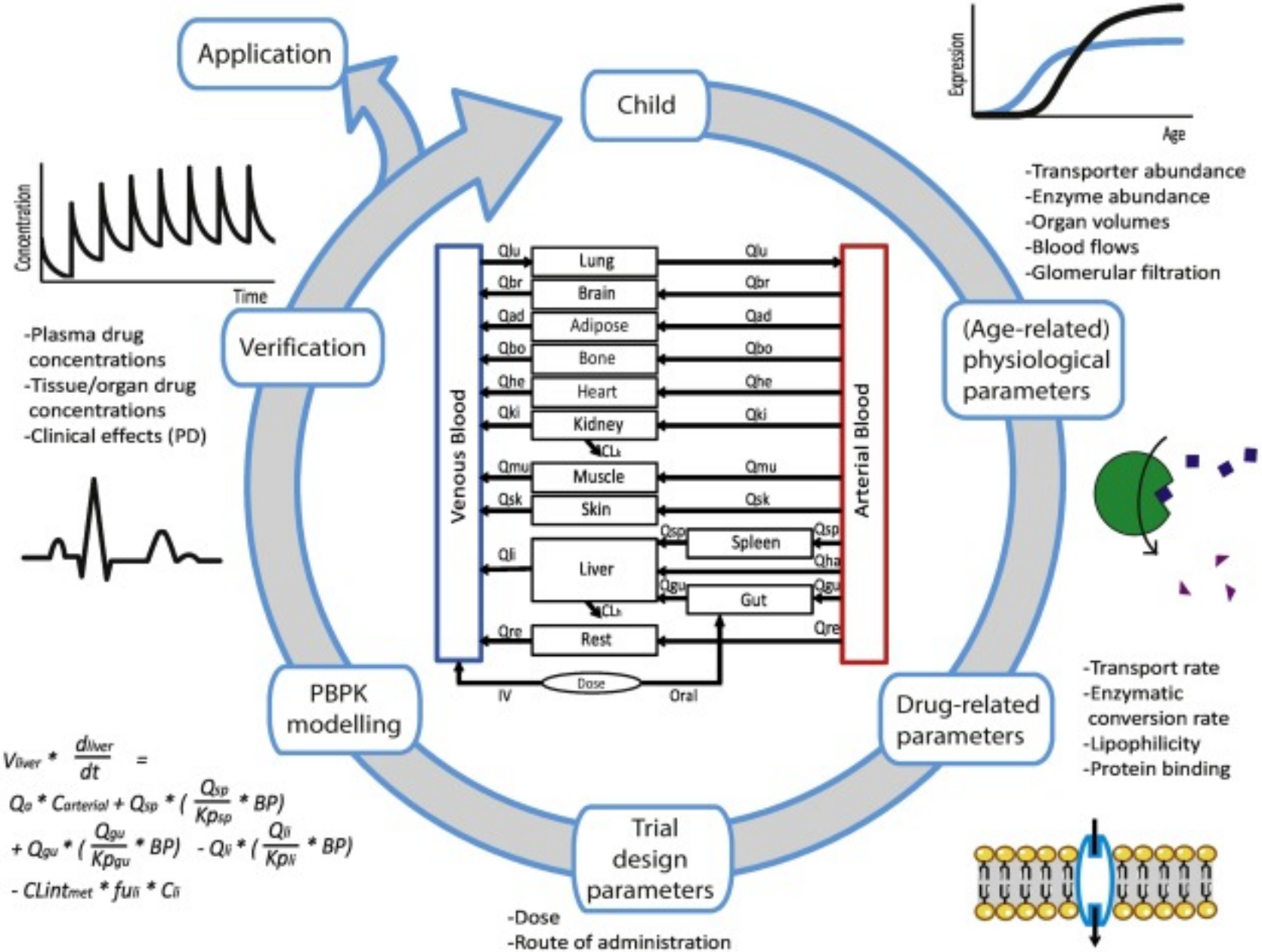
ELSEVIER

Pharmacology & Therapeutics
Volume 211, July 2020, 107541

Physiologically-based pharmacokinetic models for children: Starting to reach maturation?

Laurens F.M. Verscheijden [a], Jan B. Koenderink [a], Trevor N. Johnson [b], Saskia N. de Wildt [a, c], Frans G.M. Russel [a]

PBPK



$$V_{liver} * \frac{dliver}{dt} = Q_a * C_{arterial} + Q_{sp} * \left(\frac{Q_{sp}}{Kp_{sp}} * BP\right) + Q_{gu} * \left(\frac{Q_{gu}}{Kp_{gu}} * BP\right) - Q_{li} * \left(\frac{Q_{li}}{Kp_{li}} * BP\right) - CLint_{met} * fu_{li} * C_{li}$$

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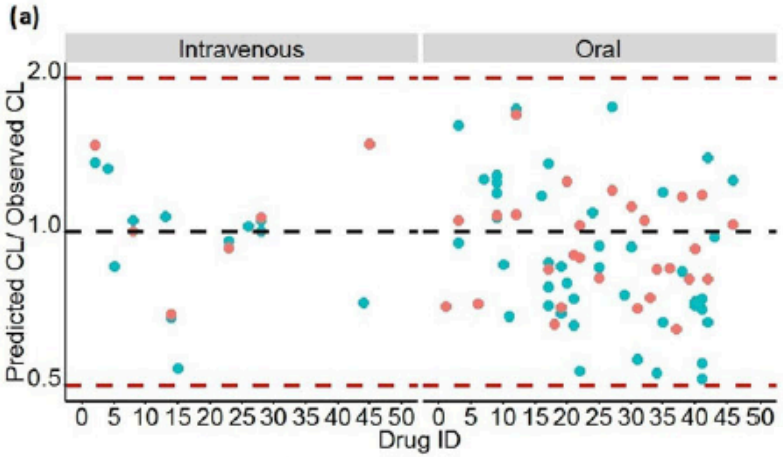
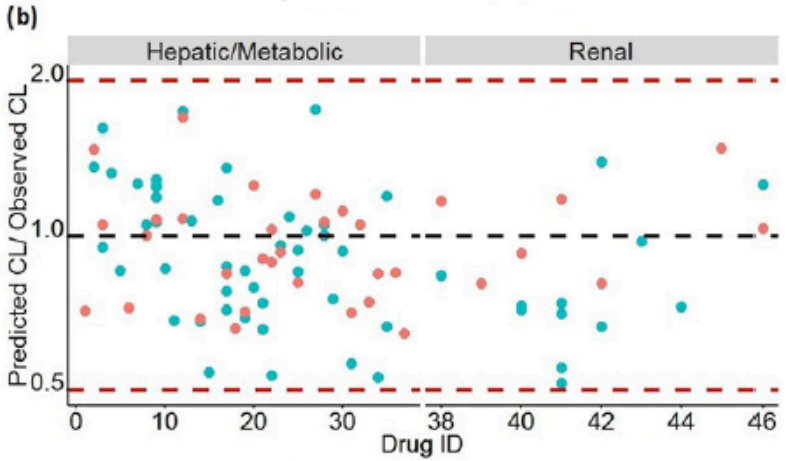
Allometry Is a Reasonable Choice in Pediatric Drug Development

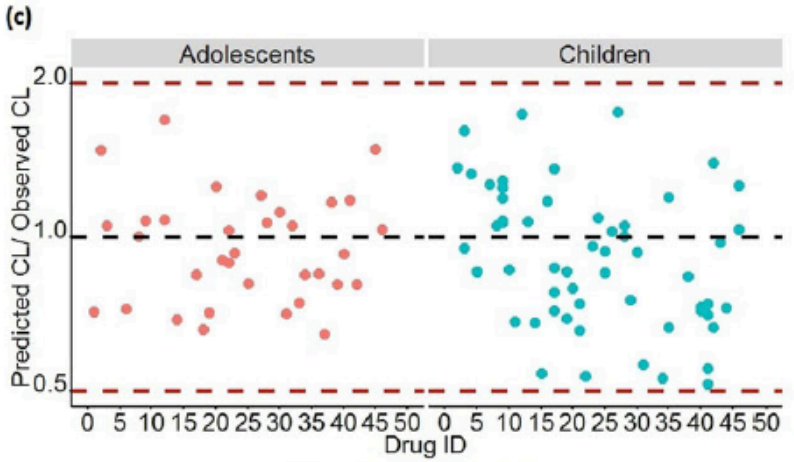
The Journal of Clinical Pharmacology
2017, 57(4) 469–475

DOI: 10.1002/jcph.831

Tao Liu, BSc[1], Parima Ghafoori, BSc[2], and Jogarao V. S. Gobburu, PhD, MBA, FCP[1]







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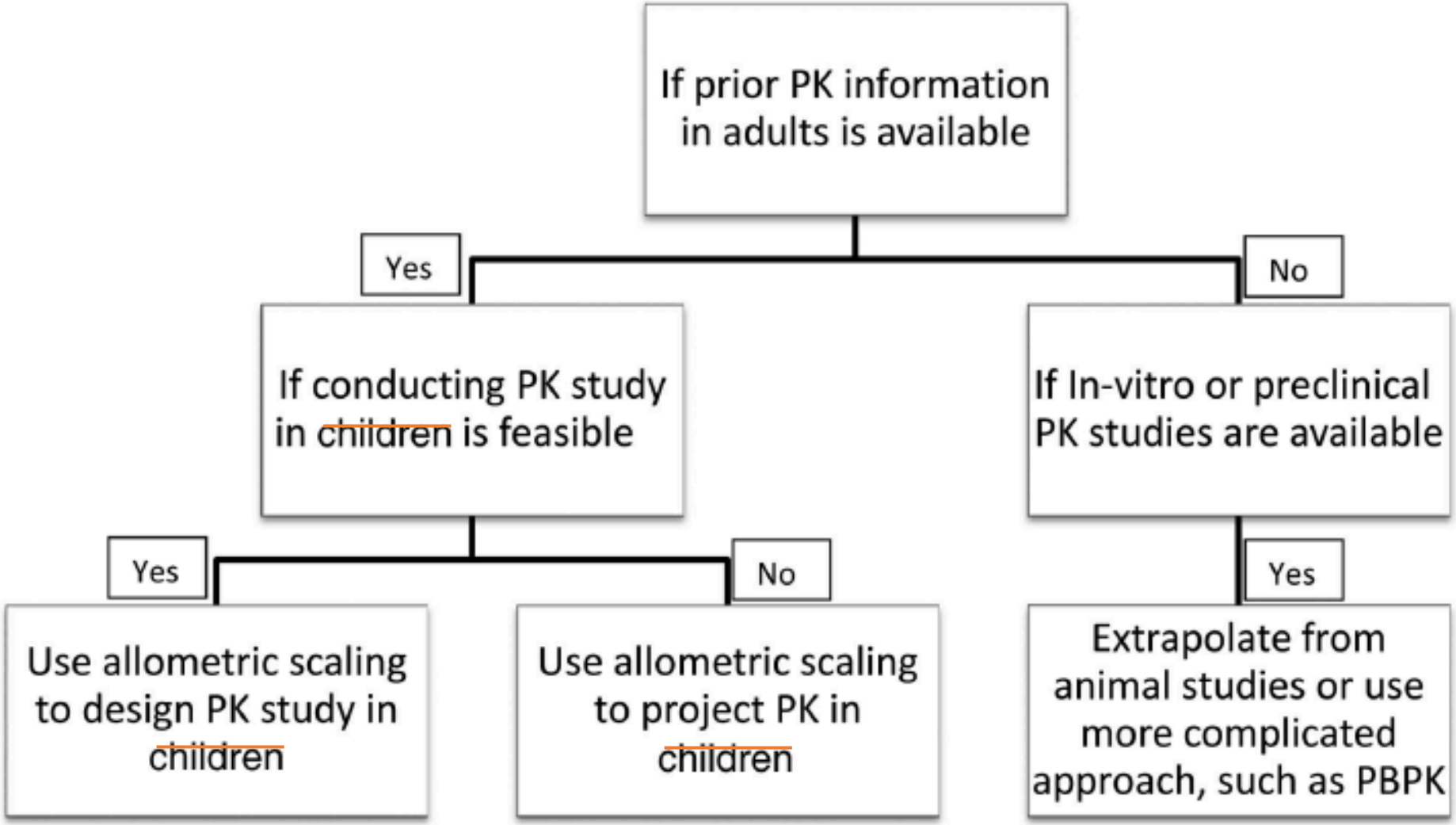
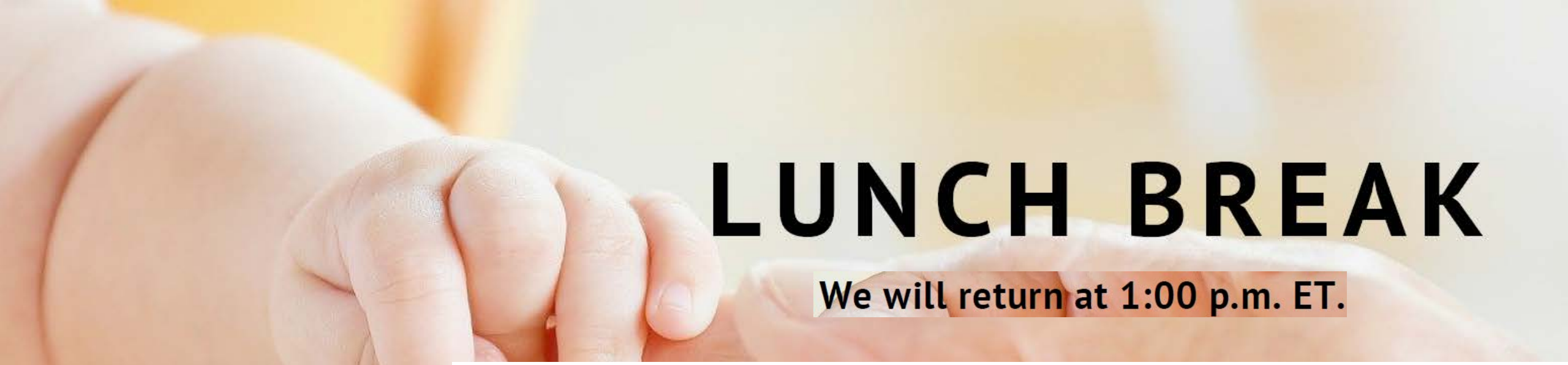
Pediatric PK Projection to Support Development



Add Maturation Model for <2 years

PBPK: Pregnant women, Fetus



LUNCH BREAK

We will return at 1:00 p.m. ET.

CERSI
University of Maryland

FDA

OPPTB Funding Opportunities:

- **Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub**
  - National resource to aggregate, present and expand the available knowledge, tools, and expertise in maternal and pediatric therapeutics to the broader research and drug discovery and development communities.
  - **RFA-HD-21-025**: MPRINT Knowledge & Research Coordination Center-P30 (KRCC)
    - **RFA-HD-21-026**: MPRINT Centers of Excellence in Therapeutics-P50 (CETs)
      - Applications Due Date **November 30, 2020**
- For more information on the MPRINT Hub visit: https://www.nichd.nih.gov/about/org/der/branches/opptb/mprint

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CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Exposure-Matching for Pediatrics with Efficacy Extrapolation

Hao Zhu, Ph.D., Mstat

(Deputy Direction, DPM/OCP/OTS/CDER/FDA)

(Pediatrics Dose Selection Workshop)

(October, 2020)

Disclaimer:
1. I have no conflict of interest to report.
2. The views presented here are my personal.

Outline

- Introduction
  - Approval Basis for Pediatric Indications.
  - Challenges in Pediatric Development Program
  - Extrapolation: Leveraging Adult Findings.
  - Exposure-matching: Dose for Extrapolation.
- Case examples
  - Case 1: Atypical Antipsychotics for Schizophrenia and Bipolar I Disorder.
  - Case 2: Antiepileptic Drugs
  - Case 3: CNS Stimulants for ADHD.
- Summary

Approval Basis for Pediatric Indications

Pediatric product development is held to same evidentiary standard as adult product development:

Must demonstrate substantial evidence of effectiveness / clinical benefit.
[21CFR 314.50]
E.g.
- **Improves symptoms**
- **Delay progression**

Evidence of Effectiveness
[PHS Act, 505(d)]]
Adequate and well – controlled investigations on the basis of which it could fairly and responsibly be concluded ….

Safety Assesment:
[FD&C 505(d)(1)]
Adequate safety information must be included in the application to allow for appropriate risk benefit analysis

Special Considerations:
1. **Ethics: [No alternative source for the information (e.g., adults), low risk, not under a disadvantage condition]**
2. **Feasibility: Lower disease prevalence / incidence.**

Challenges in Pediatric Development

Efficiency: Significant time delay between the approval of an adult indication and inclusion of pediatric related labeling information (i.e., ~ 5-7 years of delay).

Adequate Evidence: Pediatric patients should have access to products that have been appropriately evaluated (e.g., Risk vs. benefit in pediatrics)

To leverage efficacy findings from adults to support the use in pediatric patients. with diseases that are common between adults and pediatrics

Extrapolation: Leveraging Adult Findings

A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted.
[1994: Final Regulation: Pediatric Labeling Rule]

Efficacy: May be extrapolated from adults

- **Disease similarity**
- **Drug effect similarity**
- **Exposure-response relationship similarity**

Safety: Cannot be extrapolated.

Dose: Cannot be extrapolated.

Exposure Matching: Dose for Extrapolation

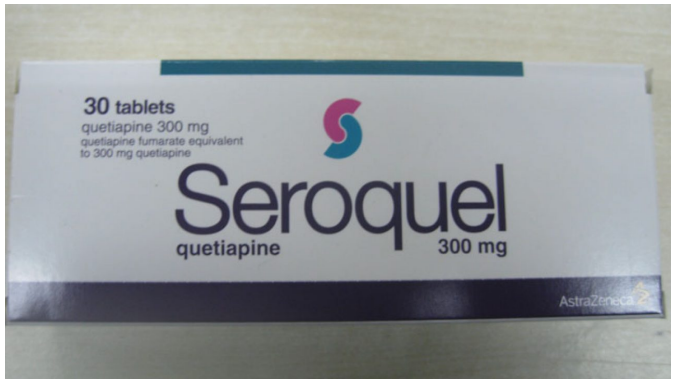
- General Considerations:
  - PK samples should be collected from the open-label, PK and safety trial in pediatric patients.
  - Sample size and sampling schedule should be planned to ensure adequate precision of the PK parameters.
  - An appropriate distribution of pediatric patients across different age range.
  - Modeling and simulation may be conducted to select the pediatric dose that is expected to achieve the exposure similar to that in adults.

Case 1: Schizophrenia and Bipolar I Disorder

- Schizophrenia and bipolar I Disorder are severe mental disorders affecting patients' interaction with the society.
  - Early onset schizophrenia, which has been seen more frequently in the past decade, accounts for 4% of all-cases of schizophrenia.
  - Recent National Comorbidity Survey Replication-Adolescent Supplement (NCS-A) found that approximately 1% of adolescents have strictly defined bipolar I disorder.
- Atypical antipsychotics have been used for the treatment of schizophrenia and bipolar I disorder.
- Historically, one or more adequate and well-controlled clinical studies are required under 505 (d) of FDC Act to demonstrate efficacy in pediatric patients with schizophrenia (> 13 years) or bipolar I disorder (> 10 years).

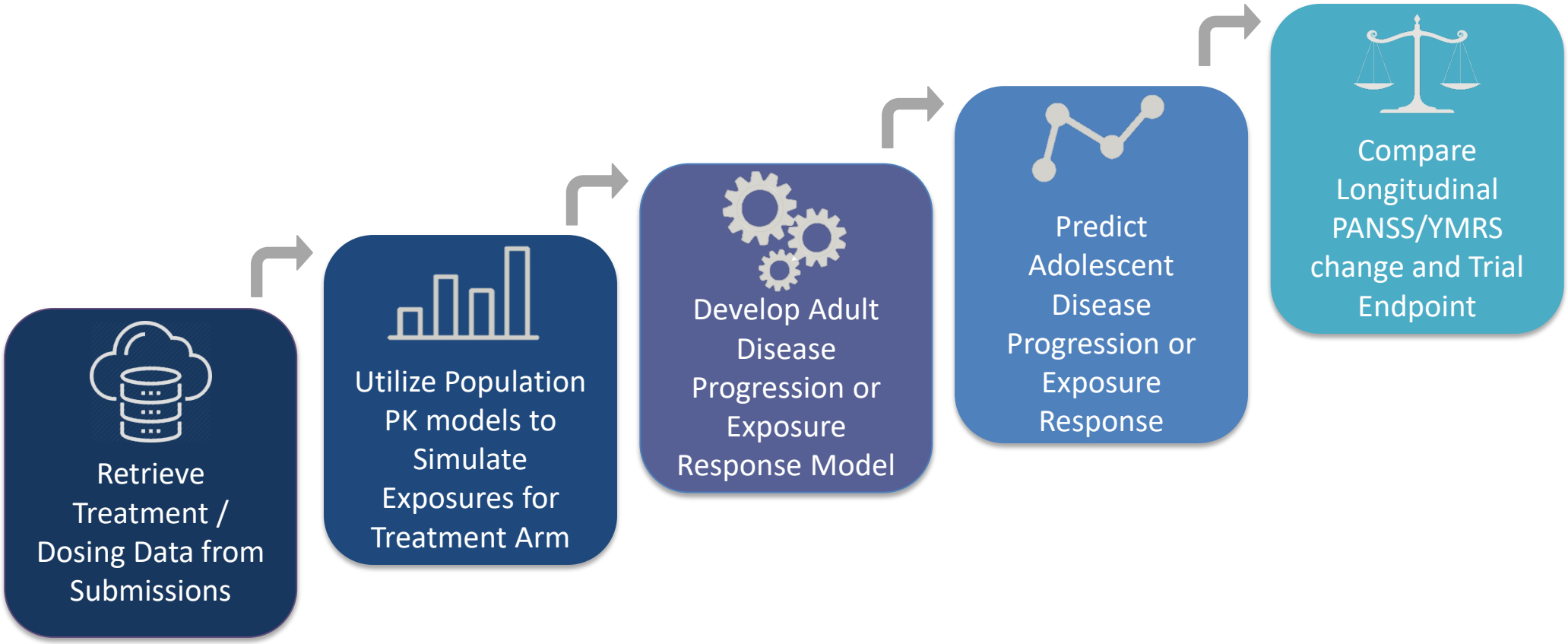
Drug Class

- The second generation, atypical antipsychotics that shared a similar proposed mechanism of action (D_2-receptor antagonism or partial agonism, 5-HT_{1A} partial agonism, and/or 5-HT_{2A} antagonism).



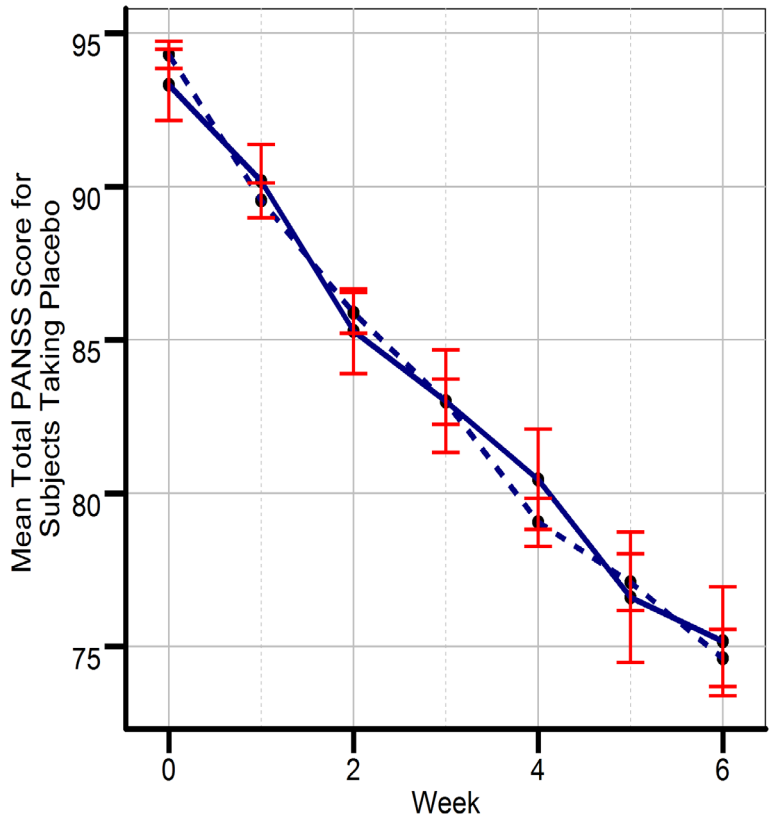
Quantitative Exposure Response Analysis Methods

Development of Drug Specific Exposure-Response Models



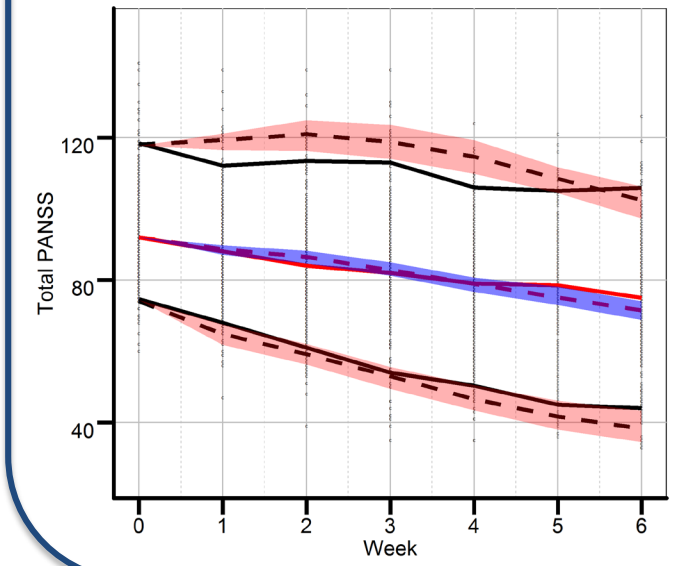
Disease Similarity for Schizophrenia

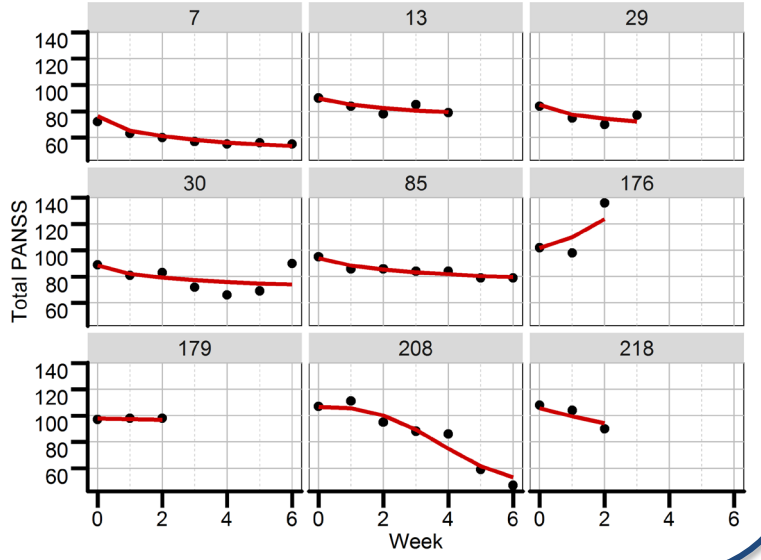
Disease Progression over a Typical 6-Week Trial is Similar Between Adults and Adolescents Completers (Observed)



Disease Progression over a Typical 6-Week Trial is Similar Between Adults and Adolescents [Model Described]

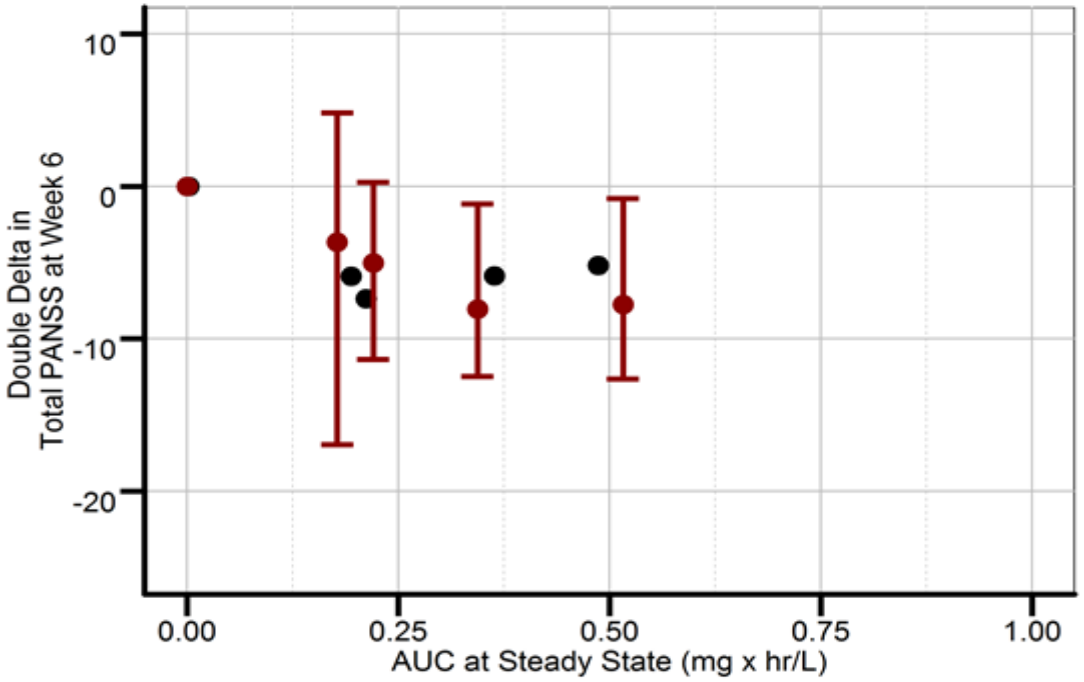
$$PANSS(t) = Baseline\ PANSS \times \left[1 - Pmax \times \left(1 - exp^{-\left(\frac{t}{TD}\right)^{POW}}\right)\right]$$



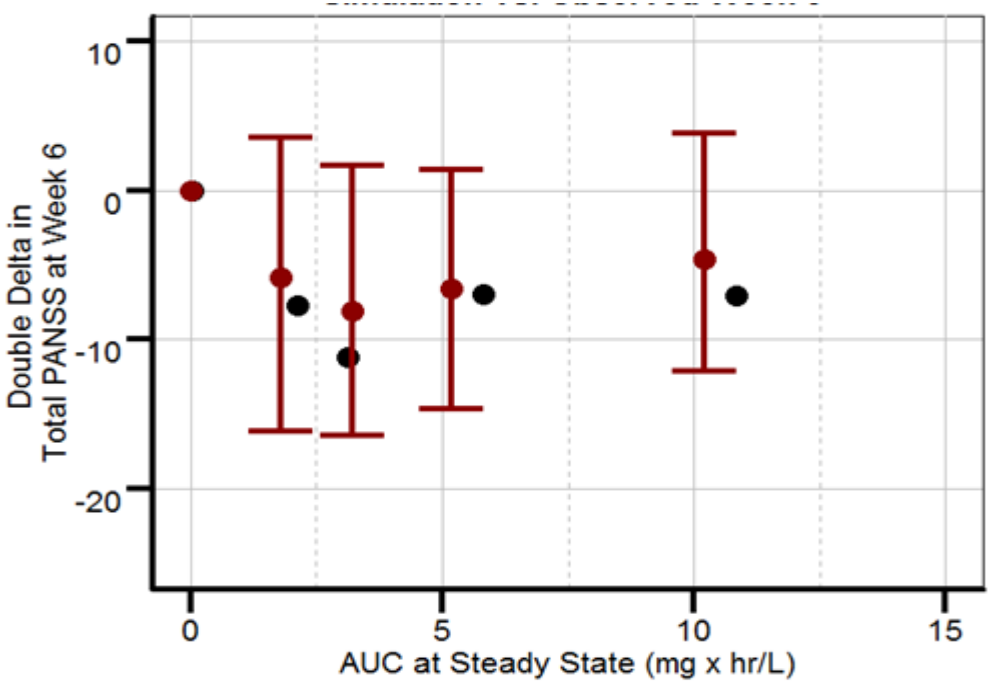


Examples for Similar E-R Relationships

Similar Exposure-Response Relationship between Adults and Pediatric Patients
[Drug A]



Similar Exposure-Response Relationship between Adults and Pediatric Patients
[Drug B]



Note: Similar approaches have been applied to demonstrate disease similarity and similar ER relationships between adults and adolescents with Bipolar I disorder.

Exposure-Matching for Dosing

To support dose selection and possible extrapolation, sponsors should collect blood concentrations of active drug and active metabolites from adequately designed pharmacokinetic and tolerability studies in pediatric patients.

Additional considerations include:

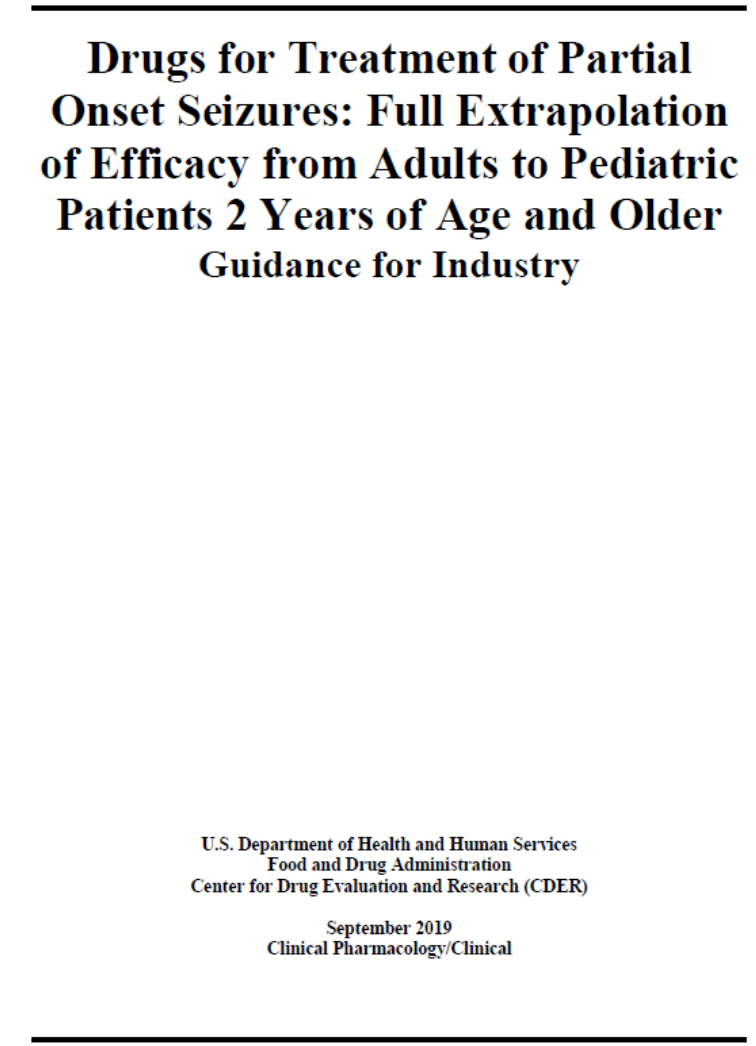
- An appropriate distribution of pediatric patients across the age range,
- Use of pharmacokinetic models and simulations to select doses expected to achieve exposures similar to those in adults,
- Sample size and sampling scheme should be planned carefully to enable characterization of pharmacokinetics with adequate precision,
- Study design that adequately characterizes the short-term tolerability over a dose range that covers concentrations known to be effective in adults,
- For clinical trials that aim to enroll pediatric and adult patients concurrently, sparse pharmacokinetic samples should be collected to adequately characterize the underlying exposure-response relationship.

Case 2: Antiepileptic Drugs

- Seizure:
  - A seizure is a sudden, uncontrolled electrical disturbance in the brain. It causes changes in patients' behavior, movements or feelings, and in levels of consciousness.
- Seizure in pediatric patients
  - Seizure accounts for about 1% of all emergency department visits for pediatric patients less than 18 years of age in hospital. At least 5% of the pediatric patients experience at least a seizure before they are 16 years of age.
- Pediatric Development Program
  - Traditionally, one or more adequate, and well-controlled studies were required under 505 (d) FDC Act to demonstrate efficacy in pediatric patients.

Efficacy Extrapolation and Dose Determination

- Efficacy extrapolation:
  - Basis for extrapolation
    - Similar progression of disease
    - Similar response of disease to treatment
    - **Similar exposure-response relationship for approved drugs with various MOAs (FDA analyses)**
  - ***Exposure-matching for Pediatric Doseing***
    - PK should be obtained from an adequately designed PK (with adequate precision) and tolerability study in which single and /or multiple doses of the investigational drug are administered in patients 2 to 16 years of age (with adequate age distribution).
    - PK data should be used to determine pediatric dosage and regimens based on PK-matching.
    - Simulation should be performed to select the dose expected to achieve the exposure similar to those known to be effective in adults with POS.



Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 2 Years of Age and Older

Guidance for Industry

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

September 2019
Clinical Pharmacology/Clinical

Examples of Exposure-matching for Dosing

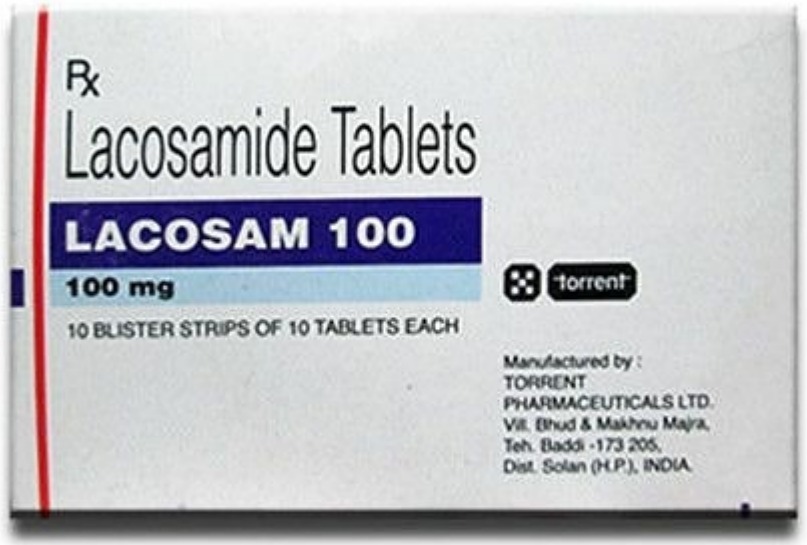
Partial Onset Seizure in Pediatric Patients > 4 Years

Drug Name	Pediatrics Indication	Evidence for Efficacy	Role of Exposure Matching
Eslicarbazepine	Partial Onset Seizure (4 years and older)	Extrapolation	Bridging efficacy and deriving pediatric dosing.
Lacosamide			
Brivaracetam			

Label Language: Section 8.4 Pediatrics: Safety and effectiveness of XXX have been established in the age groups 4 to 17 years. Use of XXX in these age groups is supported by evidence from adequate and well-controlled studies of XXX in adults with partial-onset seizures, pharmacokinetic data from adult and pediatric patients, and safety data from clinical studies in XX pediatric patients 4 to 17 years of age

Examples of Doses based on Exposure-matching

VIMPAT ® is indicated for the treatment of partial onset seizures in patients 4 years and older.



Pediatric Dosing Table

Age and Body Weight	Initial Dosage	Titration Regimen	Maintenance Dosage
Adults (17 years and older)	**Monotherapy:** 100 mg twice daily (200 mg per day) **Adjunctive Therapy:** 50 mg twice daily (100 mg per day) **Alternate Initial Dosage:** 200 mg single loading dose, followed 12 hours later by 100 mg twice daily	Increase by 50 mg twice daily (100 mg per day) every week	**Monotherapy:** 150 mg to 200 mg twice daily (300 mg to 400 mg per day) **Adjunctive Therapy:** 100 mg to 200 mg twice daily (200 mg to 400 mg per day)
Pediatric patients weighing 50 kg or more	50 mg twice daily (100 mg per day)	Increase by 50 mg twice daily (100 mg per day) every week	**Monotherapy:** 150 mg to 200 mg twice daily (300 mg to 400 mg per day) **Adjunctive Therapy:** 100 mg to 200 mg twice daily (200 mg to 400 mg per day)
Pediatric patients weighing 30 kg to less than 50 kg	1 mg/kg twice daily (2 mg/kg/day)	Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	2 mg/kg to 4 mg/kg twice daily (4 mg/kg/day to 8 mg/kg/day)
Pediatric patients weighing 11 kg to less than 30 kg	1 mg/kg twice daily (2 mg/kg/day)	Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	3 mg/kg to 6 mg/kg twice daily (6 mg/kg/day to 12 mg/kg/day)

*when not specified, the dosage is the same for monotherapy and adjunctive therapy

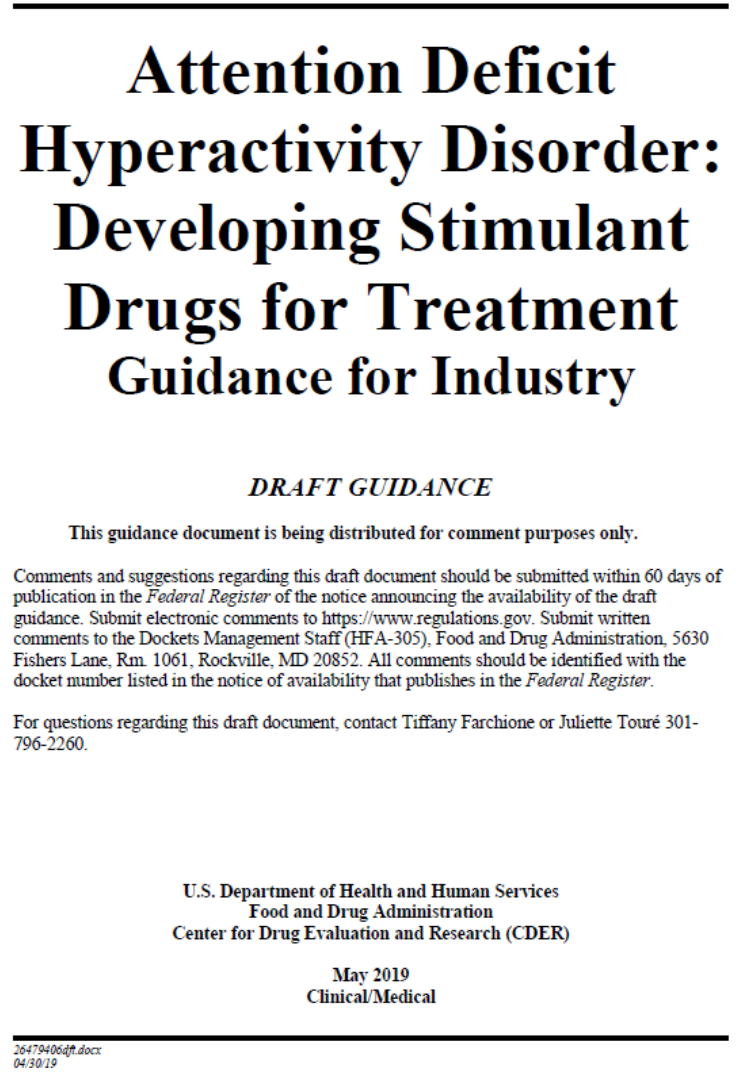
Case 3: Novel CNS Stimulant Formulations

- Attention Deficit Hyperactivity Disorder (ADHD): is a common neurobehavior disorder with the onset from childhood.
- The global prevalence of ADHD is estimated to be 6.5%, 2.7% and 2.5% in children, adolescents and adults respectively.
- CNS stimulants, such as methylphenidate and amphetamine, have been widely prescribed for the treatment of ADHD.
- Strong concentration-response relationships for efficacy and safety have been observed for CNS stimulants.
- New formulations containing the same active moiety have been developed to alter the underlying PK profile in order to generate a specific onset and duration.
- Traditionally, efficacy and safety trials were conducted in children, adolescents, and adults, separately.

Efficacy Back-extrapolation and Dose

Efficacy can be extrapolated from children to adolescents and adults with ADHD.

- Sponsors are highly encouraged to discuss their development strategy with the Agency during the Pre-IND stage. Some of the factors that should be considered to allow the extrapolation include:
  - The active ingredient of the 505(b)(2) product should only be methylphenidate or amphetamine.
  - The 505(b)(2) product should be given in the morning and target a duration of 12 hours or less.
  - ***Shape of the pharmacokinetic profile of the active moiety(ies) of the 505(b)(2) product must be similar across children, adolescents, and adults.***
  - The approved patient population of the listed drug should include children, adolescents, and adults. The dose for each patient population should be clearly defined.
  - An adequate bridging must be established between the 505(b)(2) product and the listed drug, such that the dose of the 505(b)(2) product in each patient population can be reliably derived.
  - Patients ages 4 and 5 years should be included in clinical trials. Although it is reasonable to extrapolate efficacy from older children to 4- and 5-year-old children, clinical trial data is necessary to compare the safety profile in this population to what is known about the listed drug.
- Dose may be determined by matching the exposure range.



Attention Deficit Hyperactivity Disorder: Developing Stimulant Drugs for Treatment

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 Tiffany Farchione or Juliette Touré 301-796-2260.

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

May 2019
Clinical/Medical

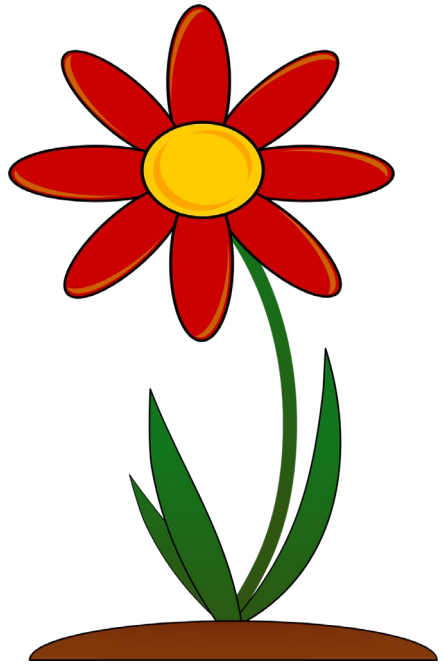
26479406dft.docx
04/30/19

Summary

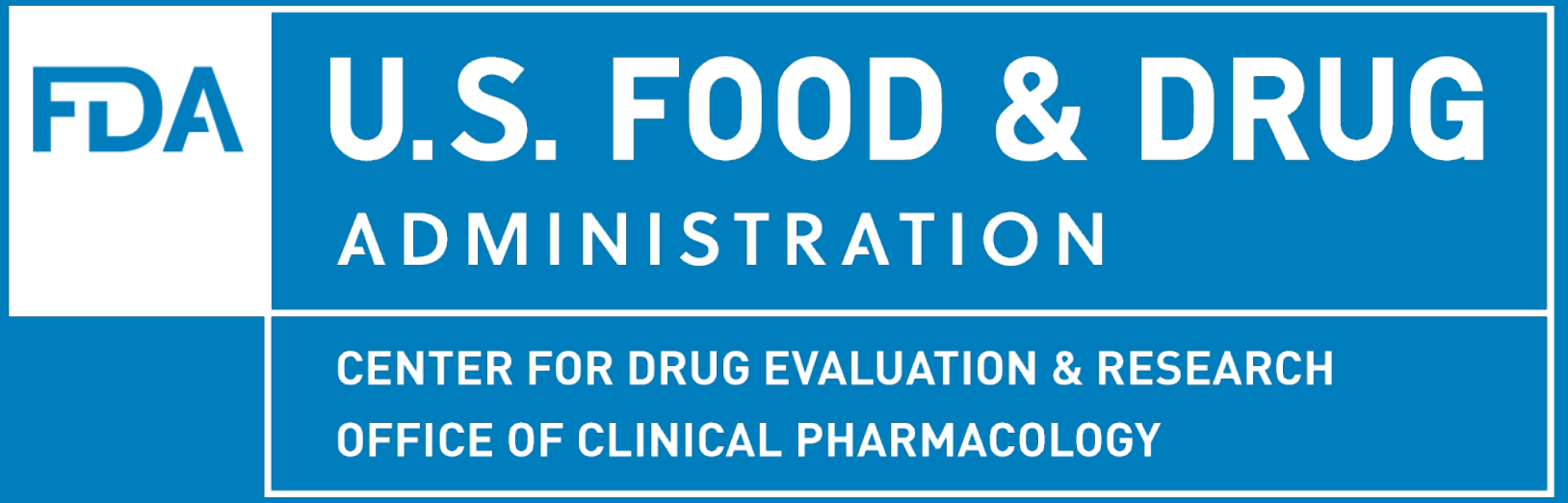
- Efficacy extrapolation provides an alternative way to support pediatric indication approval.
- Exposure-matching has been applied to support dose determination for products gain approval through pediatric extrapolation.

Acknowledgement

- Dr. Shamir Kalaria
- Dr. Angela Men
- Dr. Yaning Wang
- Dr. Tiffany Farchione
- Dr. Ramana Uppoor
- Dr. Mehul Mehta
- Dr. Shiew-Mei Huang
- Dr. Issam Zineh
- DPM Members
- DP and DN Members
- OCP Members



Questions and Comments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U.S. FOOD & DRUG ADMINISTRATION

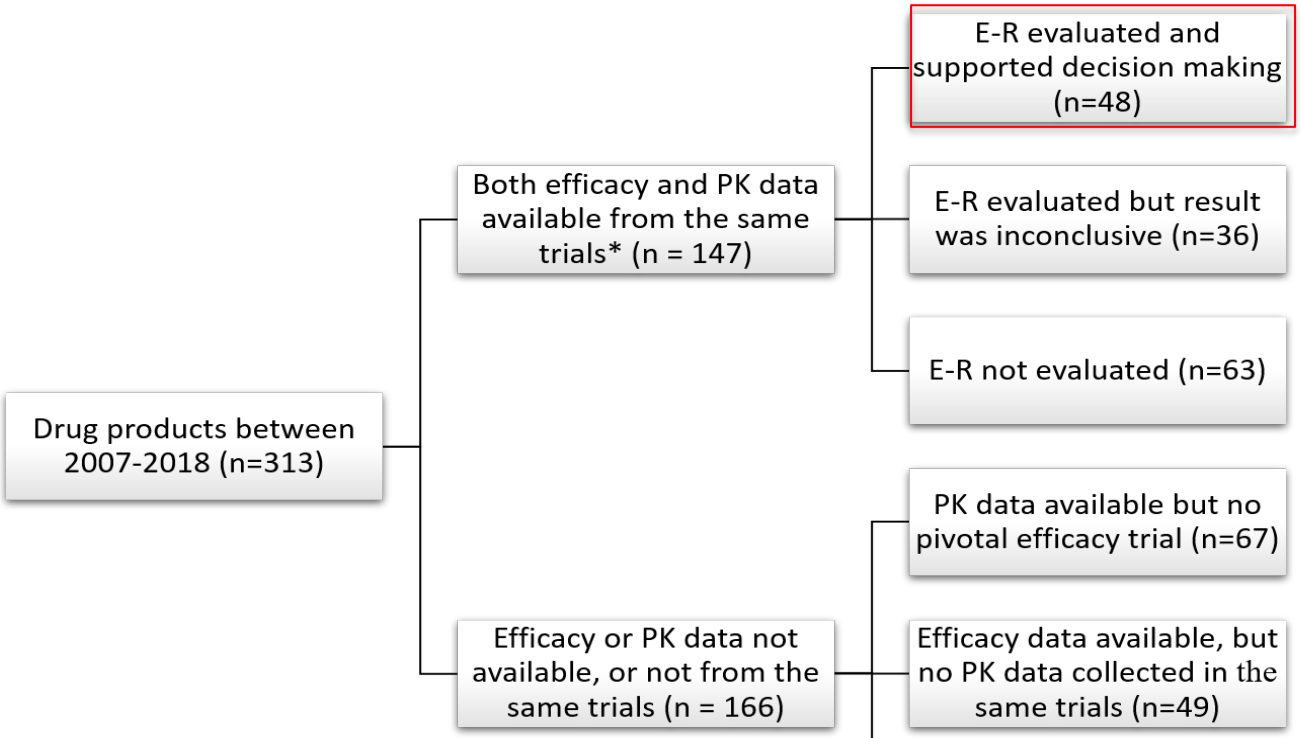
Use of Exposure-Response in Pediatric Drug Development

Jian Wang, PhD
Associate Director for Regulatory Science
Office of Specialty Medicine
Office of New Drugs
CDER, FDA

Disclosure Statement

- I do not have financial relationships with a defined commercial interest related to this educational content
- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

Exposure-Response(E-R) Assessment in Pediatric Drug Development Studies Submitted to FDA (2007-2018)



Exposure–Response Assessment in Pediatric Drug Development Studies Submitted to the US Food and Drug Administration

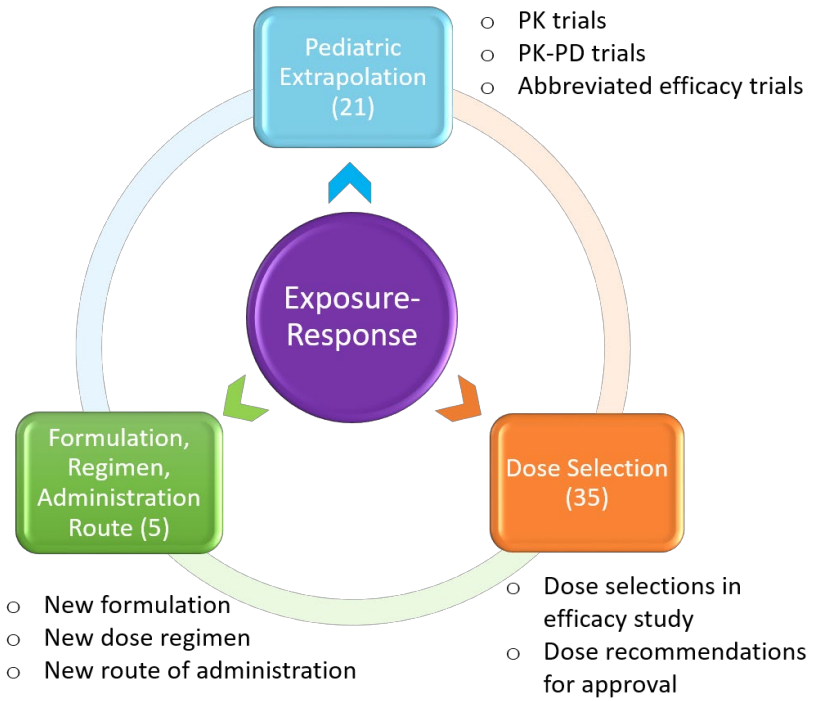
Yifei Zhang[1], Yaning Wang[2], Mona Khurana[3], Hari Cheryl Sachs[3], Hao Zhu[2], Gilbert J. Burckart[2], John Alexander[1], Lynne P. Yao[3] and Jian Wang[1,*]

Classification of products with pediatric studies between 2007–2018 based on published FDA reviews on https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2007-2012 https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present

Zhang et al, CPT, 2020 https://doi.org/10.1002/cpt.1809

Generic Name	Indication	Extrapolation/ Trial Design	Dose Selection	New Formulation/ Dosing Regimen
Abatacept	pJIA	x		
Asenapine	Bipolar disorder	x		
Brivaracetam	POS	x		
Eslicarbazepine acetate	POS	x		
Lacosamide	POS	x		
Levetiracetam	POS	x		
Naproxen and esomeprazole magnesium	JIA	x		
Omeprazole magnesium	GERD	x		
Pregabalin	POS	x		
Vigabatrin	rCPS	x		
Perampanel	POS	x	x	
Rabeprazole	GERD	x	x	
Topiramate	POS	x	x	
Paricalcitol	Secondary hyperparathyoidism	x	x	
Lamotrigine	POS	x	x	
Etravirine	HIV-1 infection	x	x	
Maraviroc	HIV-1 infection	x	x	
Tenofovir disoproxil fumarate	HIV-1 infection	x	x	
Raltegravir	HIV-1 infection	x	x	
Oxcarbazepine	POS	x		x
Zidovudine	HIV-1 infection	x		x
Aliskiren	Hypertension		x	
Aprepitant	CINV		x	
Argatroban	Thrombosis		x	
Benralizumab	Asthma		x	
Candesartan Cilexitil	Hypertension		x	
Ceftaroline fosamil	ABSSSI and CABP		x	
Ciclesonide	Allergic rhinitis		x	
Clonidine hydrochloride	ADHD		x	
Cysteamine bitartrate	Nephropathic cystinosis		x	
Eltrombopag	Thrombocytopenia		x	
Entecavir	Chronic hepatitis B (CHB) infection		x	
Everolimus	SEGA		x	
Fluticasone furoate	Asthma		x	
Fosaprepitant	CINV		x	
Guanfacine	ADHD		x	
Olmesartan Medoxomil	Hypertension		x	
Omalizumab	Chronic idiopathic urticaria		x	
Paliperidone	Schizophrenia		x	
Palonosetron	CINV		x	
Reslizumab	Asthma		x	
Sapropterin dihydrochloride	Hyperphenylalaninemia (HPA)		x	
Sumatriptan/Naproxen	Migraine		x	
Terbinafine	Tinea Capitis		x	
Valganciclovir hydrochloride	Prevention of CMV disease		x	
Esomeprazole sodium	GERD		x	x
Tocilizumab	sJIA		x	x
Posaconazole	Aspergillosis and Candida infections			x

Roles of E-R in Pediatric Drug Development (2007–2018)



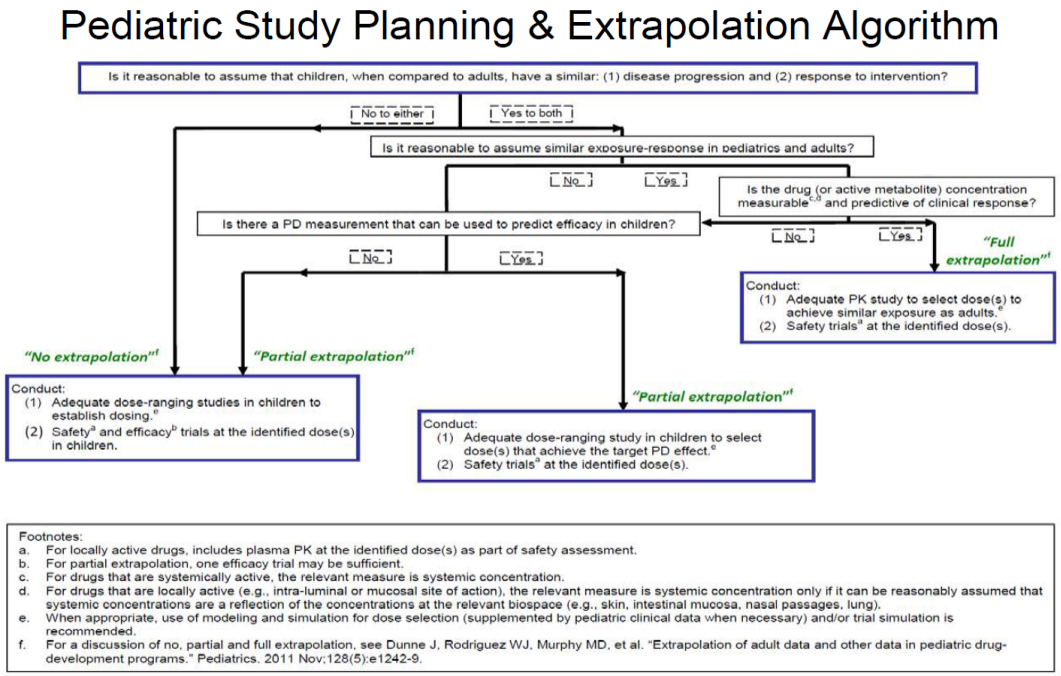
Zhang et al, CPT, 2020
https://doi.org/10.1002/cpt.1809

Pediatric Study Designs to Establish Effectiveness and Roles of E-R

Clinical Trial Design	Roles of Exposure-Response (E-R)	Examples
Randomized, controlled clinical trial	E-R for efficacy and safety informs pediatric dose selection	Oncology (Everolimus) Systemic juvenile idiopathic arthritis (sJIA) (Tocilizumab) Schizophrenia (Paliperidone, Asenapine) Bipolar disorder (Asenapine) Postoperative nausea and vomiting (PONV) and chemotherapy-induced nausea and vomiting (CINV) (Palonosetron) Migraine prophylaxis (Topiramate)
Uncontrolled Efficacy Study or PK-PD Study	E-R data support partial extrapolation and abbreviated trial design	GERD (Omeprazole delayed-release capsules) Human immunodeficiency virus (HIV) infection (Etravirine, Maraviroc, Tenofovir Disoproxil fumarate, Zidovudine) Nephropathic cystinosis (Cysteamine bitartrate) Polyarticular juvenile idiopathic arthritis (pJIA) (Tocilizumab) Secondary hyperparathyoidism (Paricalcitol)
PK Study	PK matching is based on assumptions of similar E-R relationships between pediatrics and adults	Partial-onset seizures (POS) > 4 y/o (Eslicarbazepine, Brivaracetam, Pregabalin, Lacosamide)

Zhang et al, CPT, 2020
https://doi.org/10.1002/cpt.1809

E-R in Support Pediatric Extrapolation



- Lack of uniformity in terminology of 'similarity' and quantitative measure of the similarities would be one roadblock for pediatric extrapolation (IQ white paper, 2018)

Can we develop quantitative approaches to evaluate E-R similarity between pediatric and adult patients to support pediatric drug development?

Drugs with Similar E-R in Adult and Pediatric Patients

Linear E-R Drugs

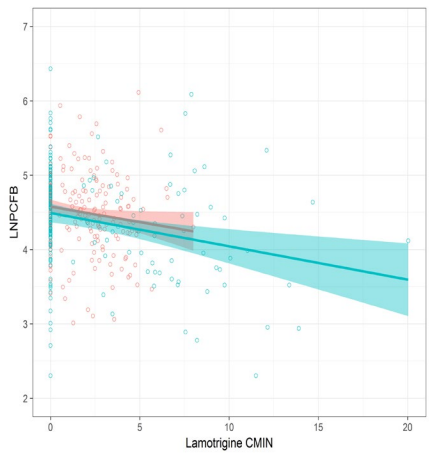
Drug name (Brand)	Indication	Subject N (pediatric/adult)
Oxcarbazepine (Trileptal)	POS	106 / 300
Levetiracetam (Keppra IR)	POS	88 / 502
Perampanel (Fycompa)	POS	44 / 713
Lamotrigine (Lamictal IR)	POS	64 / 133
Topiramate (Topamax)	POS	57 / 422

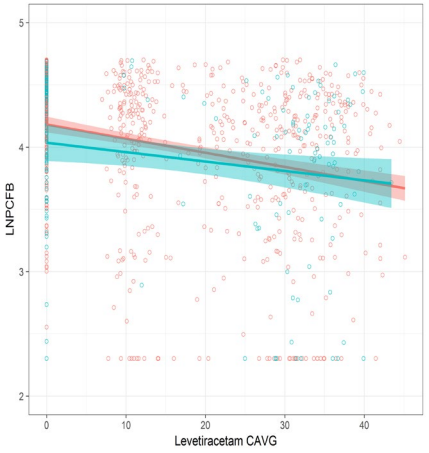
Non-Linear E-R Drugs

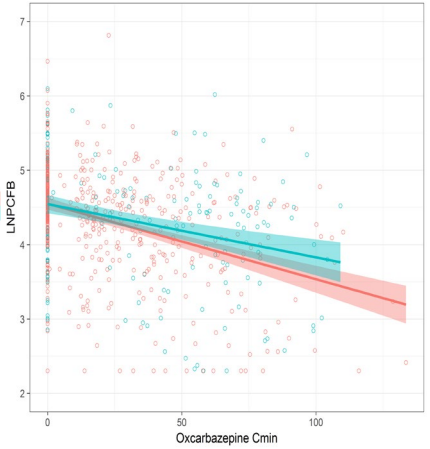
Drug name (Brand)	Indication	Subject N (pediatric/adult)
Infliximab (Remicade)	Ulcerative colitis	55 / 222
Darunavir (Prezista)	Anti-HIV	64 / 350
Esomeprazole (Nexium)	Gastroesophageal reflux (GERD)	52 / 65

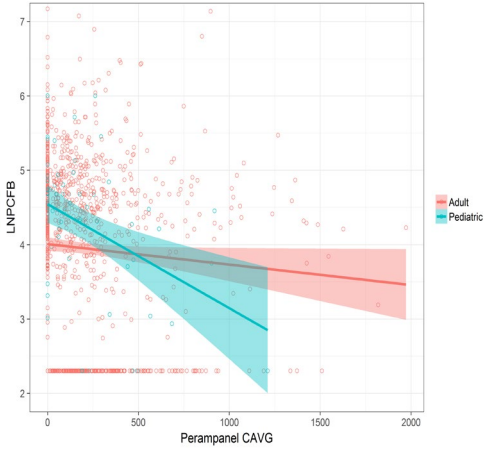
POS: Partial Onset Seizure

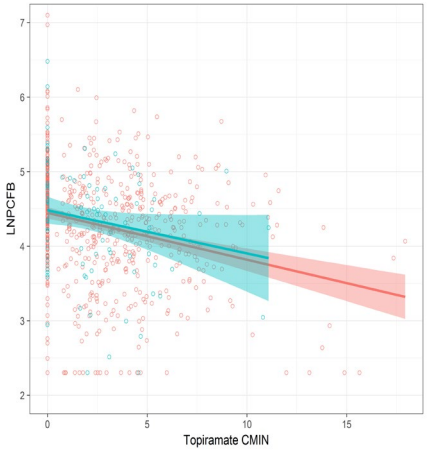
Prior Exposure-Response Data to Support Pediatric Extrapolation: Examples

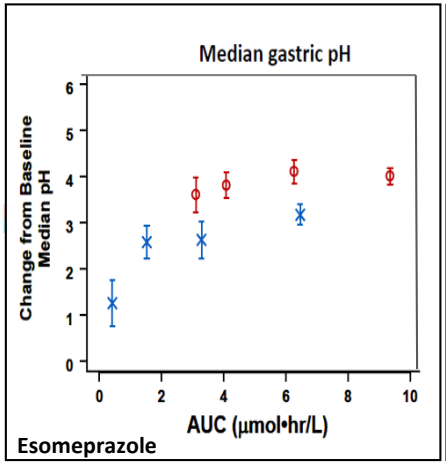


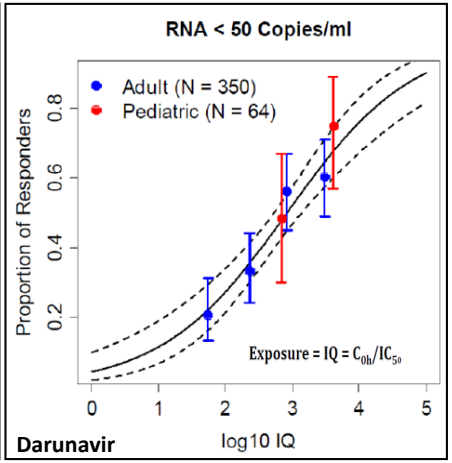


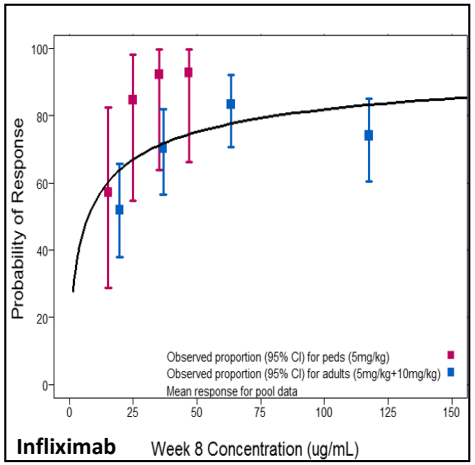








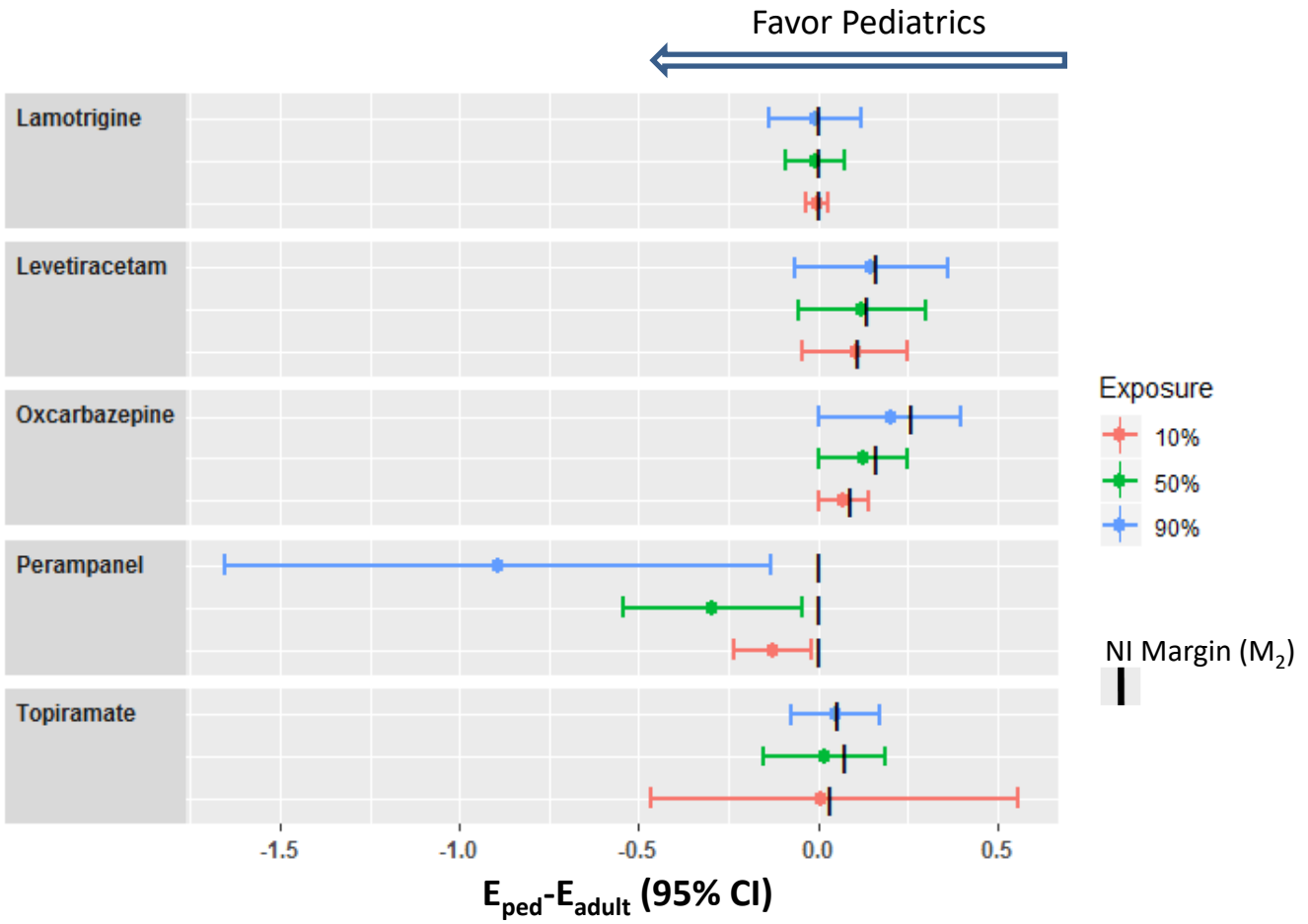




E-R Relationships in Pediatric & Adult Patients of Eight Selected Drugs

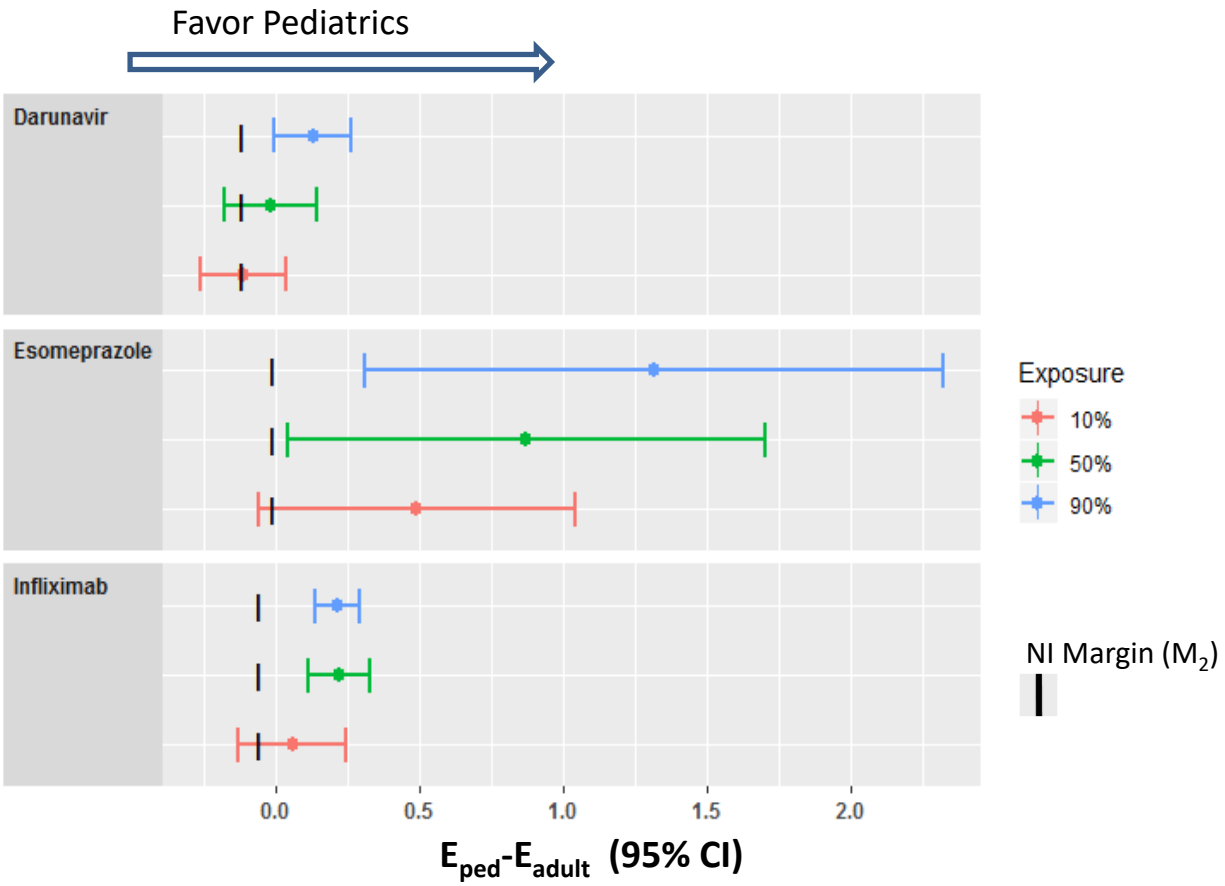
E-R Non-inferiority and Probability Estimates between Pediatrics and Adults: Linear Examples

Probability of Non-inferiority	
Bootstrap	Bayesian
57.2%	57.1%
56.1%	57.3%
56.1%	56.9%
55.2%	53.7%
55.5%	53.9%
55.6%	53.2%
65.1%	71.2%
66.3%	68.3%
66.6%	65.6%
99.6%	99.4%
99.0%	98.1%
96.1%	96.9%
58.1%	60.1%
68.1%	69.9%
60.8%	61.0%



E-R Non-inferiority and Probability Estimates between Pediatrics and Adults: Nonlinear Examples

Probability of Non-inferiority	
Bootstrap	Bayesian
99.0%	98.0%
86.2%	87.0%
52.9%	57.5%
99.3%	99.1%
98.6%	98.1%
89.8%	89.6%
100.0%	100.0%
97.6%	97.9%
88.6%	84.6%

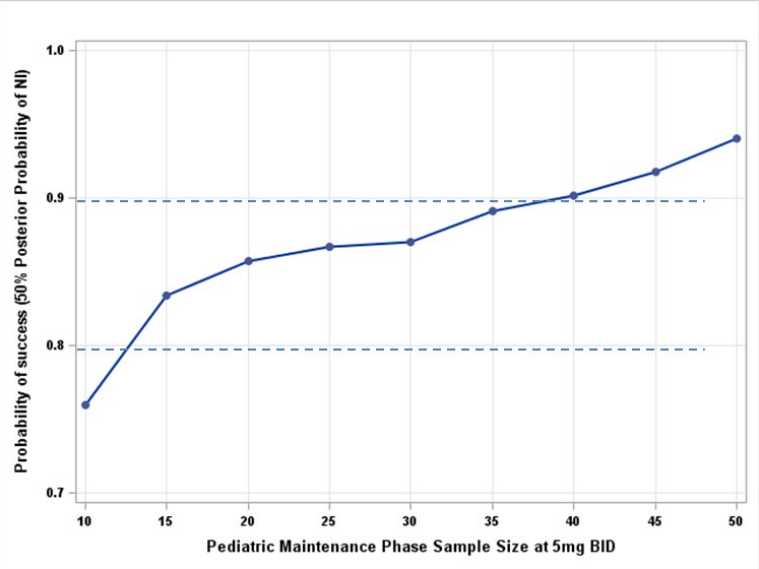


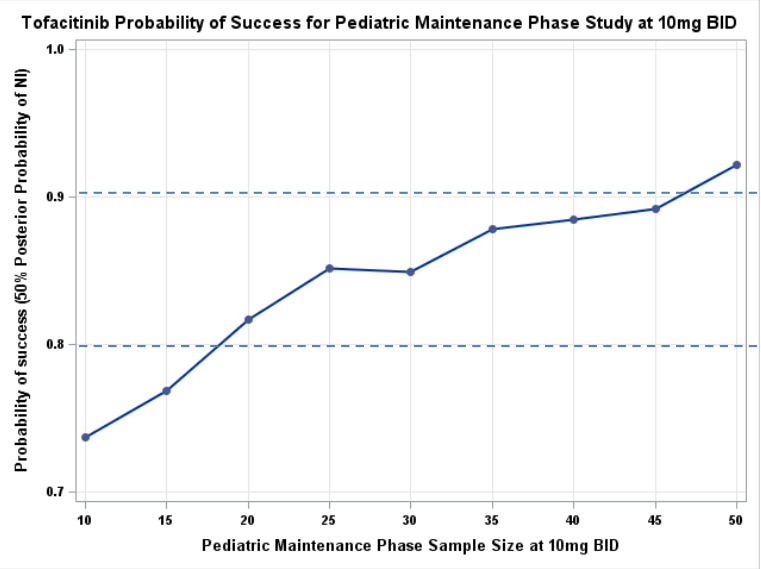
Non-inferiority Methods to Evaluate E-R: Summary

- Using a non-inferiority comparison, all eight drugs that were considered had point estimates of efficacy difference between pediatric and adult patients to have met the pre-defined non-inferiority margins M2 at the targeted exposure range.
  - Results from eight drugs' E-R were consistent;
  - However, the point estimate did not consider uncertainty.
- Bootstrap and Bayesian methods can provide probability of E-R non-inferiority estimates.
  - The results were comparable between two methods;
  - Both were in the range of 53-100% for all eight drugs..
- To address the uncertainty, a threshold (e.g. 60%) for the probability of E-R non-inferiority between pediatric and adult patients can be pre-specified with clinical judgment.
- This developed approach can be used to support the extent of pediatric extrapolation of efficacy for future drugs and inform pediatric trial design.

Pediatric Sample Size Estimate:

E-R based Clinical Trial Simulations





Dose	Sample size (N)*	Probability of success (%)
5 mg	10	76
	13	80
	20	86
	25	87
	30	87
	35	89
	40	90
	45	92
	50	94
10 mg	10	74
	15	77
	18	80
	25	85
	30	85
	35	88
	40	89
	47	90
	50	92

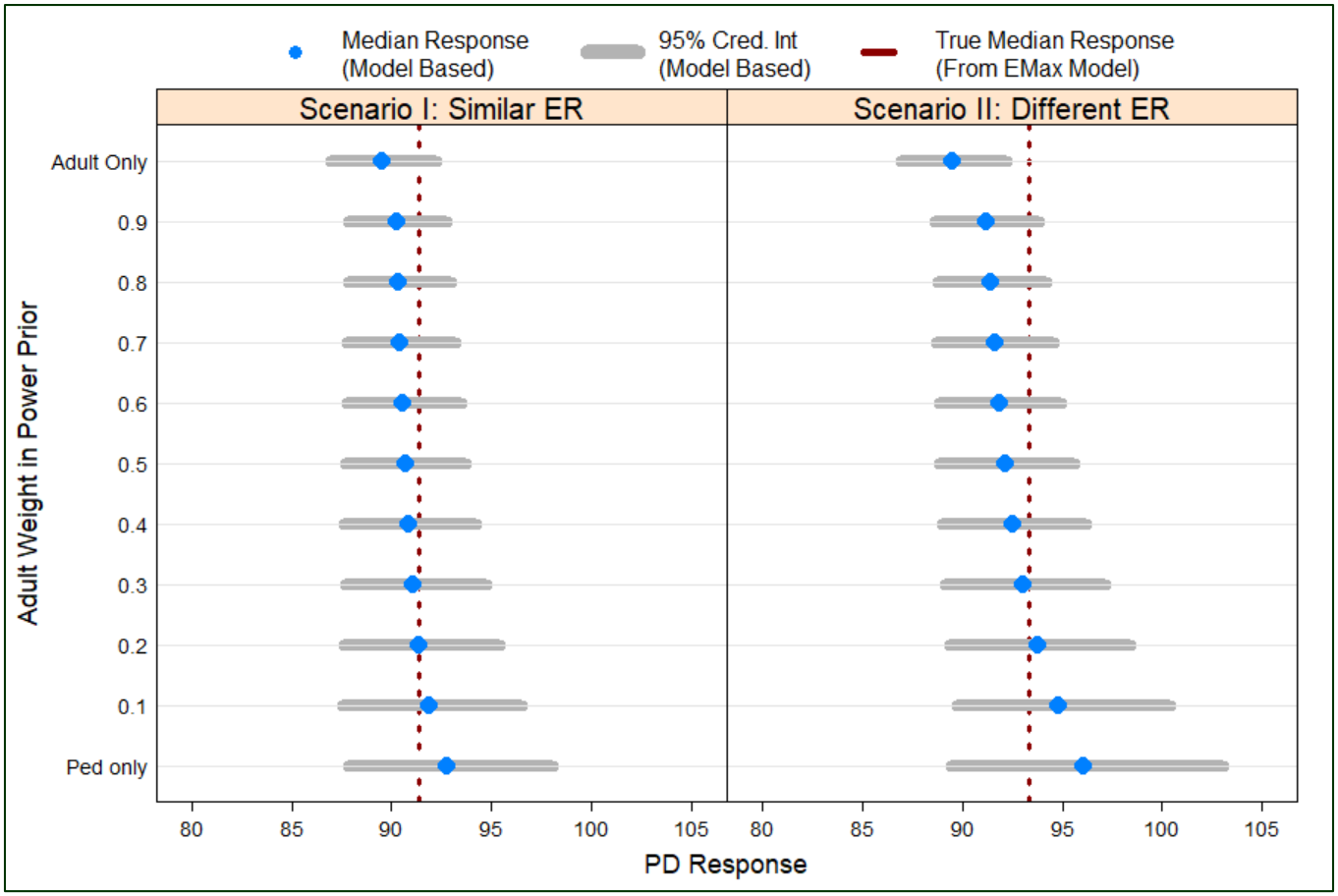
*Trial success was defined as in each pediatric virtual trial that the point estimate of efficacy difference is greater than the non-inferiority margin at the exposure ranges at 5mg and 10mg doses

Borrowing Adult E-R to Analyze Pediatric Data: Bayesian Methods

Methods	How to Relate Adult Data (Prior Knowledge) to Pediatrics
Pediatric Only	• NONE • Uses non informative prior distribution
Pooled Analysis	• 100% adult Information • One common model (Exchangeability)
Power Prior	• Discounted adult information (down-weighted, 0-100%) • Exchangeability
Robust Meta-Analytic Predictive (MAP) Prior	• Mixture Distribution: - Discounted adult information (down-weighted, 0-100%) using non-informative priors - Non-informativeness to account for population differences
Commensurate Prior	• Introduce pediatric-adult relationship (“similarity” parameter) • Amount of adult information is based on estimated similarity

Application of Bayesian Methods to Analyzing Pediatric Data by Leveraging Adult Exposure-Response Relationship:

An Example Based on Virtual Clinical Trials



Leveraging adult information may

- increase the precision of the parameters of interest (shorter credible intervals);
- introduce additional bias if two populations are not “similar”.

Summary (1)

- The pediatric E-R studies submitted to U.S. FDA between 2007 - 2018 were surveyed in the context of various types of trial designs supporting drug approval in the pediatric population.

- The applications of E-R evaluation in pediatric drug development programs are mainly focused on three areas:
  - supporting extrapolation of efficacy when the E-R relationships are similar between the pediatric and adult populations;
  - dose selection to balance the benefit-risk profile based on the change in efficacy and safety response with different exposure levels; and
  - new formulation, new dosing regimen, or new route of administration, where E-R evaluation helps quantify the change in clinical response between the old and new strategies.

Summary (2)

- E-R comparison between the pediatric and adult populations can be quantitatively assessed using noninferiority methods
  - To support degree of similarity of disease, pharmacology and response to therapy
- E-R can be utilized for CTS to inform trial design, optimize sample size, etc.
  - To support clinical trial design and data necessary
- Bayesian approaches, including model-informed approaches make use of prior E-R information
  - To maximize the efficiency of drug development for children

DOSE DETERMINATION IN NEONATES

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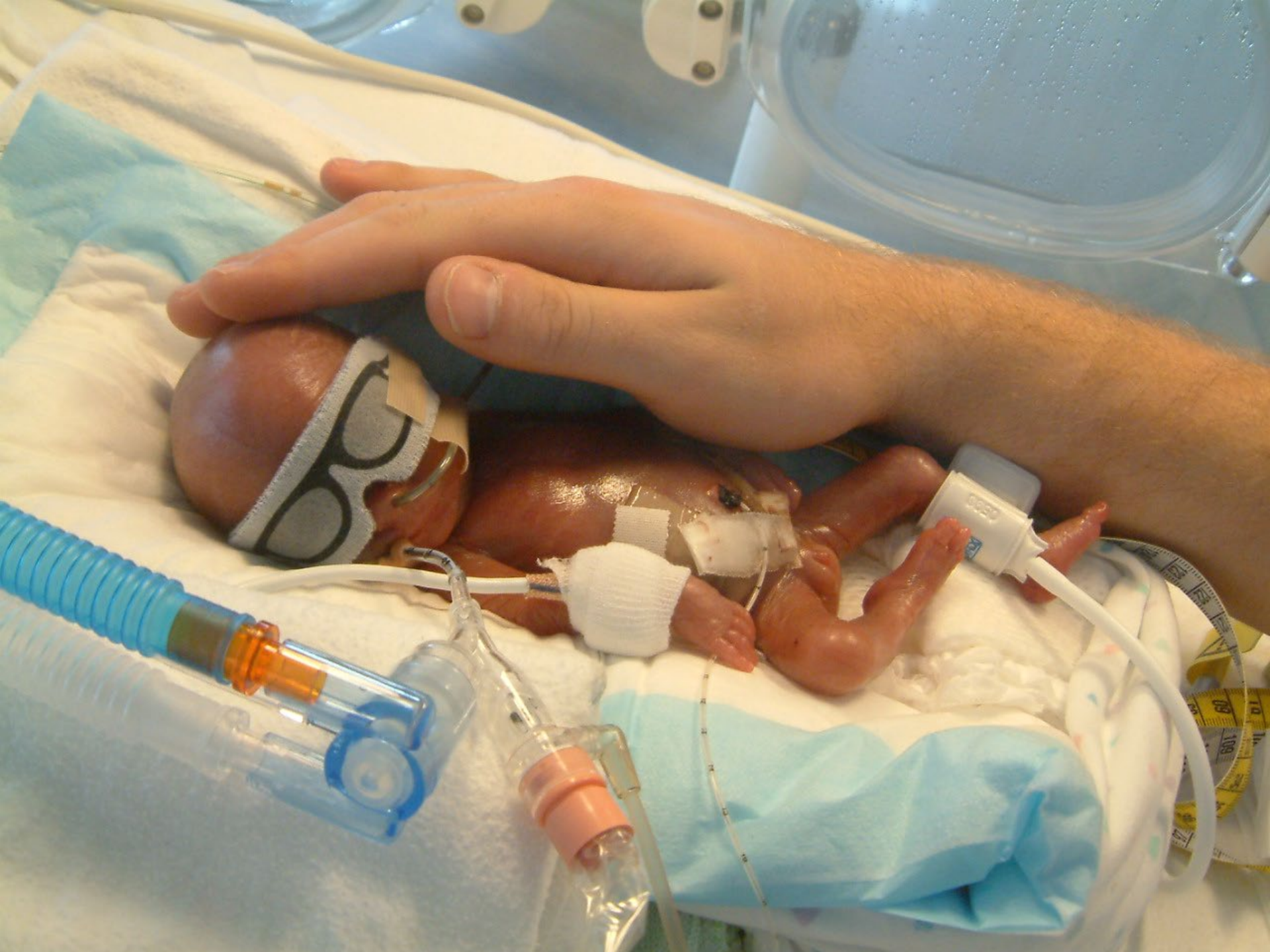
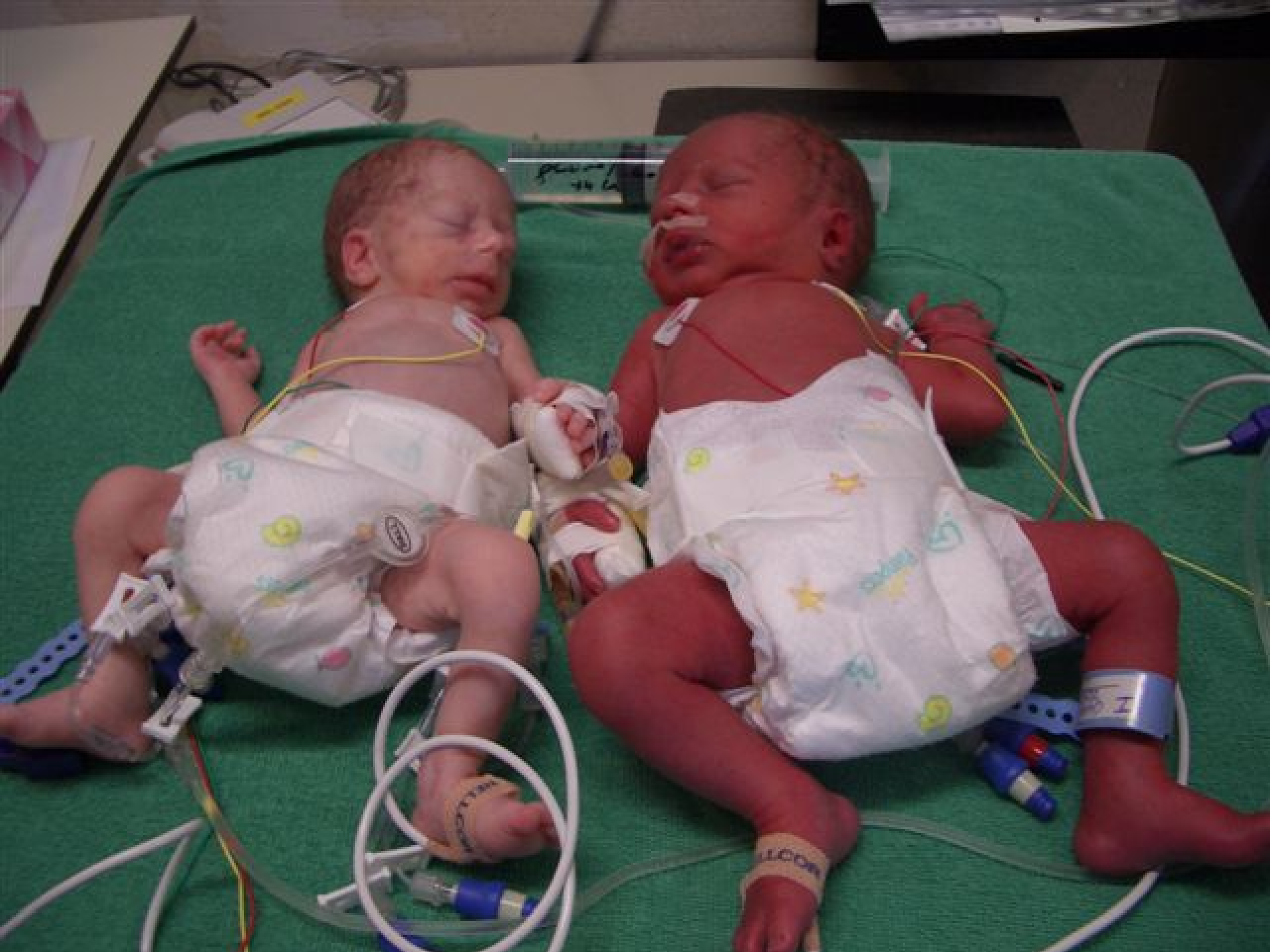
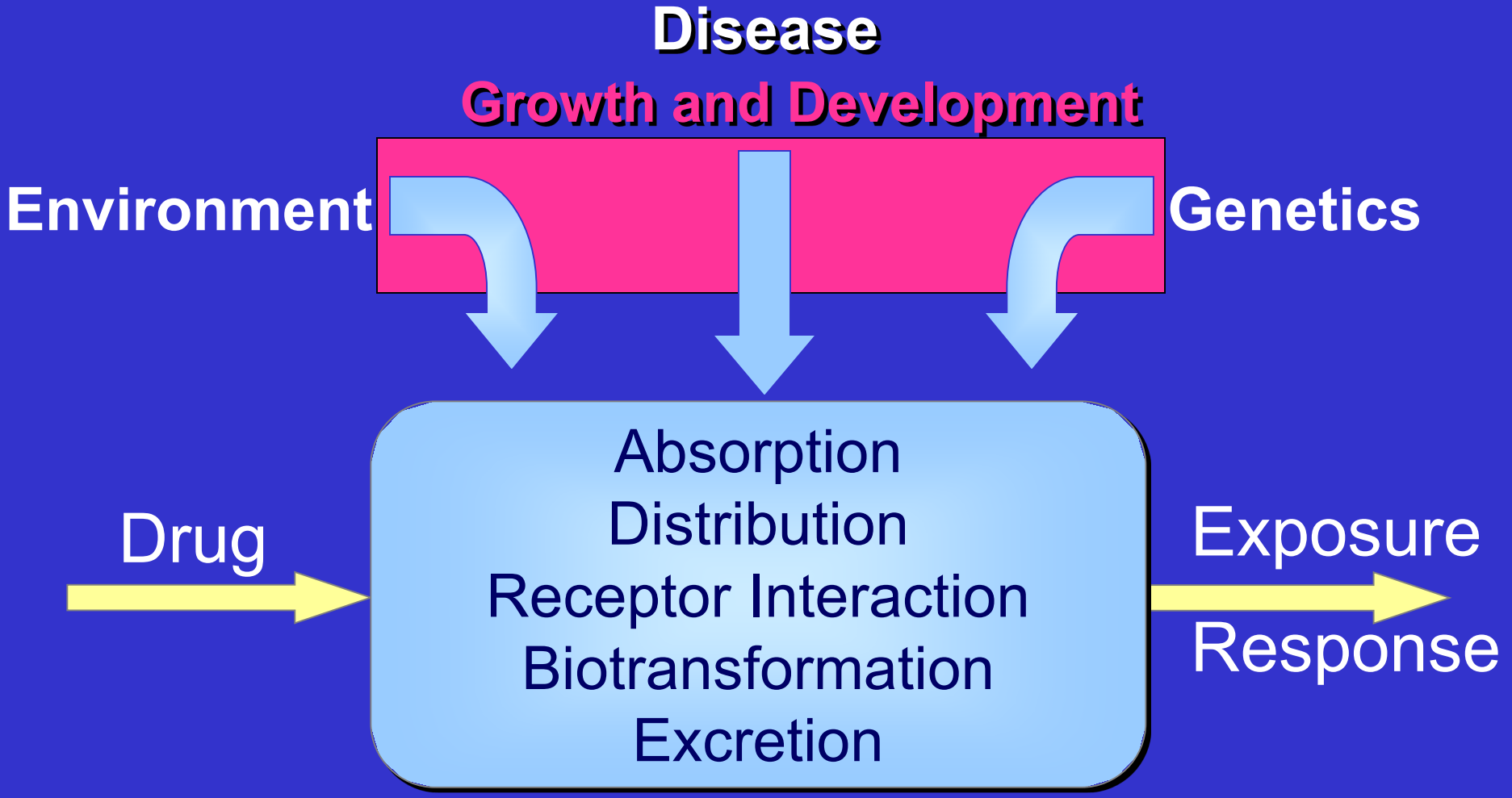
- Evan and Cindy Jones Endowed Chair in Pediatric Clinical Pharmacology & Chief, Division of Clinical Pharmacology, Children's National Hospital, Washington, DC, USA
- Eckenstein-Geigy Distinguished Professor of Pediatric Pharmacology, University Children's Hospital Basel, University of Basel, Switzerland





Determinants of Drug Response in Neonates



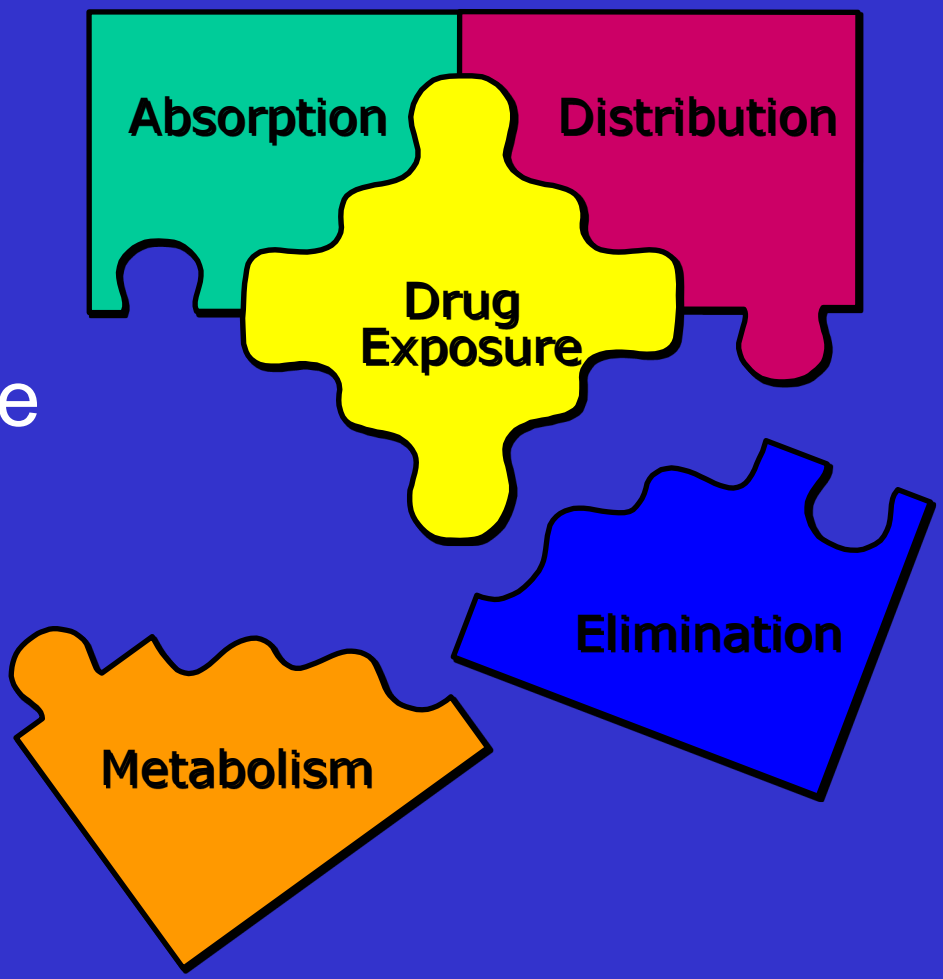
The Challenge of Neonatal Clinical Pharmacology: Determining the Source(s) of Variability

Ontogeny

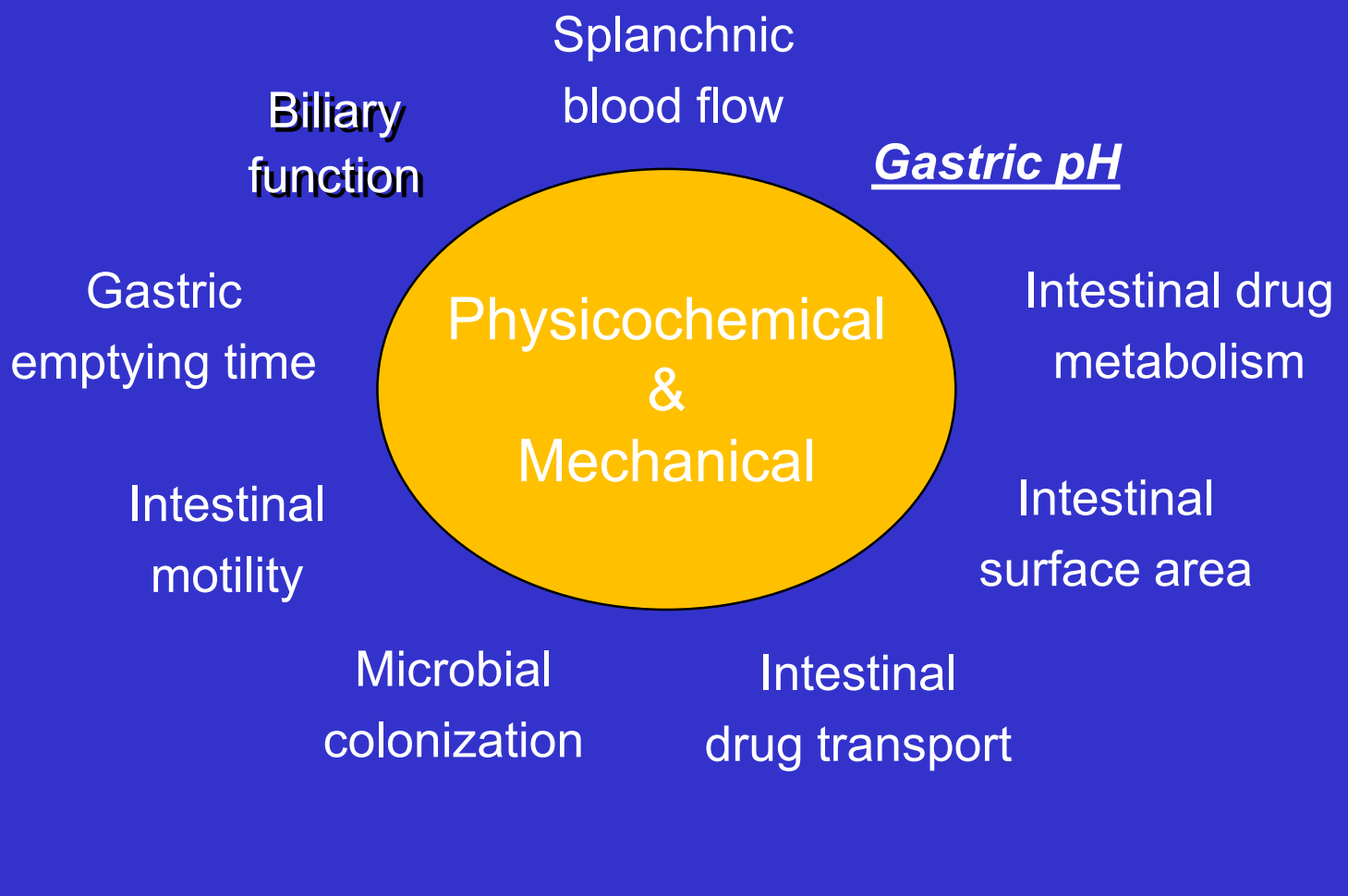
Pharmacogenetics

Critical Role of Pharmacokinetics in Pharmacotherapy……

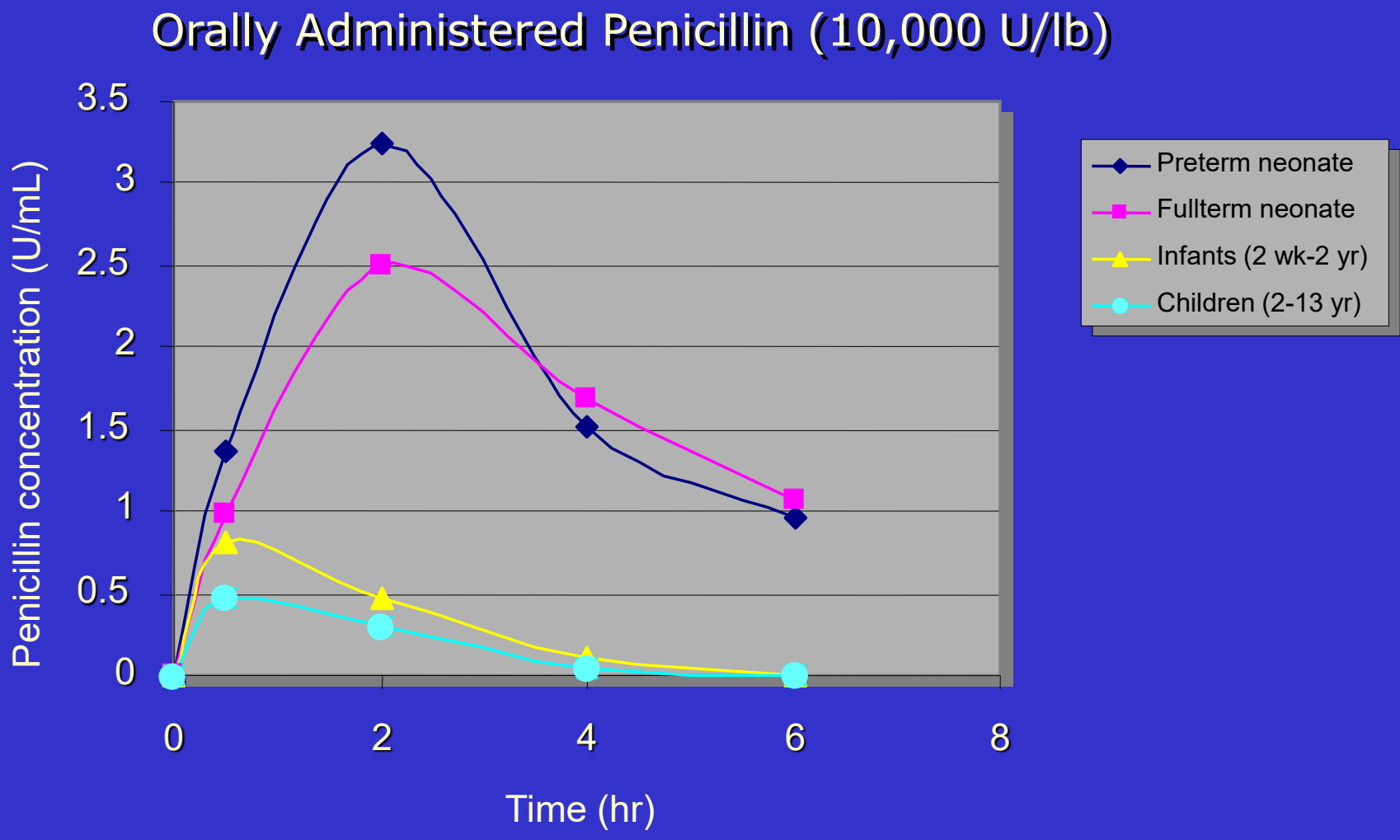
- The combination of ADME dictate exposure which dictates dose.



Factors Influencing Oral Drug Absorption



Developmental Alterations in Intestinal Drug Absorption Influence of Higher Gastric pH



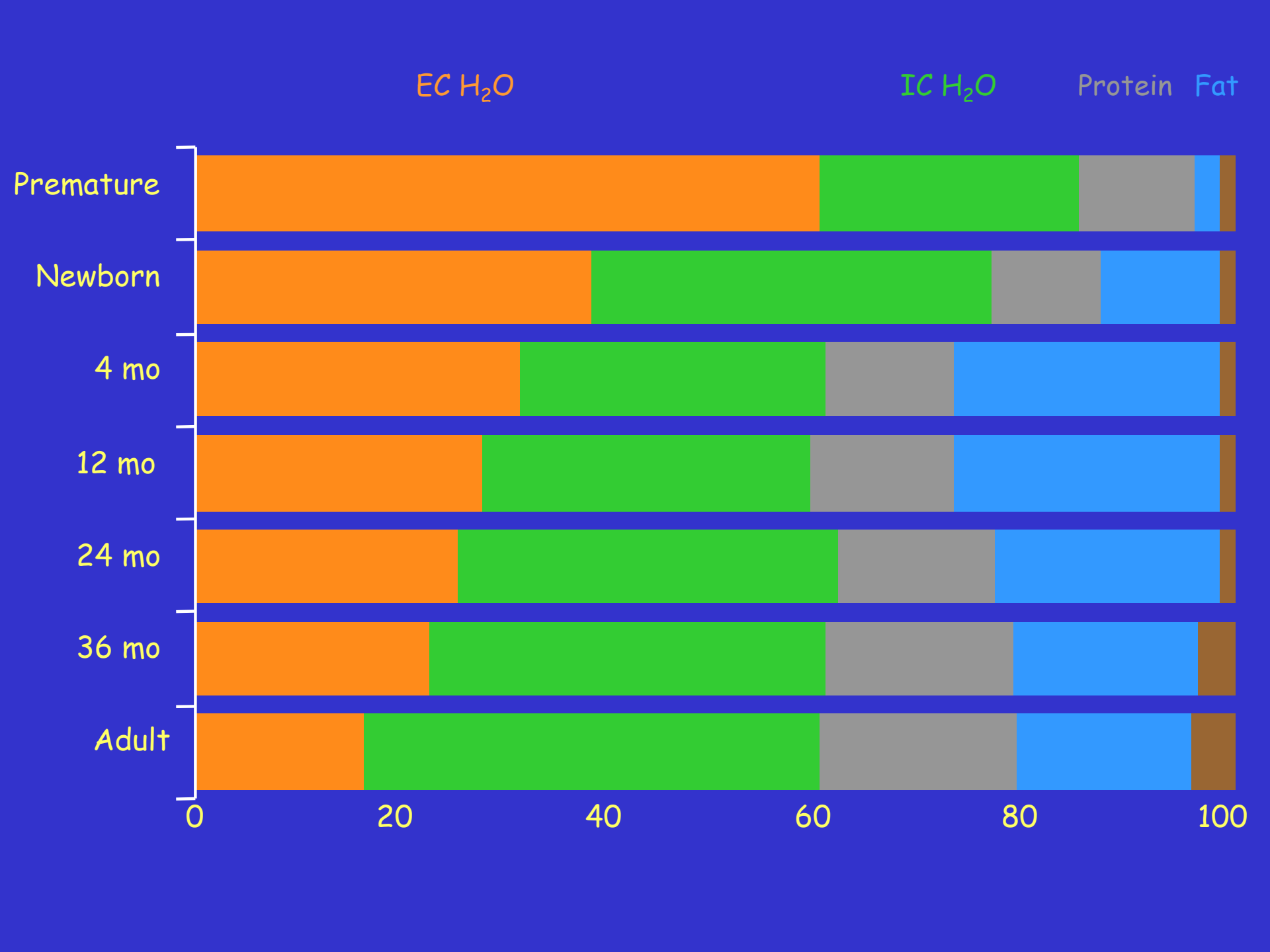
Huang et al. J Pediatr 1953;42:657

65 Years Later!!

No consensus about the ontogeny of gastric acid production (rate and amount) and secretion or on its impact on drug absorption in the preterm/full term infant and during infancy

Very limited understanding of the effect of age on the rate and extent of gastric emptying in the neonate and during early infancy

Van den Anker J et al. J Clin Pharmacol 2018;58(S10):S10-S25)


EC H_2O
IC H_2O
Protein
Fat
Premature
Newborn
4 mo
12 mo
24 mo
36 mo
Adult
0
20
40
60
80
100

Amikacin Administration in Neonates: Pharmacokinetic Variables

	Vd (L/kg)	Half - life (h)	Cl (ml/kg/h)
	mean ± 1 sd	mean ± 1 sd	mean ± 1 sd
<28 w	**0.700 ± 0.151**	12.20 ± 3.83	0.73 ± 0.148
28 - < 31 w	**0.660 ± 0.120**	8.40 ± 1.36	0.87 ± 0.127
31 - < 34 w	**0.614 ± 0.013**	7.71 ± 0.31	0.98 ± 0.025
34 - < 37 w	**0.573 ± 0.013**	6.77 ± 0.32	1.09 ± 0.061
37 - 41 w	**0.520 ± 0.021**	5.55 ± 0.49	1.15 ± 0.036

Langhendries et al, Med Mal Infect,1993;23:44

HARRIET LANE 2005 (2002): Gentamicin

PCA (wks)	PNA (days)	**Dose (mg/kg)**	Interval (hr)
< 29	0-7	**5 (2.5)**	48
	8-28	**4 (2.5)**	36
	> 28	**4 (3)**	24
30-33	0-7	**4.5 (3)**	36
	> 7	**4 (2.5)**	24
>34	0-7	**4 (2.5)**	24
	>7	**4 (2.5)**	18

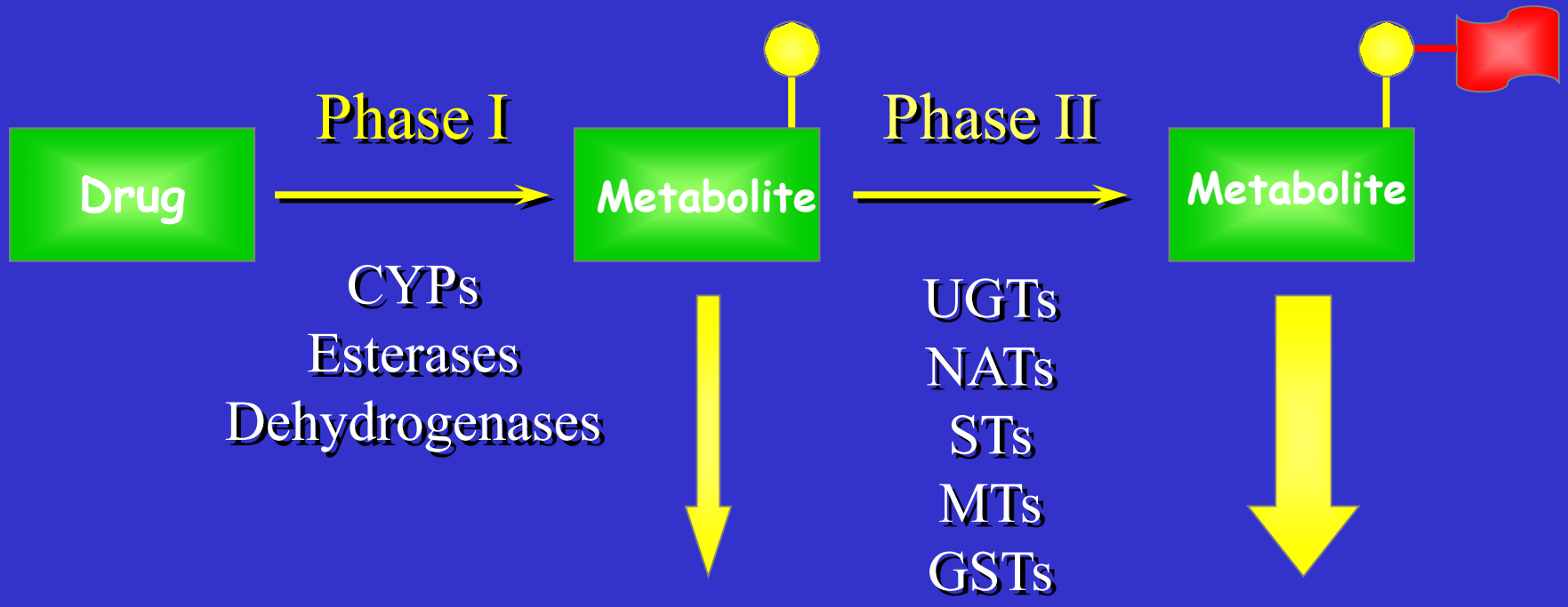
Quantitative Analysis of Gentamicin Exposure in Neonates and Infants Calls into Question Its Current Dosing Recommendations.

Current gentamicin neonatal guidelines (*4-5 mg/kg*) allow to achieve effective peak concentrations for MICs ≤ 0.5 mg/liter but not higher.

Model-based simulations indicate that to attain peak gentamicin concentrations of ≥10 mg/liter, a dose of *7.5 mg/kg* should be administered using an extended dosing interval regimen.

van Donge T et al. Antimicrob Agents Chemother. 2018 Mar 27;62(4).

Drug Biotransformation

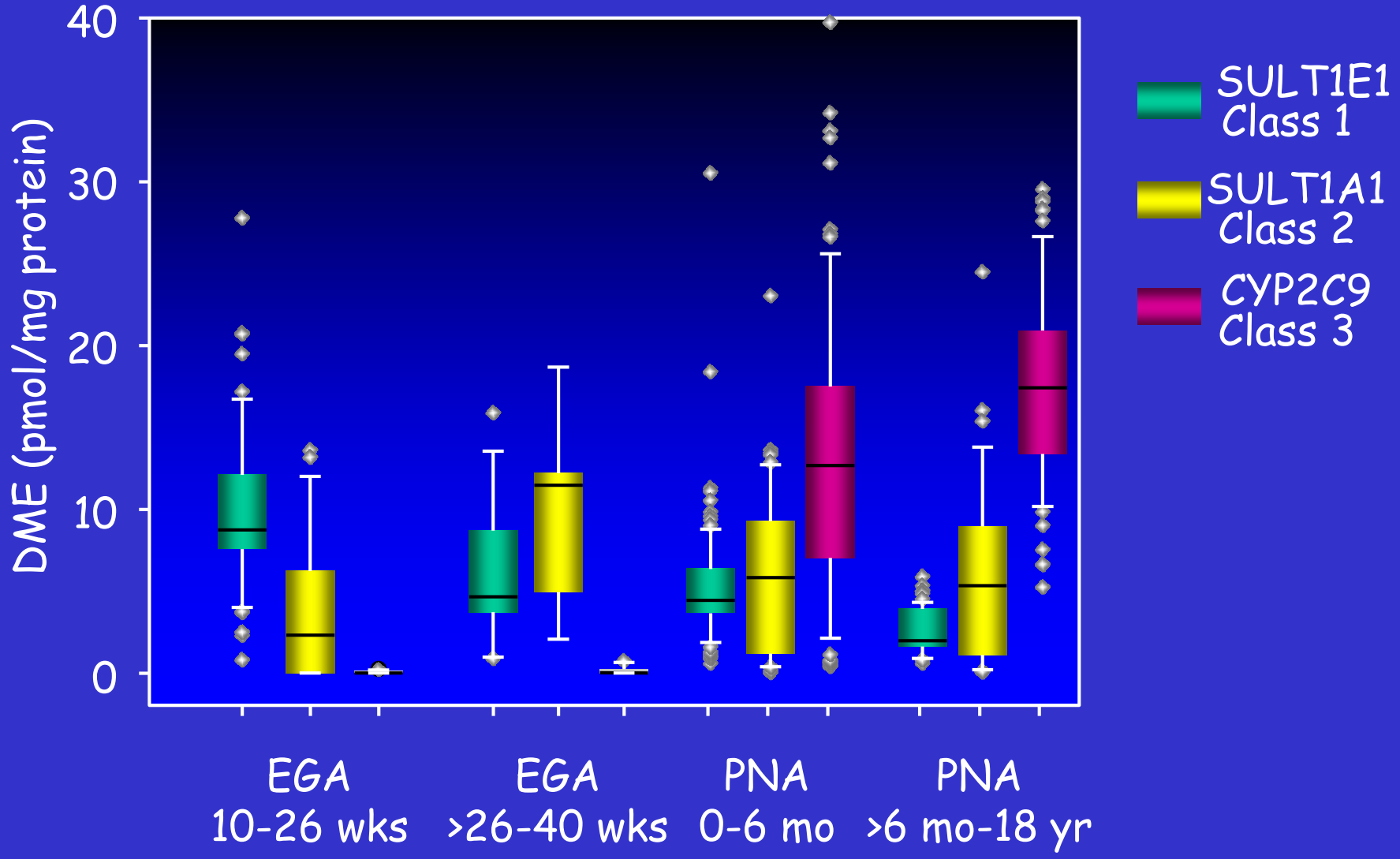


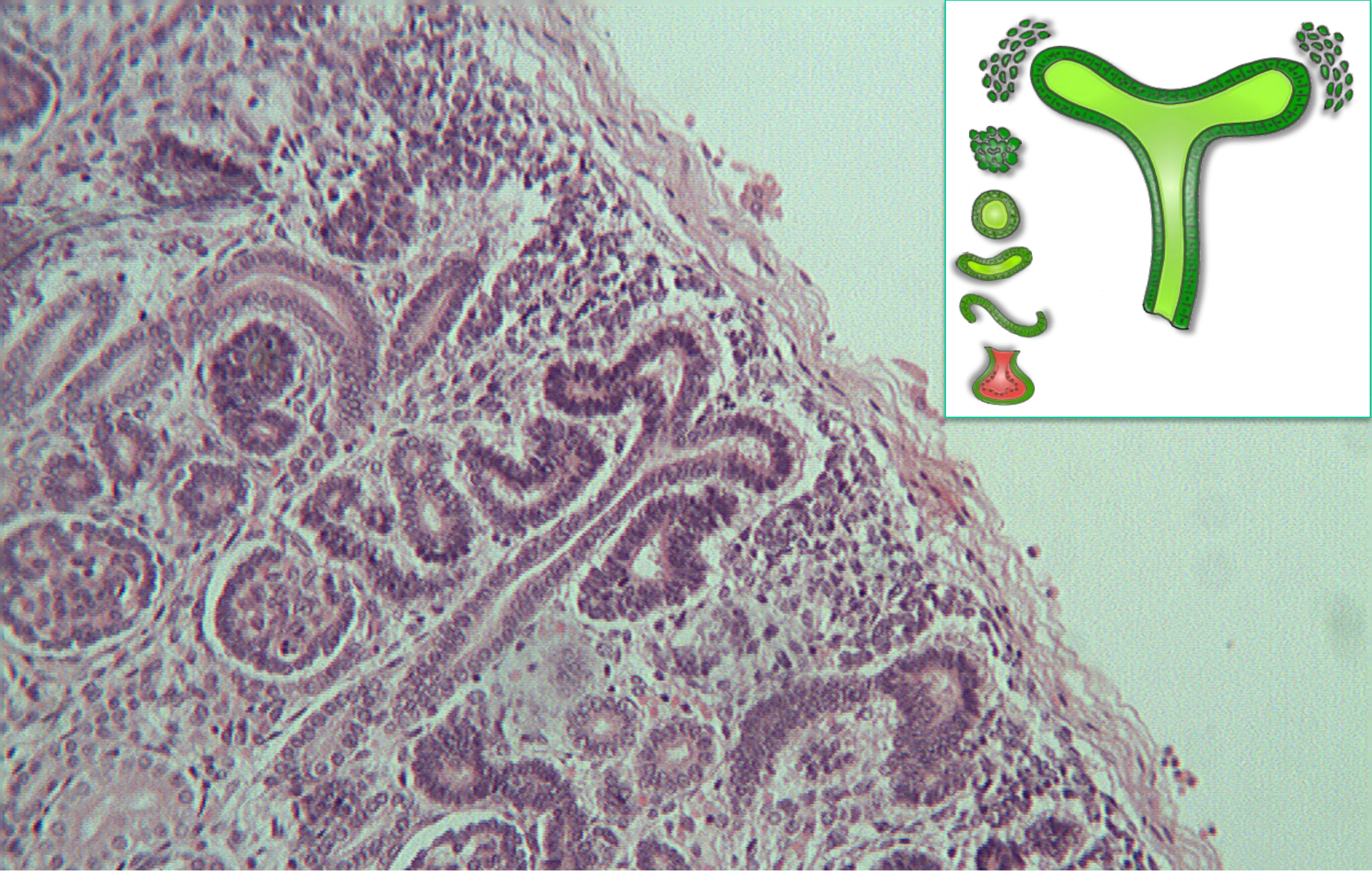
Human Hepatic DME Ontogeny

Class 1	Class 2	Class 3	
ADH1A	CYP2C19	ADH1B	EPHX2
CYP3A7	CYP3A5	ADH1C	FMO3
FMO1	GSTA1	AOX	GSTM
GSTP	GSTA2	CYP1A2	SULT2A1
SULT1E1	SULT1A1	CYP2C9	UGT1A1
SULT1A3		CYP2D6	UGT1A6
		CYP2E1	UGT2B7
		CYP3A4	PON1
		EPHX1	

Hines, Pharmacol & Therap. 2008;118:250-267

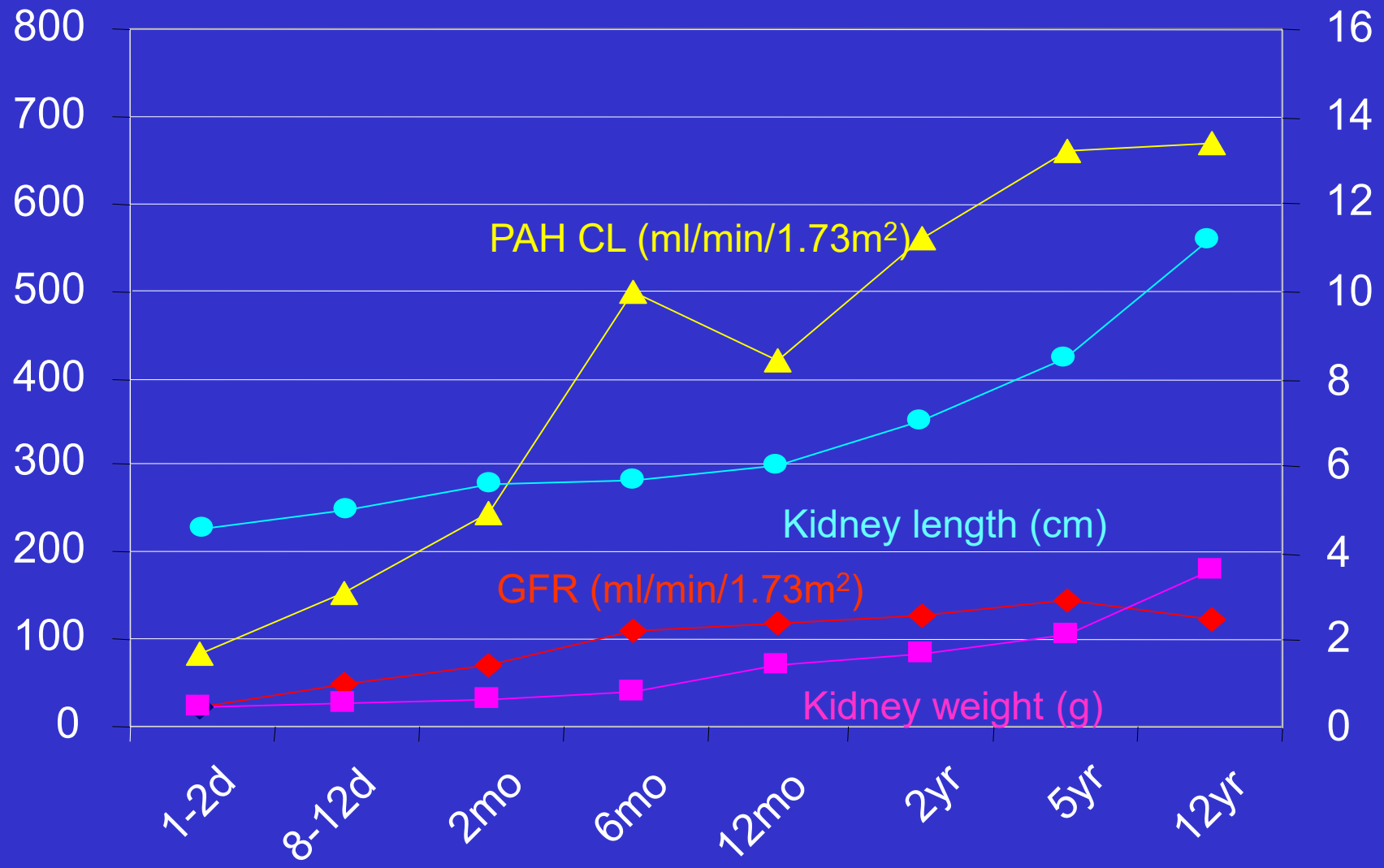
Human DME Ontogeny



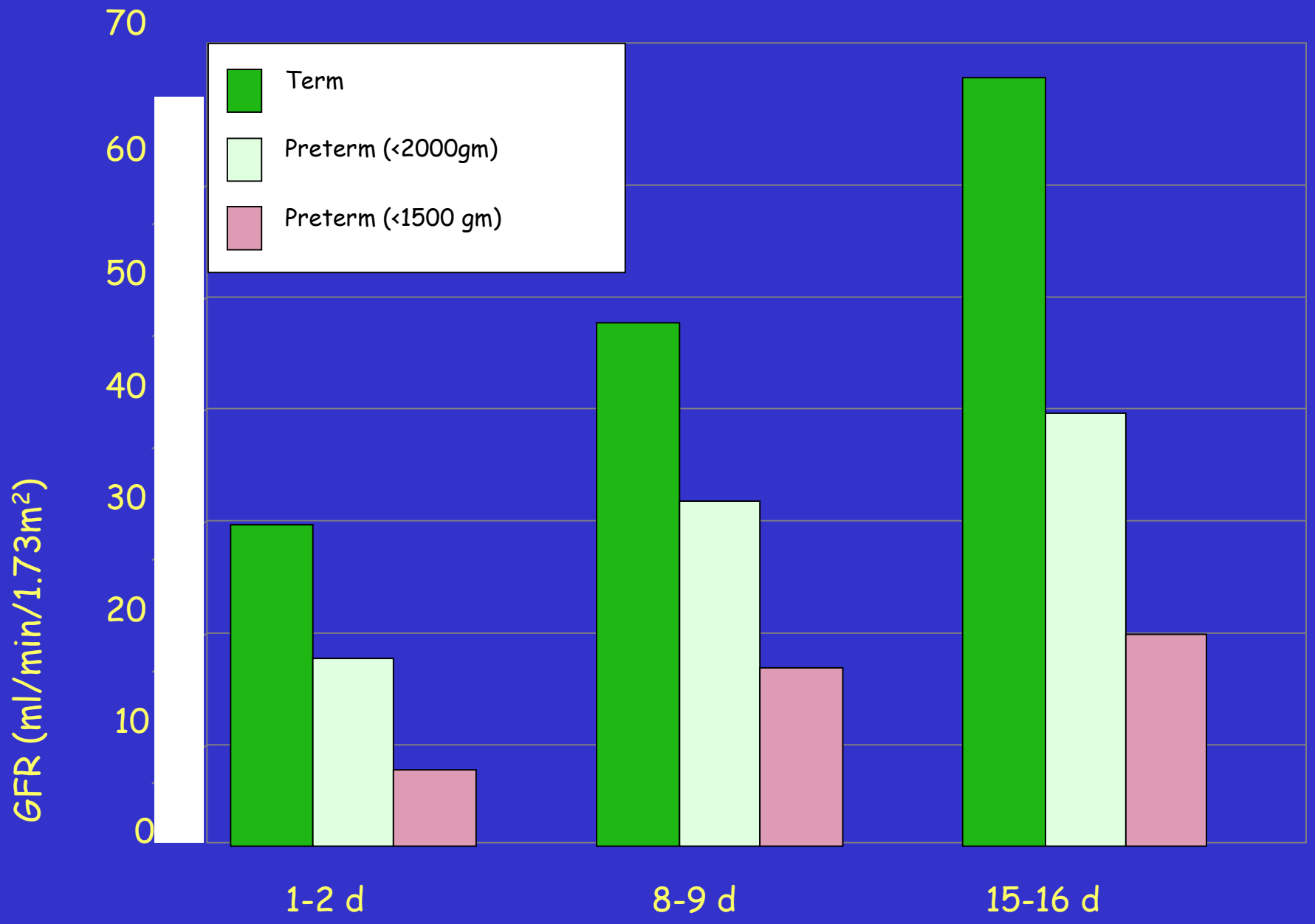


Active glomerulogenesis

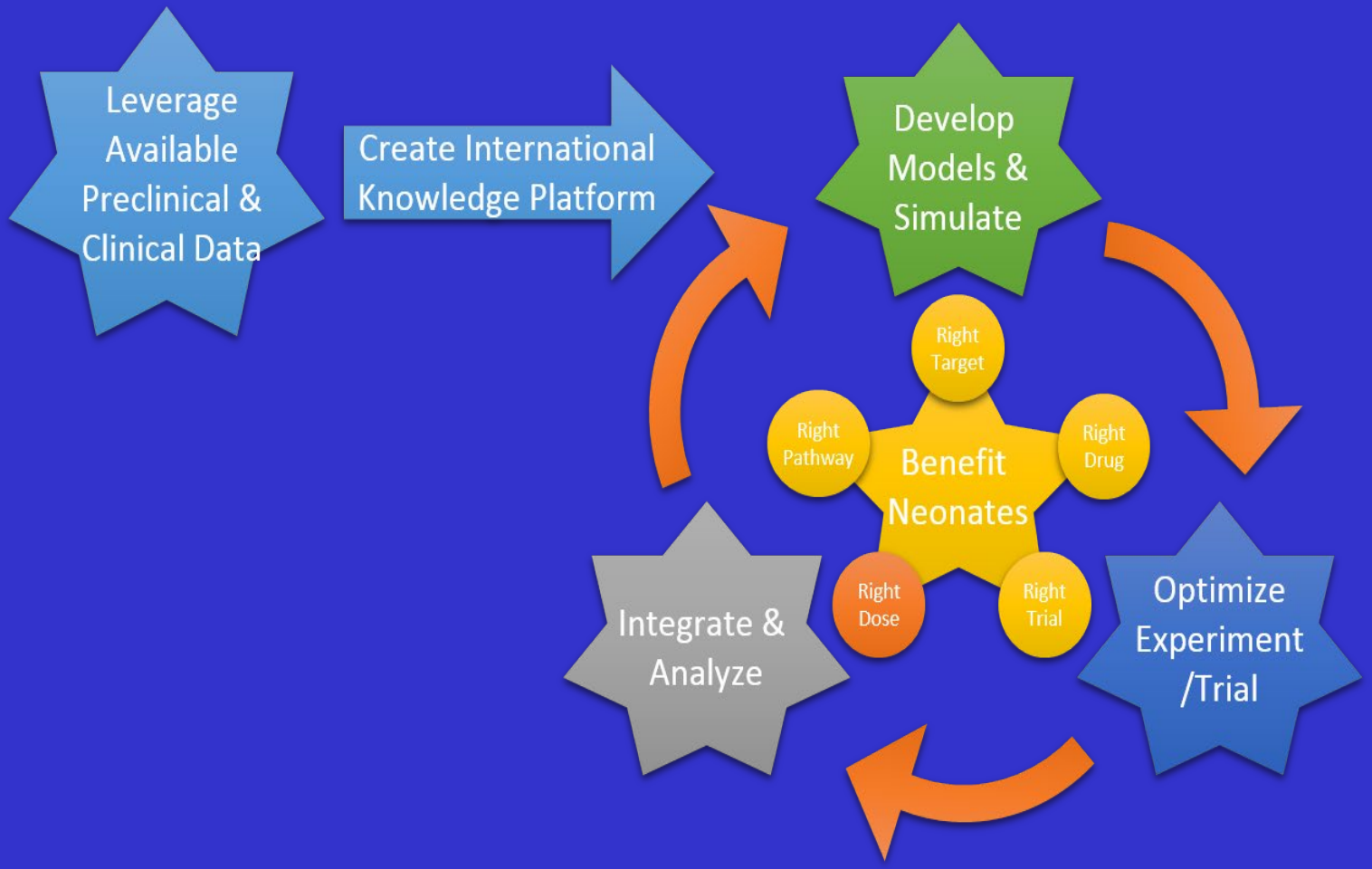
Maturation of Renal Function



John TR, Moore WM, Jeffries JE (eds.), Children are Different: Developmental Physiology,2nd edition, Ross Laboratories, 1978


70
60
50
40
30
20
10
0
GFR (ml/min/1.73m²)
Term
Preterm (<2000gm)
Preterm (<1500 gm)
1-2 d
8-9 d
15-16 d

Future Perspectives



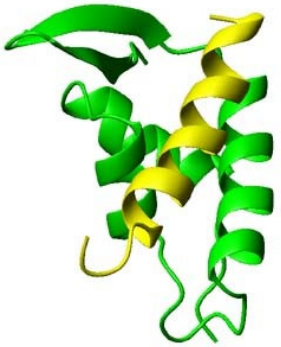
Allegaert K & van den Anker J. Clin Pharm Ther 2015 Sep;98(3):288-97

FDA & University of Maryland CERSI Workshop on Pediatric Dose Selection
October 22-23, 2020

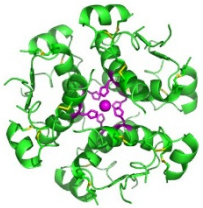
Biologicals Dosing in Pediatrics

Bernd Meibohm, PhD, FCP, FAAPS
Professor & Associate Dean for Research & Graduate Programs
College of Pharmacy
The University of Tennessee Health Science Center
Memphis, TN, USA

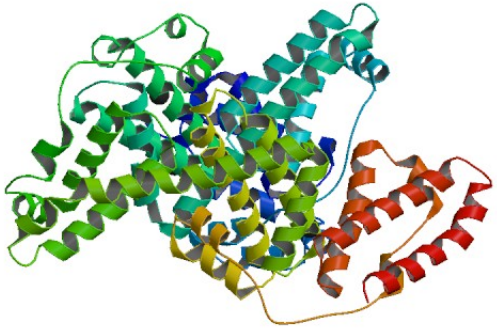
Therapeutic Proteins



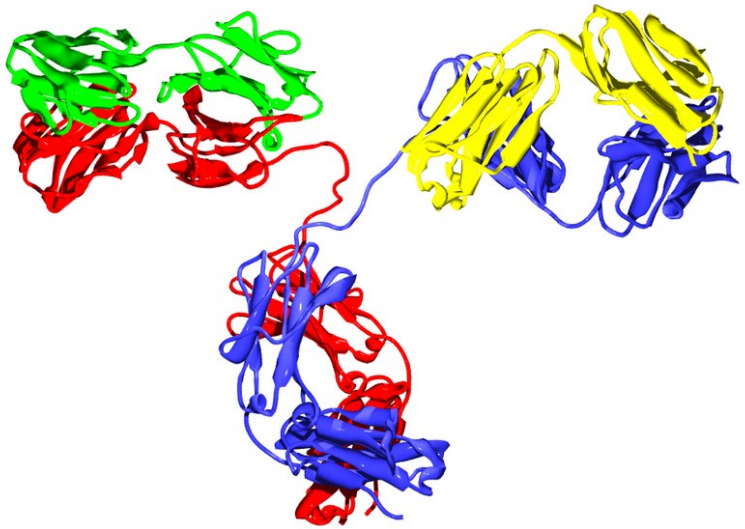
Structural Diversity



Insulin
MW ~5.8 kDa
51 AA

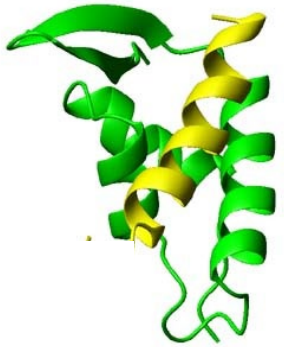


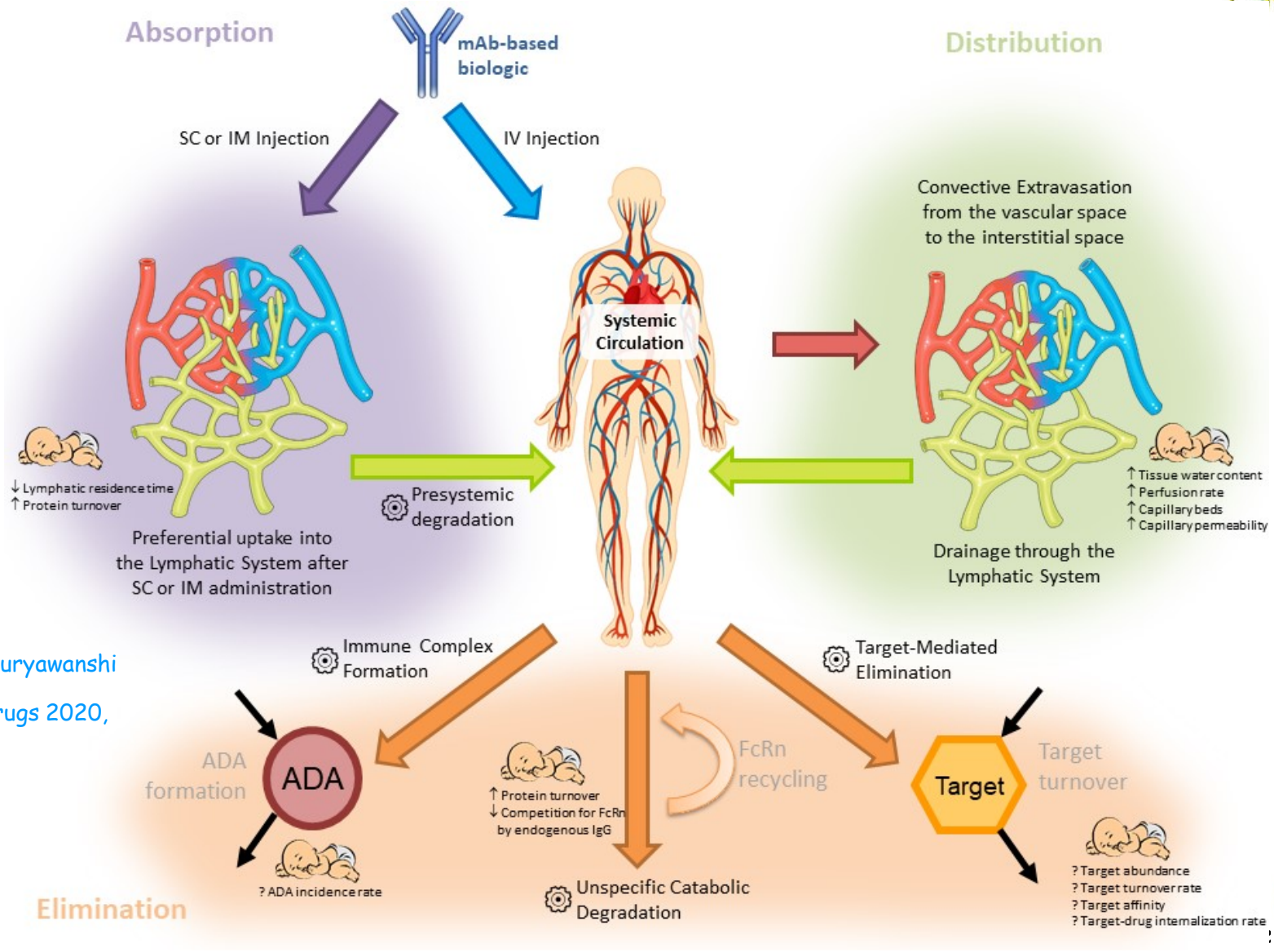
Albumin
MW ~66.5 kDa
583 AA



IgG
MW ~150 kDa
~1,300 AA

PK of Therapeutic Proteins in Pediatrics





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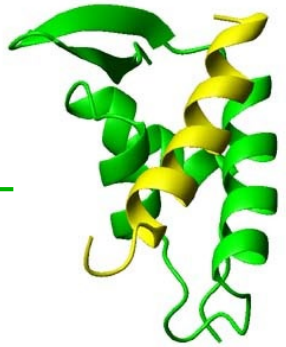
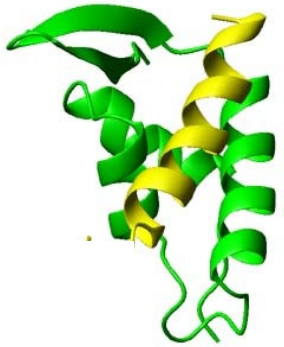
Absorption of Therapeutic Proteins

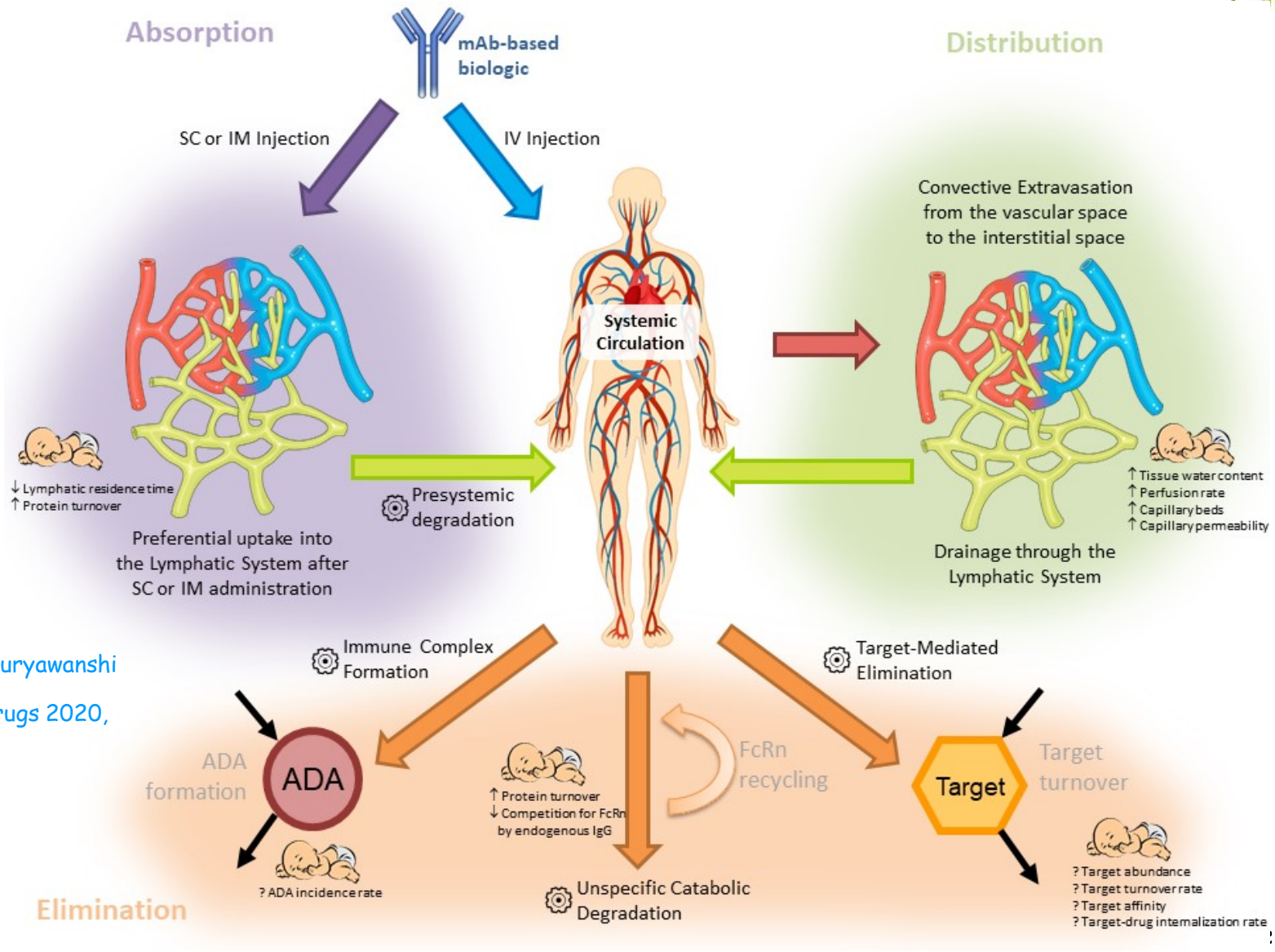


In Pediatrics

- Route of administration
  - ✓ Older pediatric patients: Similar preference for SC over IV and IM
  - ✓ Younger pediatric patients: IM and IV often preferred
    - Ease of injection to the muscles (vastus lateralis) of the thigh
- Increased rate of absorption expected after SC or IM administration in young children:
  - ✓ Increased extracellular fluid volume
  - ✓ Higher perfusion rates (assumed to be equally affected for plasma and lymph [~0.2% of plasma flow rate])
- Palivizumab IM administration:
  - ✓ 3 times faster absorption rate in children
  - ✓ No difference in extent of absorption (bioavailability)
    - Potentially increased extent of absorption counter-balanced by an increased endosomal protein turnover in children

PK of Therapeutic Proteins in Pediatrics





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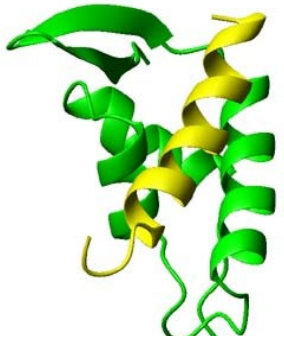
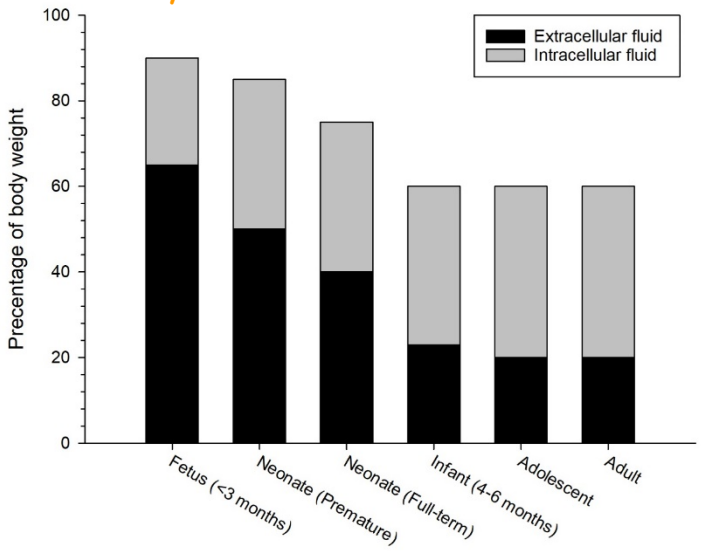
Distribution of Therapeutic Proteins



In Pediatrics

- Well-known differences in tissue water content of newborns and infants relative to older children and adults
  - ✓ Fraction of total body volume available for distribution expected to be higher in children for hydrophilic macromolecules such as mAbs
- Capillaries in infants
  - ✓ Larger capillary beds and thus a larger capillary surface area per tissue volume
  - ✓ Larger proportion of 'leaky' organs and tissues (liver, kidneys, spleen) relative to body size

Body Water Distribution in Children



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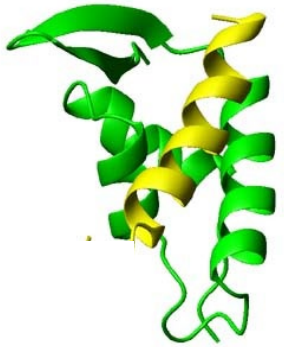
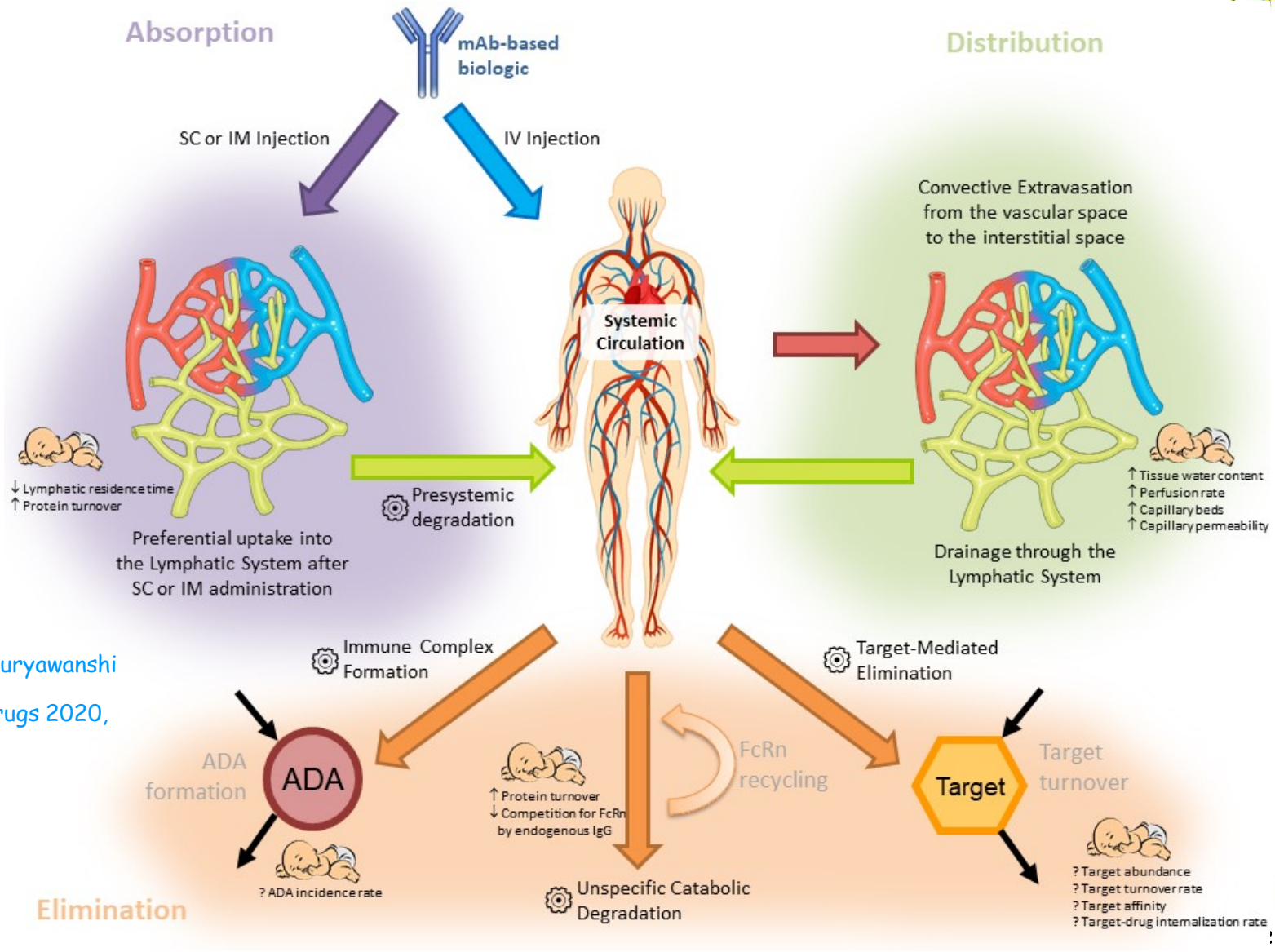
- Taken together, extravasation is expected to be faster and concentration differences between vascular and extravascular drug concentrations lower in newborns and infants compared to older children and adults

PK of Therapeutic Proteins in Pediatrics





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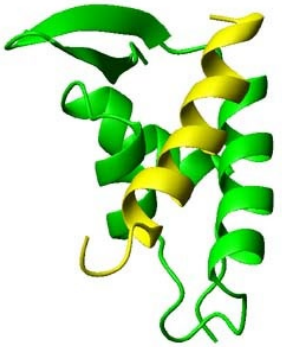
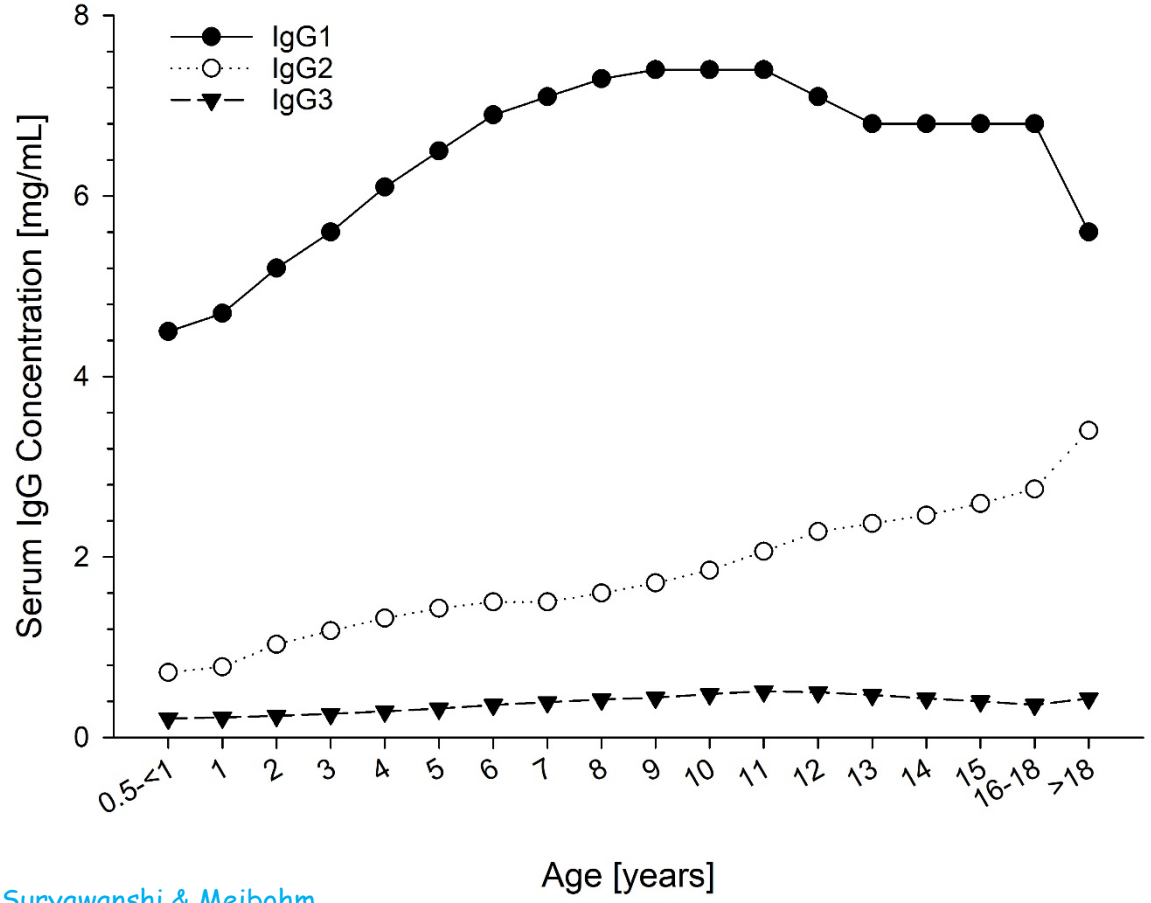
FcRn and IgG Elimination



Endogenous Immunoglobulin in Children



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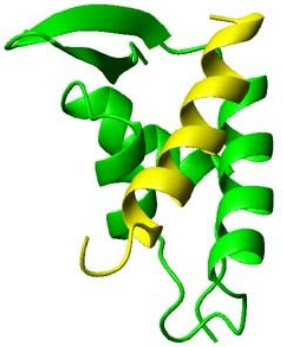
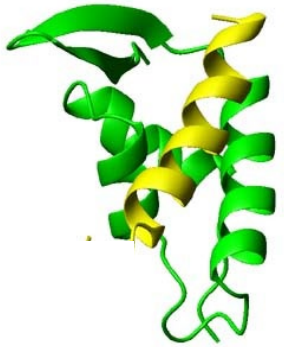
Elimination of Therapeutic Proteins

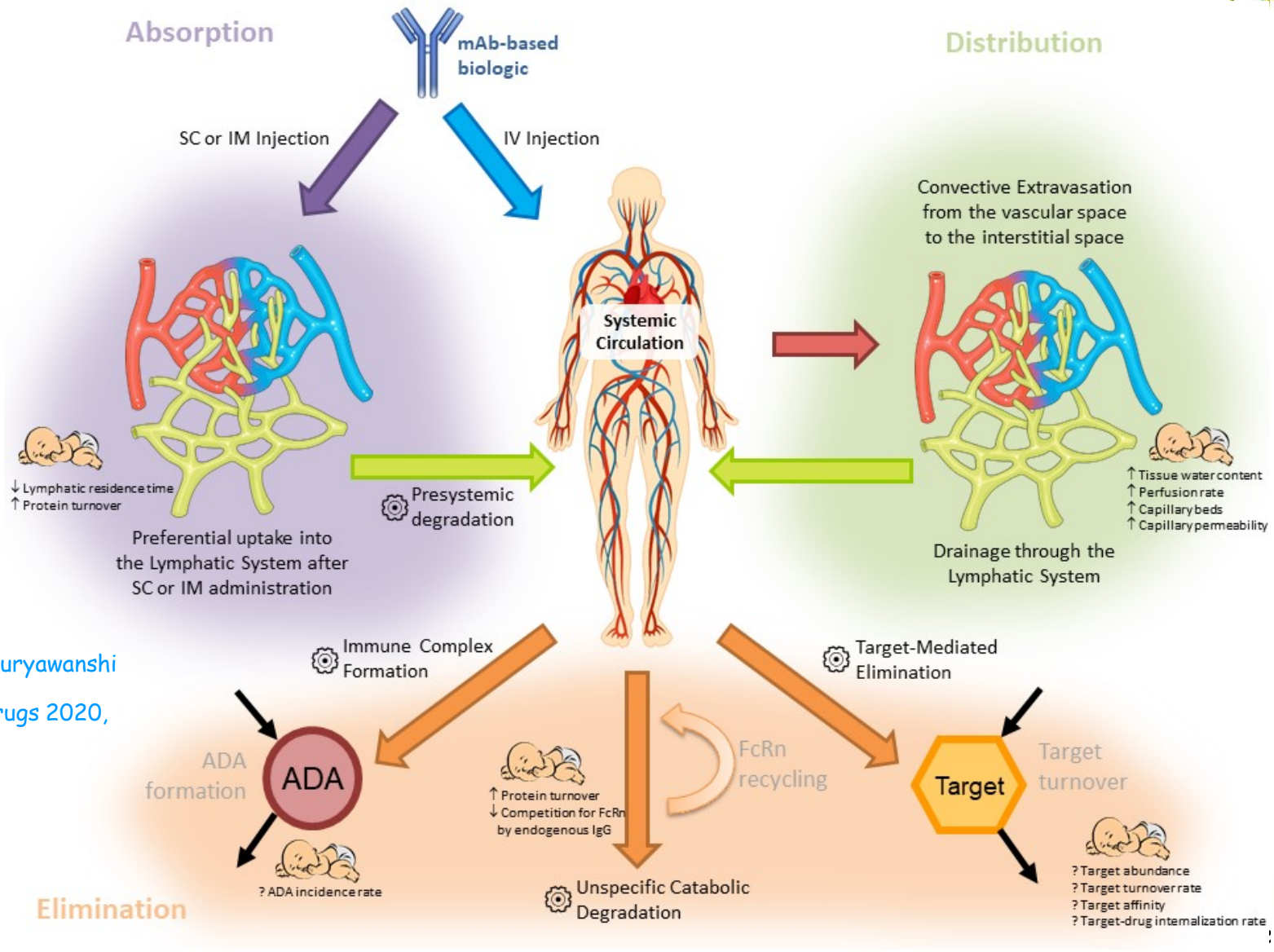


In Pediatrics

- Lysosomal protein turnover and efficiency of FcRn recycling could be potential mechanisms for elimination differences between children and adults after correction for body size differences
  - ✓ Since children, including infants, are able to maintain the homeostasis of immunoglobulins, they are assumed to eliminate therapeutic proteins, especially mAbs, through the same endosomal clearance pathway
    - Based on preliminary results, expression of FcRn is likely not substantially different between children and adults
  - ✓ Infants have substantially lower reference values for endogenous IgG subclasses compared to older children and adults once residual maternal IgG has been lost
    - Less competing endogenous IgG present: more efficient FcRn recycling and thus a reduced clearance of mAbs expected
  - ✓ Protein turnover (i.e. catabolism in general): substantially higher in young pediatric patients compared to adults
    - For low-birth-weight infants, protein metabolism has been described as 2-3 times faster than in adults when normalized for kg of body weight ➔ Increased clearance
- Whether age effects related to elimination cancel out, or actually achieve clinically detectable differences in elimination of therapeutic proteins remains to be determined in future studies

PK of Therapeutic Proteins in Pediatrics





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Pediatric Dosing of Therapeutic Proteins

General Considerations

- Dosing regimens for therapeutic proteins in pediatric patients need to take into account differences between children and adults with regard to
  - ✓ Target exposure range
  - ✓ Size differences
  - ✓ Ontogeny of absorption & disposition processes relevant for TPs
- Pediatric dosing as compromise between precision medicine and practicability
  - ✓ Balance between sufficient granularity to account for size- and age-related differences and limited clinical complexity to avoid overburdening healthcare providers and avoid medication errors.
  - ✓ High tolerability (often no defined MTD) and very limited off target toxicity may allow for less precise dose selection for many TPs in the individual patient
  - ✓ Lack of biomarkers indicative of drug disposition processes
    - o Small molecules: E.g. creatinine clearance as indicators of renal function
    - o Therapeutic proteins: Albumin as indicator of protein turnover(?)

Pediatric Dosing of Therapeutic Proteins

Dosing Approaches (I)

1. Flat dosing
   - ✓ Results in high exposure difference
   - ✓ Only acceptable for TPs with flat exposure-response relationship
     - Example: Avelumab: 800 mg IV every 2 weeks for adults and children ≥12 years
2. Body weight (BW)-based dosing
   - ✓ Not optimal based on the common nonlinearity between TP CL and BW
     - Example: Infliximab: 5 mg/kg at week 0, 2, and 6, then every 8 weeks
   - ✓ BSA rarely used, likely because of the complexity and inaccuracy of estimating BSA based on height and BW.
3. Allometrically adjusted dosing
   - ✓ Based on theoretical consideration that TP CL and Vd are related to BW with allometric exponents of 0.75 and 1, respectively.
   - ✓ While addressing nonlinearity in the relationship between CL and BW, not practical in clinical practice.
     - No examples

Pediatric Dosing of Therapeutic Proteins

Dosing Approaches (II)

4. Tiered-fixed dosing
   - ✓ One or several BW or age-defined patient strata that receive different flat doses.
   - ✓ Highly attractive due to simplicity of implementation
     - Example: Adalimumab: BW 10 - <15 kg (and ≥ 2 yr): 10 mg SC EOW
BW 15 - <30 kg (and ≥ 2 yr): 20 mg SC EOW
BW ≥30 kg (and ≥ 2 yr): 40 mg SC EOW

5. Tiered body-weight based dosing
   - ✓ One or several BW or age-defined patient strata that receive different BW-based doses.
   - ✓ Granular dose individualization
     - Example: Tocilizumab: BW <30 kg (and ≥ 2 yr): 12 mg/kg IV every 4 wk
BW ≥30 kg (and ≥ 2 yr): 8 mg/kg IV every 4 wk

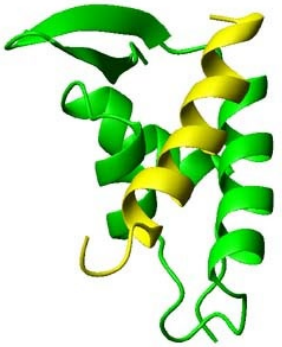
Pediatric Dosing of Therapeutic Proteins

Dosing Approaches (III)

6. Hybrid dosing
   - ✓ Combining tiered fixed dosing and tiered body weight based dosing
   - ✓ Attractive for TPs that use flat dosing in the adult population, but require dose adjustments below a certain age range
     - Example: Etanercept: BW <63 kg (and ≥ 2 yr): 0.8 mg/kg SC weekly
BW ≥63 kg: 50 mg SC weekly

7. Pharmacodynamic endpoint-based dosing
   - ✓ Useful if target-mediated drug disposition affects disposition and the target is easily quantifiable
     - Example: Omalizumab: SC dosing every 2 or 4 weeks based on weight strata and pretreatment serum IgE levels according to dosing table; Separate dosing tables for ages 6-<12 years and ≥12 years

Take Home Messages



- Therapeutic proteins use different drug disposition and elimination pathways compared to small molecules
  - For many therapeutic proteins, there is only limited knowledge on which elimination pathways contribute to their disposition and to what extent
  - For most known elimination pathways for therapeutic proteins, ontogeny information in pediatric patients is emerging but limited
- Due to the limited understanding of the molecular and physiologic processes relevant for drug disposition and their ontogeny, approaches used in pediatric extrapolation such as PBPK modeling remains challenging with oftentimes substantial uncertainties for therapeutic proteins at the current time
- Numerous approaches are used in pediatric dosing of therapeutic proteins that strike a balance between individualization and complexity in clinical use