When does exposure matching require additional consideration?

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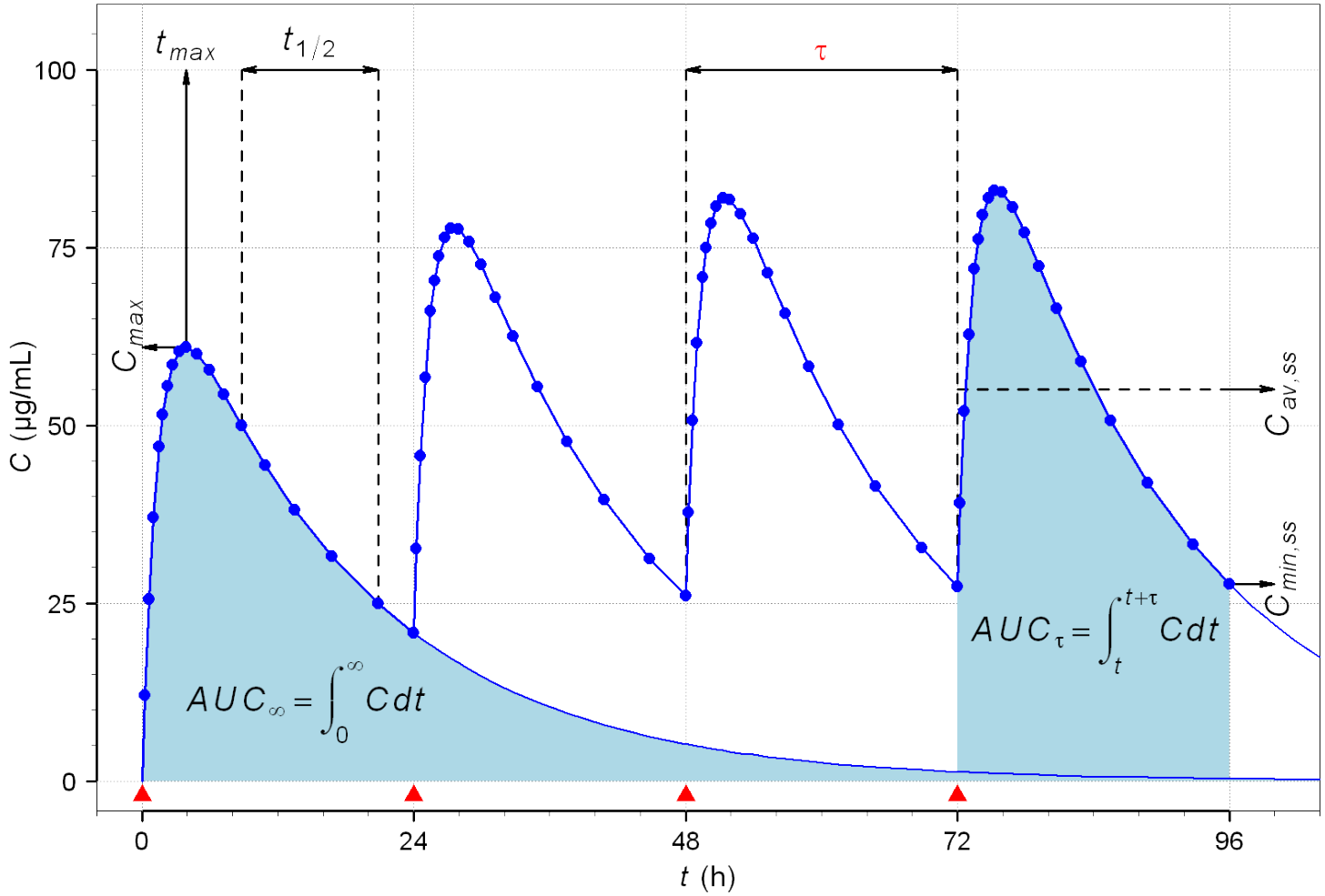
Exposure Matching Framework

- Assumptions regarding the suitability and/or appropriateness of exposure matching:
  - Similar disease process
  - Exposure is a reasonable surrogate for drug actions
  - The “target” is the same or similar in pediatrics vs adults
- Metrics for comparison
  - Choice criterion?
  - Is there a decision tree that makes sense?
  - Are there some settings that are not easily addressed?

Exposure Matching Metrics - Choices



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Exposure Matching Metrics - Choices

Characteristic	Description	Example value	Symbol	Formula
Dose	Amount of drug administered.	500 mg	D	Design parameter
Dosing interval	Time between drug dose administrations.	24 h	τ	Design parameter
C_{max}	The peak plasma concentration of a drug after administration.	60.9 mg/L	$C_{\max}$	Direct measurement
t_{max}	Time to reach C_{max}.	3.9 h	$t_{\max}$	Direct measurement
C_{min}	The lowest (trough) concentration that a drug reaches before the next dose is administered.	27.7 mg/L	$C_{\min,ss}$	Direct measurement
Volume of distribution	The apparent volume in which a drug is distributed (i.e., the parameter relating drug concentration to drug amount in the body).	6.0 L	V_d	$= \frac{D}{C_0}$
Concentration	Amount of drug in a given volume of plasma.	83.3 mg/L	C_0, C_{ss}	$= \frac{D}{V_d}$
Elimination half-life	The time required for the concentration of the drug to reach half of its original value.	12 h	$t_{\frac{1}{2}}$	$= \frac{ln(2)}{k_e}$
Elimination rate constant	The rate at which a drug is removed from the body.	0.0578 h^{-1}	k_e	$= \frac{ln(2)}{t_{\frac{1}{2}}} = \frac{CL}{V_d}$
Infusion rate	Rate of infusion required to balance elimination.	50 mg/h	k_{in}	$= C_{ss} \cdot CL$
Area under the curve	The integral of the concentration-time curve (after a single dose or in steady state).	1,320 mg/L·h	$AUC_{0-\infty}$	$= \int_0^\infty C \, dt$
			$AUC_{\tau,ss}$	$= \int_t^{t+\tau} C \, dt$
Clearance	The volume of plasma cleared of the drug per unit time.	0.38 L/h	CL	$= V_d \cdot k_e = \frac{D}{AUC}$
Bioavailability	The systemically available fraction of a drug.	0.8	f	$= \frac{AUC_{po} \cdot D_{iv}}{AUC_{iv} \cdot D_{po}}$
Fluctuation	Peak trough fluctuation within one dosing interval at steady state	41.8 %	$\%PTF$	$= \frac{C_{max,ss} - C_{min,ss}}{C_{av,ss}} \cdot 100$ where $C_{av,ss} = \frac{1}{\tau} AUC_{\tau,ss}$

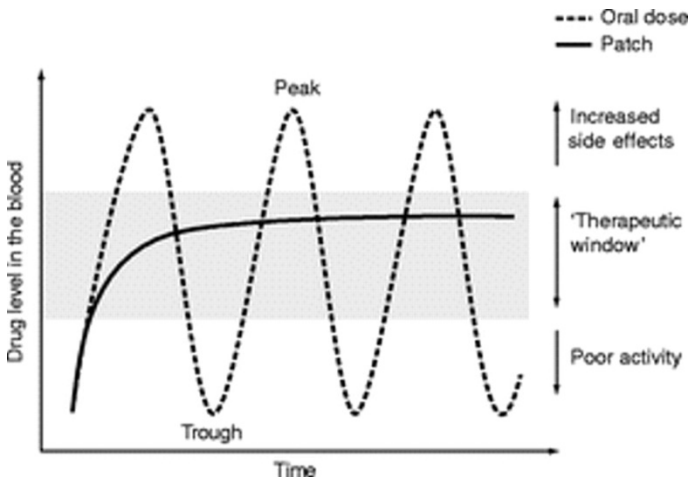
- Alignment of metric with drug attributes (exposure of relevance)?
- Which of these are more (or less) vulnerable to age or developmental effects?
- Multiple criteria? Ranking?
- Are there default metrics of choice?

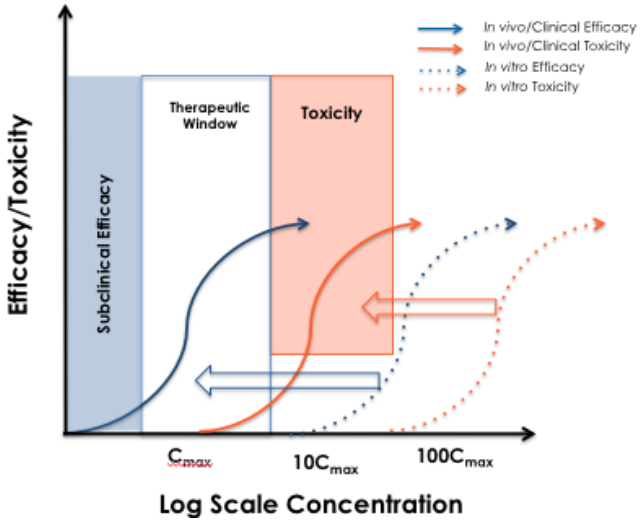
http://upload.wikimedia.org/wikipedia/commons/e/ee/Linear_PK_Example.png

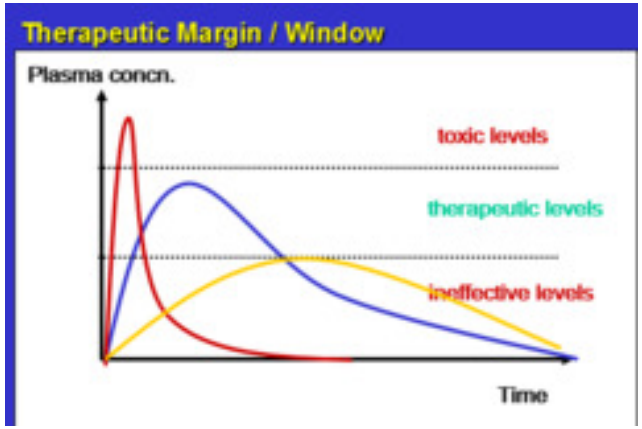
Exposure Matching Metrics – What's relevant?

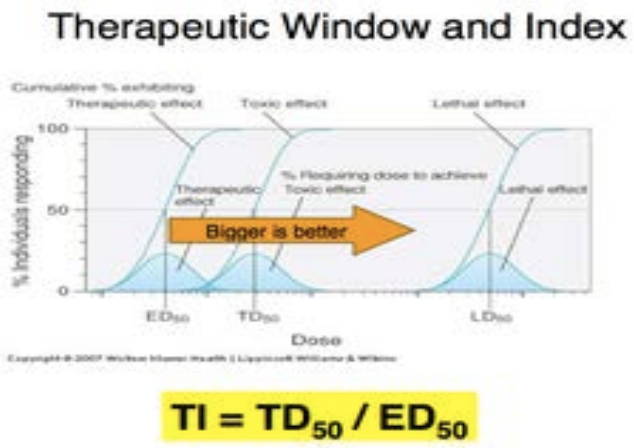
- Assignment of the appropriate metric(s) to attributes of the therapeutic window:
  - Drug/disease dependence
  - Mechanistic plausibility
  - Time dependency considerations
  - Route / formulation considerations
  - Biomarker / PD relationships
- Bridging strategies and interpretation
  - Value of the healthy volunteer BE trial?
  - Portability of lifestyle effects known to impact PK (e.g. food effects, time of dosing considerations)

Conceptual misconceptions about the therapeutic window – translation to pediatrics?

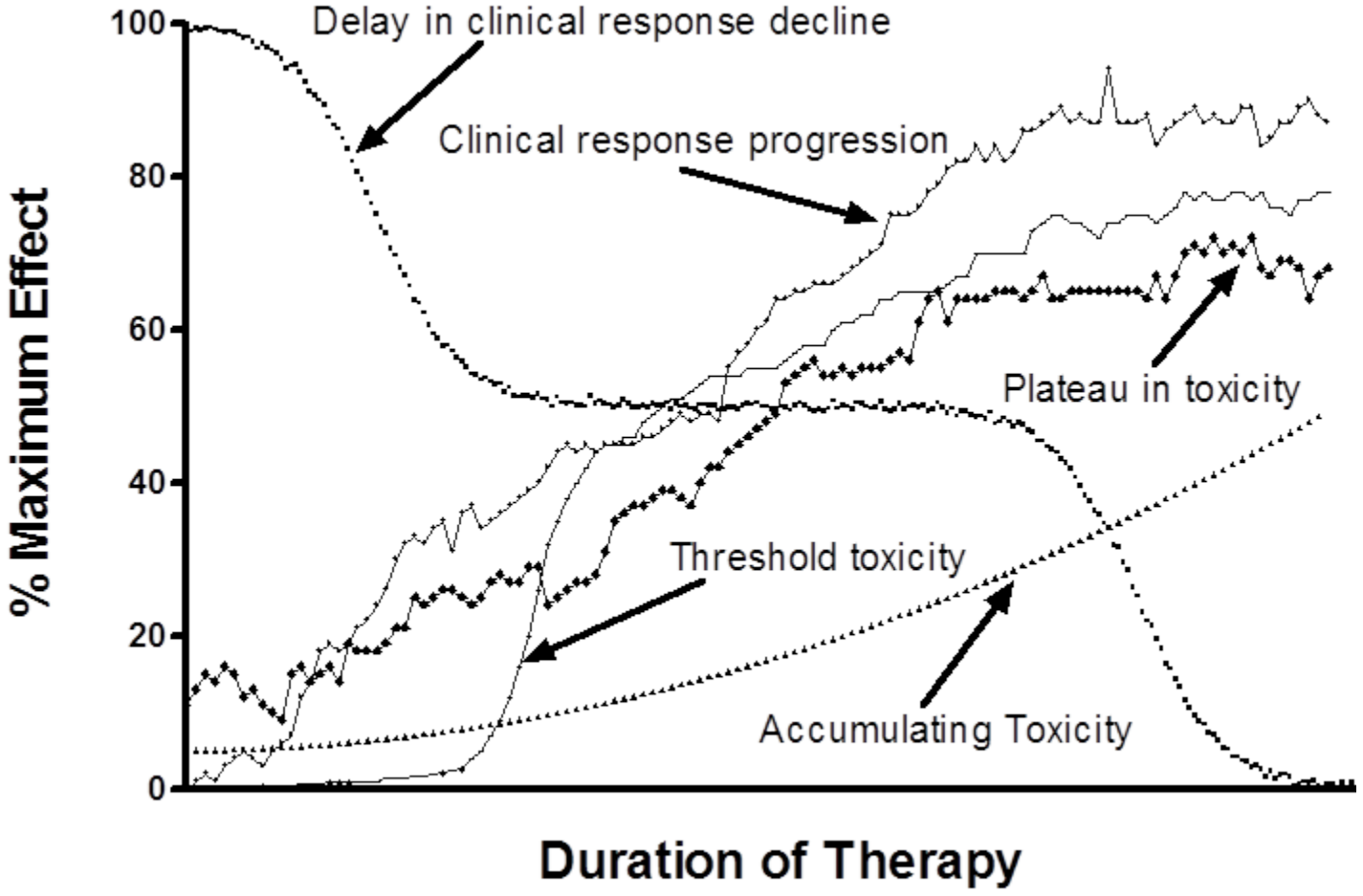




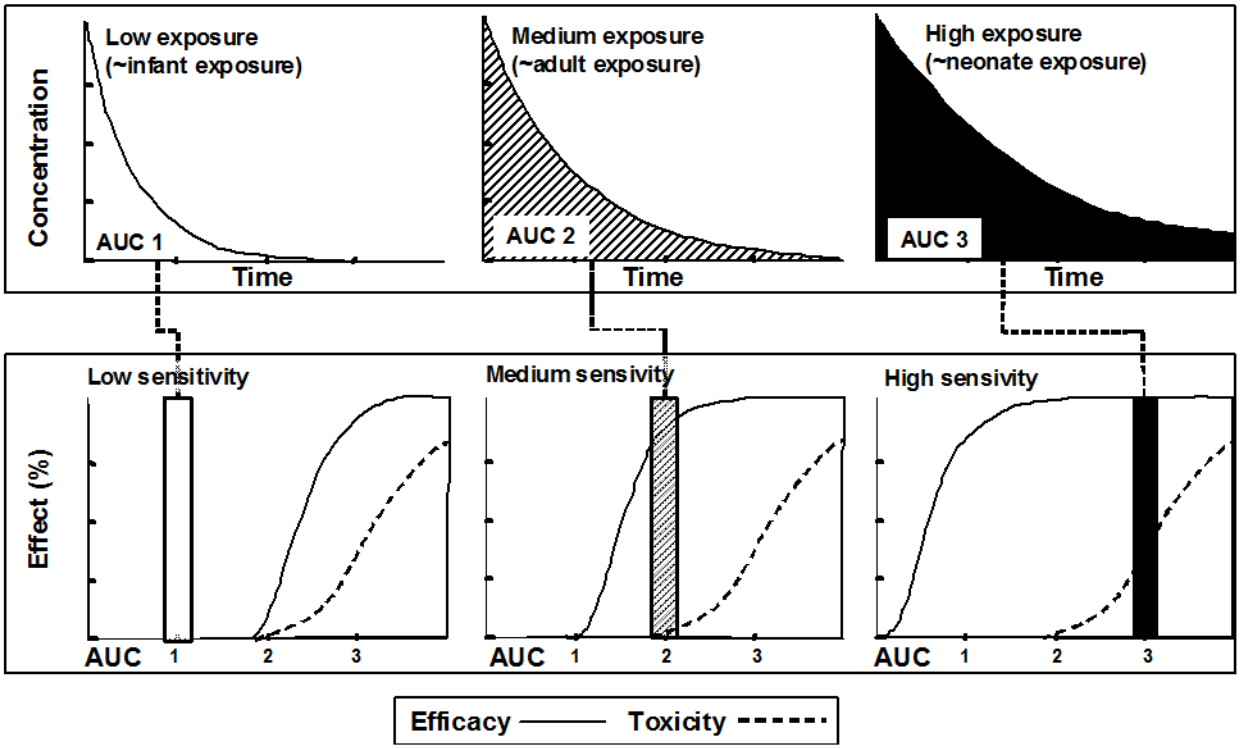




The therapeutic window – Not two-dimensional



Equivalence and the therapeutic window



	Low sensitivity	Medium sensitivity (~ adult sensitivity)	High sensitivity
Low exposure (~ infant exposure)	No efficacy No toxicity	No efficacy No toxicity	Therapeutic efficacy No toxicity
Medium exposure (~ adult exposure)	No efficacy No toxicity	Therapeutic efficacy No toxicity	Therapeutic efficacy No toxicity
High exposure (~ neonate exposure)	Therapeutic efficacy Toxicity	Therapeutic efficacy Toxicity	Therapeutic efficacy Toxicity

Lack of Comfort Zone

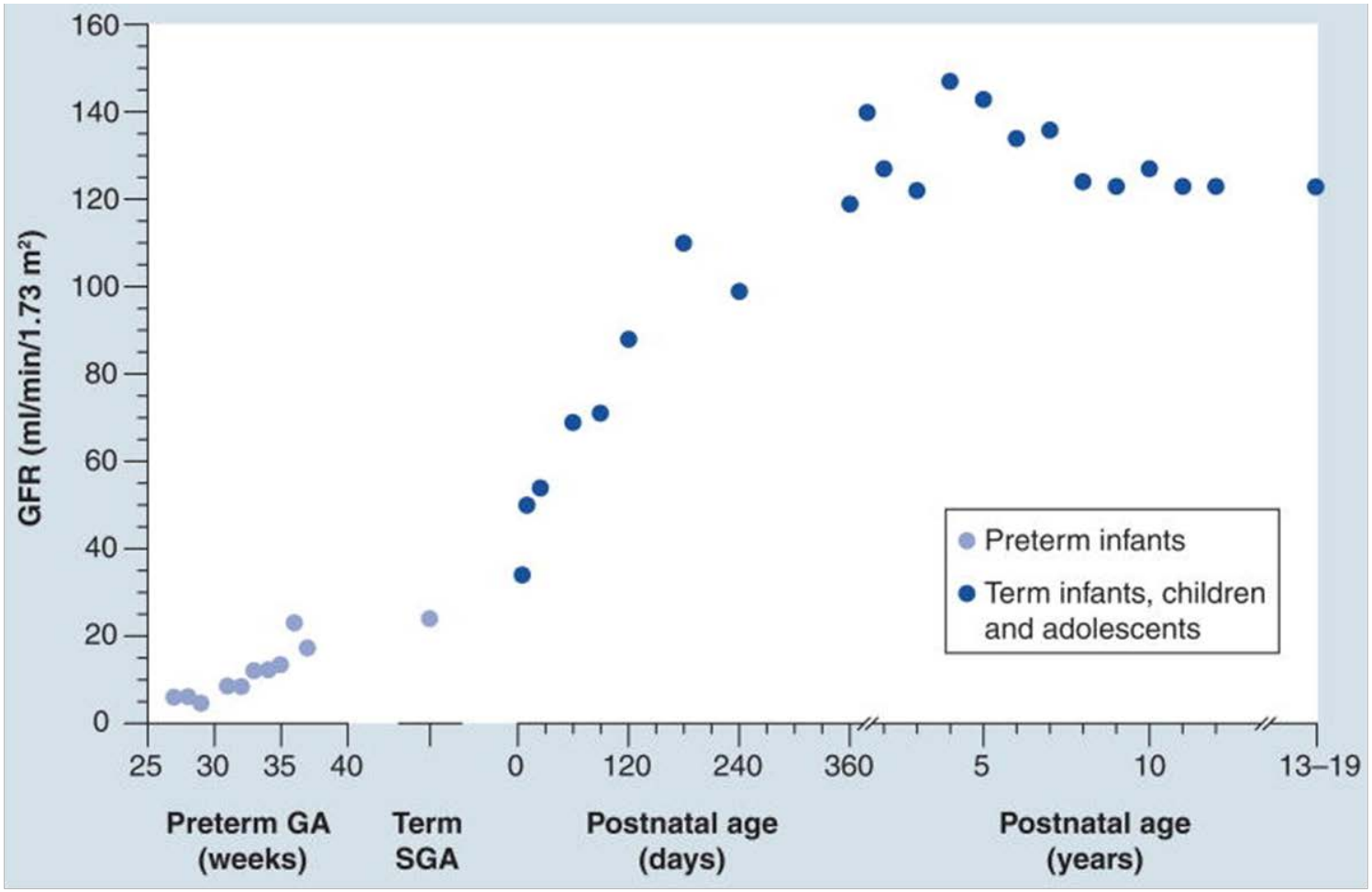
- Tier 1 – The Obvious
  - Exposure-response relationship is different in peds vs adults
  - Disease is different in pediatrics e.g. different severity or different target expression
  - Different co-morbidity or co-therapy in pediatrics
- Tier 2 – The Disease Target
  - Ontogeny of receptors and receptor pathways is largely unknown
  - Differences in antigenic response (vaccine performance in pediatrics vs the elderly)
- Tier 3 – The Drug Product
  - Humanized antibodies, where the “drug” is the hypervariable region of the antibody
  - ER/CR oral formulations, other extravascular routes, etc – choice of metric may be difficult to prioritize on.

Lack of Comfort Zone – Examples
Uncertain E-R Translation

Pathway or System	Developmental Considerations	Drug Classes Affected	PD Response
Coagulation	Changes in hemostatic response - number and nature of platelet membrane receptors, clotting factors	Antithrombotics, antiplatelet agents, vitamin K antagonists	Antifactor-Xa activity, IPA (%), bleeding rate and extent, etc
Pulmonary system	Vascular wall composition of pulmonary and systemic capacitance vessels and their intravascular pressure changes through development	Corticosteroids, calcium channel blockers, prostacyclins, endothelin-1 inhibitors	Collagen, major growth factors (TGF-beta, IGF-2, and bFGF), and cytokine gene expression
Immune system	Development of the immune system is a partial explanation for the increase in the incidence of infectious sequelae	Antibiotics, anti-infectives, antiretrovirals, etc	MIC determination, cell-kill curves, etc.
Cutaneous system	Newborns have an immature cellular immune defense system that leads to increased susceptibility to infections	Topical antibacterials	Infection susceptibility
Brain stem	Developmental aspects of phasic sleep parameters, REM density and body movement, and the executive system	Drugs which promote loss of sleep as side effect or agents to treat disorders such as ADHD	Correlation of sleep parameters with age likely reflects brain-stem maturation

Lack of Comfort Zone – Examples

Pediatric biomarkers, a moving target



Goldman J et al., Development of biomarkers to optimize pediatric patient management: what makes children different? Biomark Med. 2011 December; 5(6): 781–794.

Lack of Comfort Zone – Examples
Pediatric biomarkers, dealing with time dependencies

Examples of commonly utilized laboratory tests with age-dependent reference ranges

Hematology
Factors V and IX
Hemoglobin
Partial thromboplastin time
Prothrombin time

Hepatology
Alkaline phosphatase
Aspartate aminotransferase
γ-glutamyl transpeptidase
Indirect bilirubin

Endocrine
IGF-1
Follicle-stimulating hormone
Luteinizing hormone
Thyroxine

Immunology/renal
White blood cell count
Immunoglobulins (IgA, IgM, IgG and IgE)
Complement C3 and C4
Creatinine

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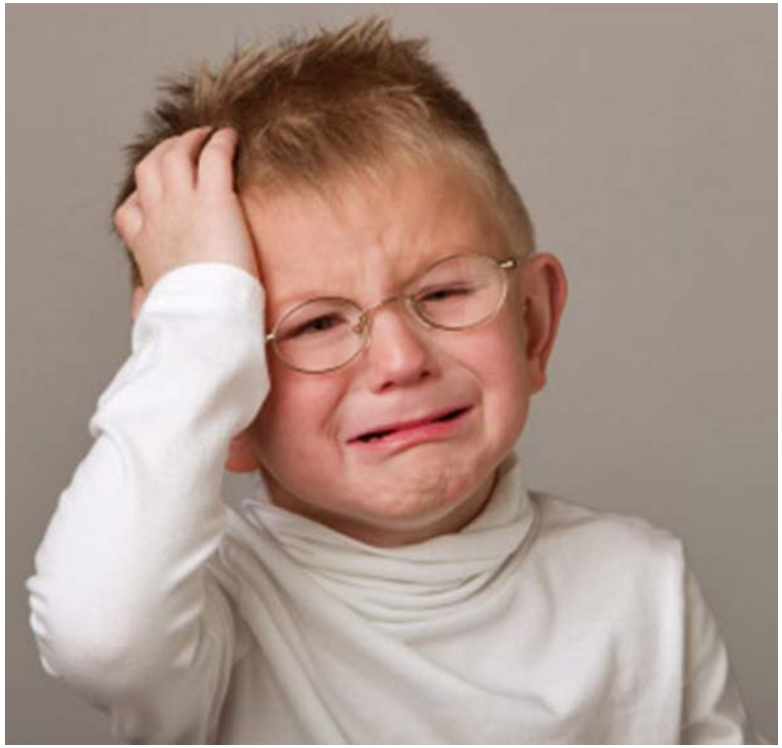
Therapeutic Proteins in Children

- Do we need to have a mechanistic understanding of the pathways of SC absorption of TPPs and the potential for certain factors to promote differences in bioavailability across species and variability in F in patients?
- Is there a relationship between the low mAB tissue concentrations and toxicity?
- How quantitative does the description of nonlinear elimination sources need to be to guide dosing?
- Is there a rationale for the ADA response in adults to be different between adult and pediatric populations?

We still would like an exposure target to pick doses . . . right?



- Project teams desperately search for a target exposure (exposure range) for pediatric indications.
- Assumptions need to be made and defended with data when available.
- Plans for re-evaluation of these assumptions and/or decision trees built on assumptions and experimental work flows are essential.
- In the end . . . we still need to pick a dose, do a trial and make recommendations for what comes next.

Practical Guidance

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Commentary

Theme: Challenges and Opportunities in Pediatric Drug Development
Guest Editors: Bernd Meibohm, Jeffrey S. Barrett, and Gregory Knipp

Practical Considerations for Dose Selection in Pediatric Patients to Ensure Target Exposure Requirements

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Abstract. Pediatric dosing recommendations are often not based on allometry, despite recognition that metabolic processes in mammals scale to the ¾ power. This report reviews the allometric size model for clearance and its implications for defining doses for children while considering practical limitations. Fondaparinux exposures in children were predicted using allometric and mg/kg dosing. Additional simulations further refined the dose based on the predicted Cmax, target exposure range, complexity of the dosing regimen, and previous exposure/response data. The percent reduction of the adult dose of an oral lozenge fixed-dose formulation which would predict similar exposures in children and adults was recommended based on simulations. Allometric dosing predicted a consistent fondaparinux exposure across the weight range. Size-optimized mg/kg dosing, which partially approximates the allometric relationship, allows for consistent fondaparinux exposures (i.e., 0.12 mg/kg ≤35 kg or 0.1 mg/kg >35 kg). Simulations of the oral lozenge formulation demonstrated rapidly changing clearance in children less than 6 years prohibiting practical dosing recommendations for satisfying all conventional exposure metrics (Cmax and AUC) in this age group. In children between 13 and 18 or 6 and 13 years, a 8.6% and 54% reduction in dose would maintain target exposures but dose reductions of 12.5% or 62.5% were ultimately recommended as deemed manufacturable. Dose selection in children should consider the known and/or predicted covariate relationships which affect exposure. Presented examples applied the allometric model in dose selection with the goal of PK bridging and considered practical limitations in dose selection.

KEY WORDS: allometry; dose selection; pediatrics; population pharmacokinetics.

INTRODUCTION

Pediatric clinical trials are becoming more prevalent and are now typically mandatory within clinical development plans. While it is understood that the aim of dose selection in children is to elicit the target pharmacodynamic (PD) effect, far more pediatric studies focus on pharmacokinetics (PK) rather than PD or PK/PD (1). This is likely due to the numerous challenges that arise during pediatric clinical trials which may not be apparent during clinical trials in adults such as recruitment difficulties, lower limits on blood collection volumes, the lack of surrogate markers which predict clinical outcome and the difficulty of dose selection in a rapidly changing population.

Although a PD target linked to clinical outcomes is most appropriate for pediatric dose selection, as mentioned above, in the absence of information on the exposure/response relationship, a PK bridging approach is often taken. In this approach, the dose in pediatric patients targets exposures similar to those achieved in adults that are known to be safe and efficacious, making the assumption that exposure/response relationships (both efficacy and safety) are similar between adults and pediatric patients (2). The relationship between ontogeny and PK is complex and dependent on a compound's unique ADME (absorption, distribution, metabolism, and excretion) properties, requiring careful consideration when developing an initial pediatric dosing strategy. The ontogeny of drug metabolism has been well-reviewed elsewhere (3). Once the maturation processes are complete, dosing in pediatric patients is primarily determined based on body size, i.e., body weight considerations.

It is well-established that metabolic processes in mammals, such as clearance, scale to the ¾ power (4). Most pharmacometricians understand this and develop appropriately scaled clearance models when developing population PK models. However, once these models are developed, simulations are often then performed using mg/kg dosing. Although this method of describing doses has the appearance of accounting for size, in fact, it has some undesirable properties which are often not well-appreciated, despite

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- Reviews the allometric size model for clearance and its implications for defining doses for children while considering practical limitations
- Dose selection in children should consider the known and/or predicted covariate relationships which affect exposure.
- Presented examples applied the allometric model in dose selection with the goal of PK bridging and considered practical limitations in dose selection.

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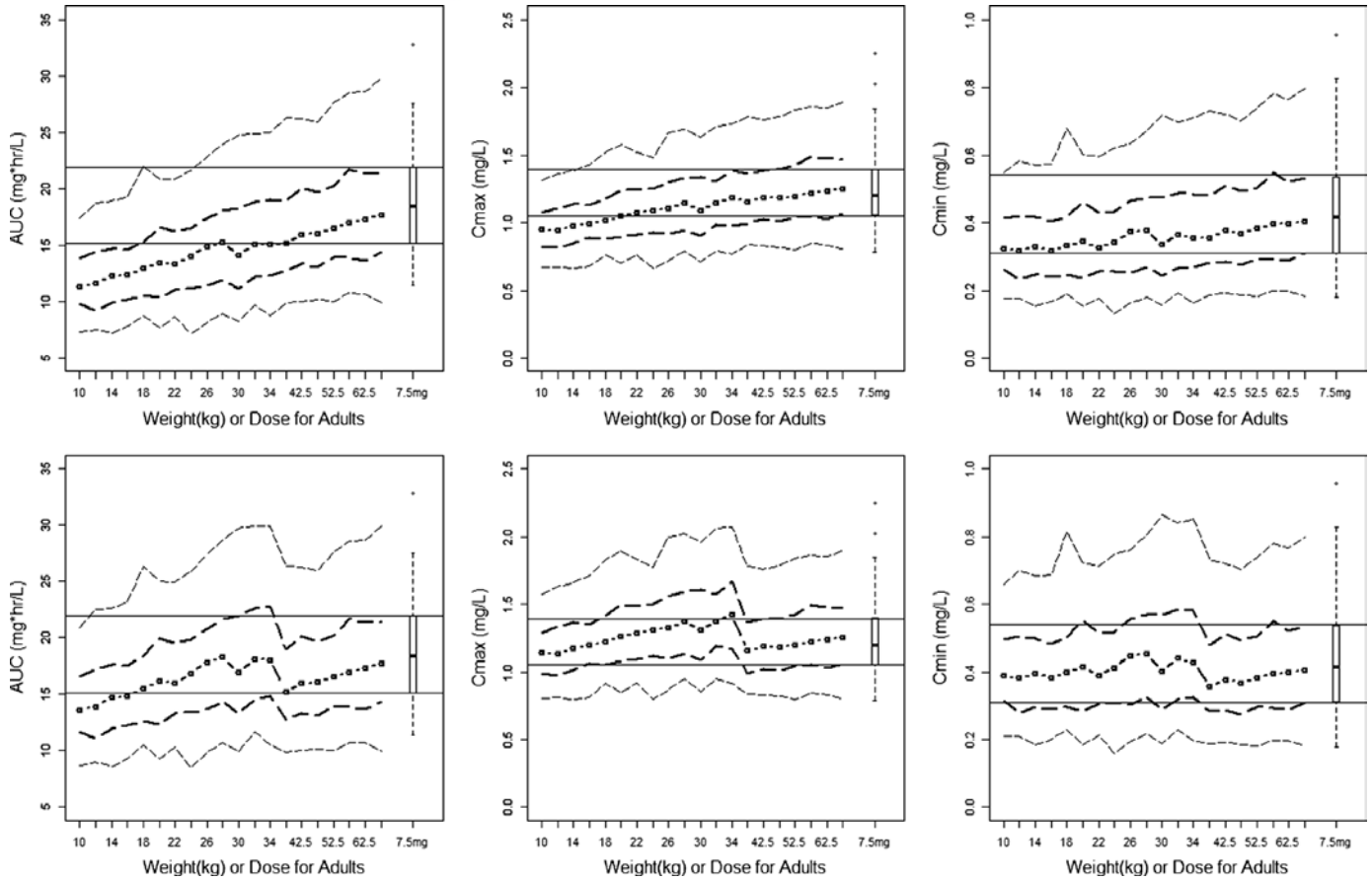
Evaluating Exposure Matching

Proper planning at the design stage



- Not easy to match all exposure metrics; often a question of risk management and formulation options
- Size / developmental continuum needs to be fully evaluated

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Other concerns from the sponsor side . . .

- Value of the healthy volunteer bridging study
  - **Why, when, how . . .**
  - **Transitivity of the healthy volunteer bridge?**
- Metric considerations
  - **Flexibility to propose drug / disease specific metrics**
  - **Risk analysis considerations for one vs multiple indices; hard to support metrics you know you can't pass for valid reasons.**
- Common sense
  - **Start with the pragmatic, learn the relevant clinical indices for comparison, proceed with the patient's interests in mind**
  - **In the absence of 100% clarity on PK/PD translation, move forward in constructive and safe manner**

Conclusion . . .
Let’s keep the conversation going . . .