New England Drug Metabolism Discussion Group
Summer Symposium, June 14, 2011, Shrewsbury, MA

The In Silico Child: PK/PD Modeling in Pediatric Drug Development

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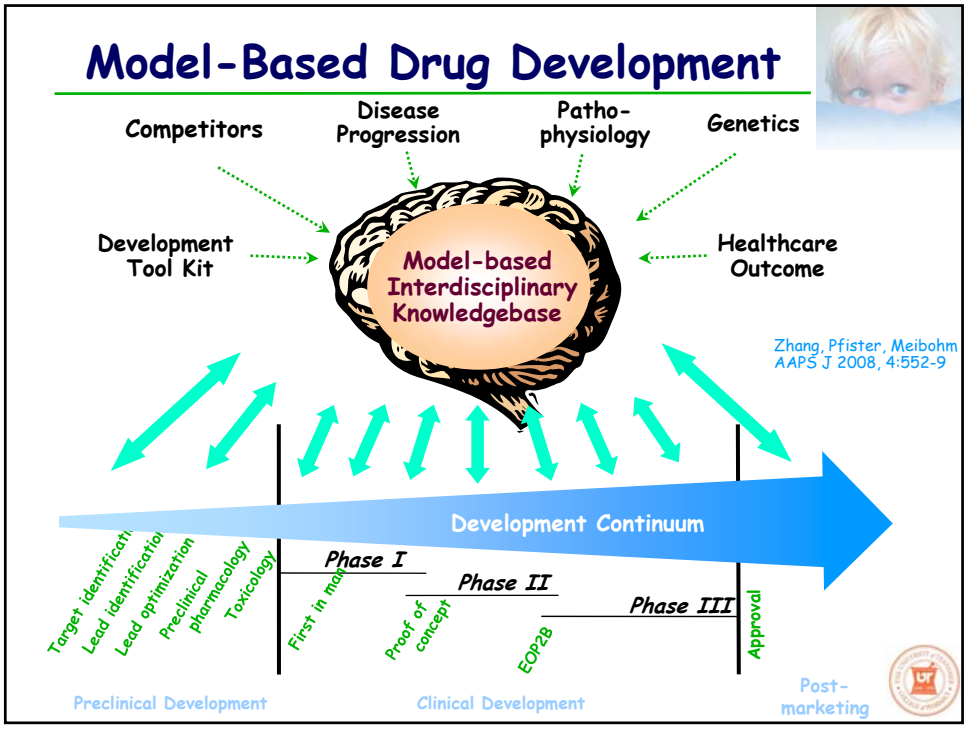
Model-Based Drug Development

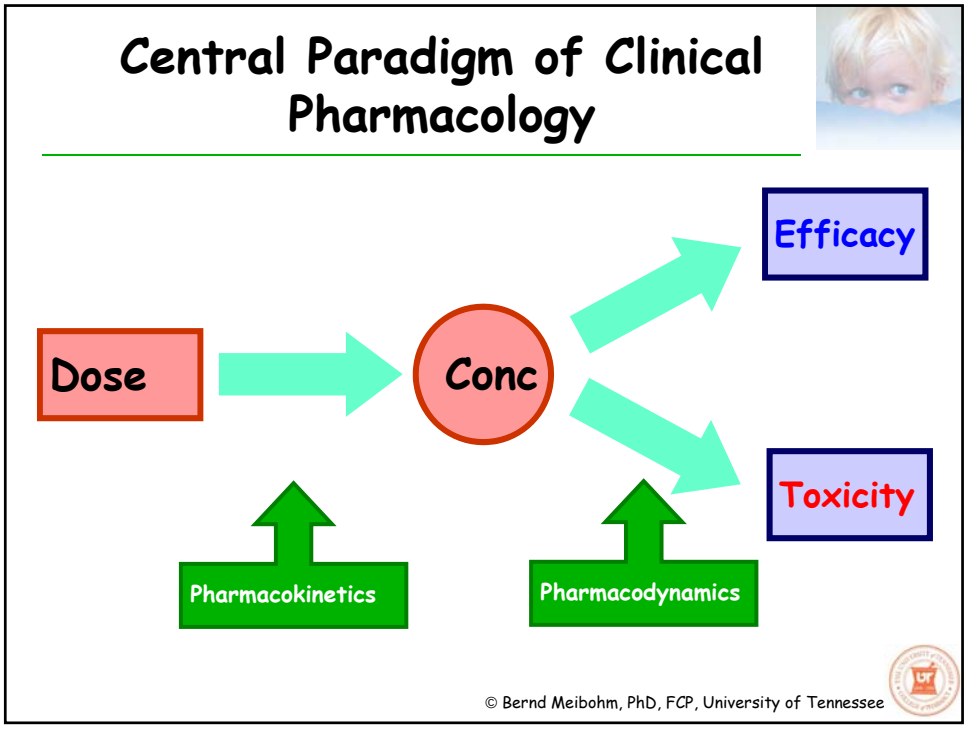
A multi-disciplinary approach that integrates the relationships between diseases, drug characteristics, and individual variability

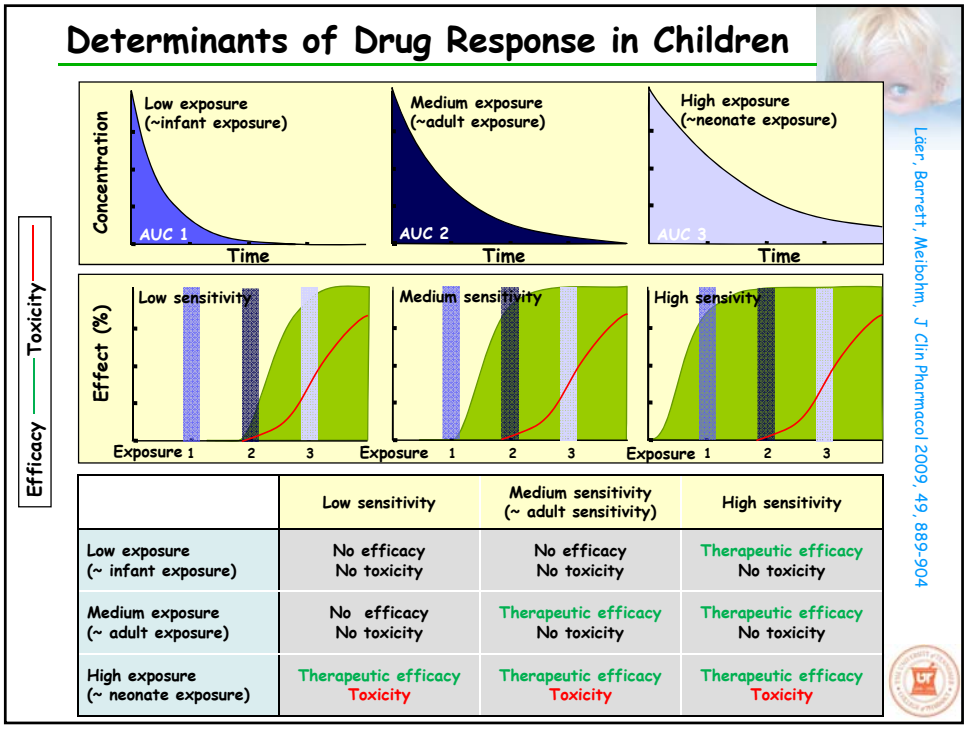
- ✓ A framework for synthesizing information and extrapolating beyond what is traditionally studied in RCTs
- ✓ A tool for rationale, critical decision making
- ✓ From drug discovery to post-marketing
- ✓ A mathematical explanation of the relationships needed to explain clinical outcomes over a timeframe of interest at its core
- ✓ Away from study centric approach: seamless data mining and knowledge management strategy that quantitatively integrates data across studies and development phases



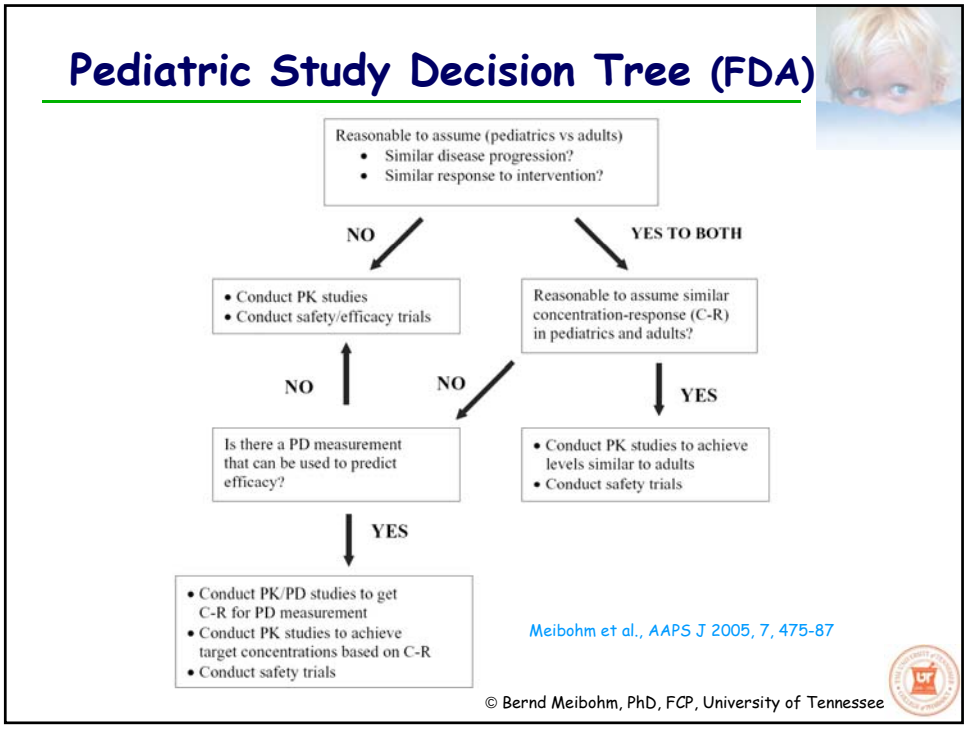
Challenges in Pediatric Pharmacotherapy

- Molecular & physiologic processes determining PK & PD undergo developmental changes based on a child's maturational progress
- Different patients follow different developmental trajectories so that usual predictors such a PNA, PMA, or GA do not fully capture the variability in PK and PD related to developmental changes
- Clinical studies in pediatric patients are challenging and limited due to ethical and logistic constraints
- Off-label use more the rule rather than the exception
- Development of dosing recommendations
  - Scaling from adult information
  - Preclinical information
  - Empirical: Anecdotal evidence/personal experience





	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


Pediatric Study Decision Tree (FDA)
Reasonable to assume (pediatrics vs adults)
• Similar disease progression?
• Similar response to intervention?
NO
YES TO BOTH
• Conduct PK studies
• Conduct safety/efficacy trials
Reasonable to assume similar concentration-response (C-R) in pediatrics and adults?
NO
NO
YES
Is there a PD measurement that can be used to predict efficacy?
• Conduct PK studies to achieve levels similar to adults
• Conduct safety trials
YES
• Conduct PK/PD studies to get C-R for PD measurement
• Conduct PK studies to achieve target concentrations based on C-R
• Conduct safety trials
Meibohm et al., AAPS J 2005, 7, 475-87
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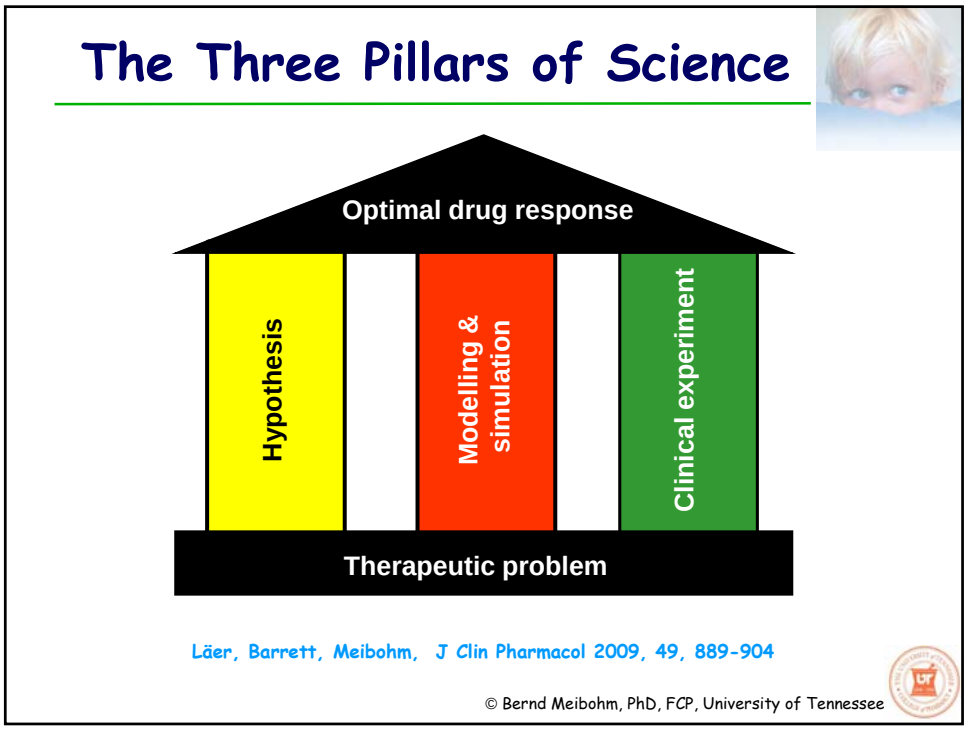
The Three Pillars of Science
Optimal drug response
Hypothesis
Modelling & simulation
Clinical experiment
Therapeutic problem
Läer, Barrett, Meibohm, J Clin Pharmacol 2009, 49, 889-904
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Modeling & Simulation

Modeling

- Models are simplified descriptions of certain aspects of reality by mathematical means, thereby allowing to concentrate on the factors believed to be important
- Summarizing measured data by integrating different measures and prior knowledge about biological processes
- Identify the best model that sufficiently describes the data (Rule of Parsimony: simplest model)
- Purpose-driven: Level of model complexity defined by its intended use

Simulation

- Modeling is a prerequisite for simulations: Application of the developed model
- Predictions beyond the measured data: inter- or extrapolations
- Validity of simulations depends on model (and the purpose is was developed for)
- Prediction error and uncertainty

Simulation Approaches

Deterministic vs. Stochastic

Deterministic

- "Best guess" parameter point estimates used for simulation
- One discrete outcome of simulation
  - E.g. a discrete drug concentration vs. time profile
- Parameters may be dependent on covariates
- Pro: Simplicity; ease of understanding
- Con: No uncertainty in parameter estimates considered

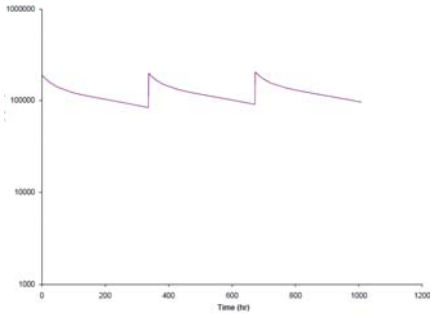
Stochastic (Monte-Carlo Simulations)

- Distributions for each specific parameter that capture the degree of uncertainty
  - Repeated random sampling of parameters from these distributions to simulate the outcome based on the underlying structural model.
- Distribution of outcomes with central tendency and spread
- Pro: provides inherently a measure of credibility and likelihood for simulation outcomes
- Con: increased complexity and thus difficult understanding and acceptance

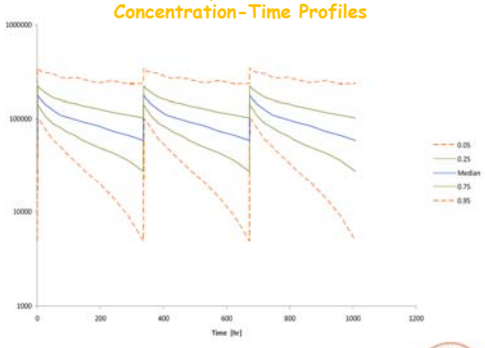
Simulation Approaches

Deterministic vs. Stochastic

Discrete Concentration-Time Profile



Probability Distribution of Concentration-Time Profiles



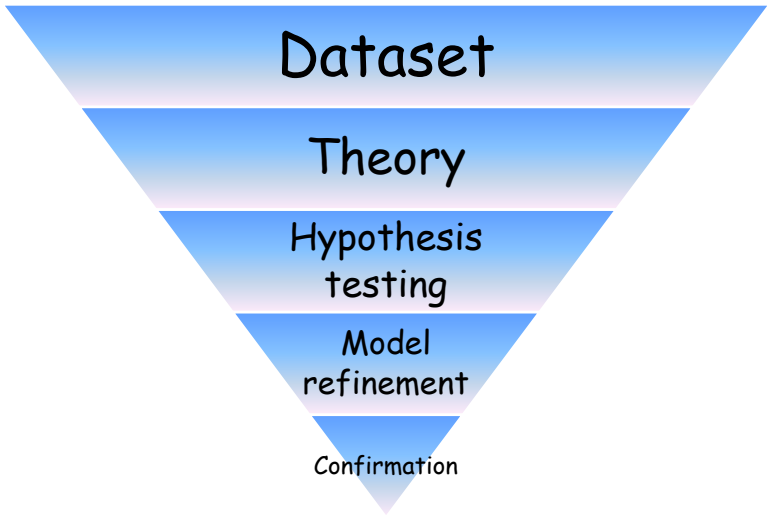
Top Down Approaches

Deductive or Analytic Approaches

- **Based on generalized concepts in medical sciences**
  - ✓ Verification-driven data mining process
  - ✓ Allows expression of preconceived facts or theories in model terms
  - ✓ Testing their validity within the context of the model system and the available data
  - ✓ Identify reasons for the validation or invalidation
  - ✓ Constant rebuilding and refinement of the model given the results of the continuous hypothesis testing
  - ✓ Only limited assumptions necessary
- **Data-driven process, in which the model is iteratively refined to optimally describe observed data**

Top Down Approaches

Deductive Reasoning



Vancomycin

Clinical Issues in Pediatrics

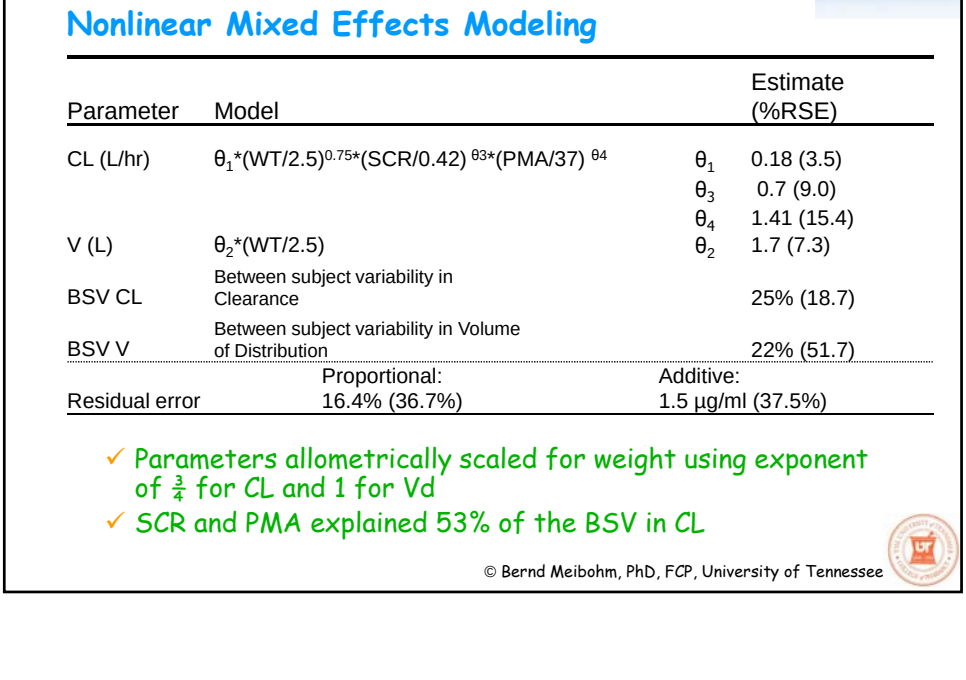
- **Current dosing guidelines**
  - ✓ Different dosing regimens are proposed for vancomycin in pediatrics over last several years
    - o One standard dose for all neonates (DR1)
    - o PMA based dosing (DR2)
    - o PMA and PNA based dosing (DR3)
    - o Serum creatinine based dosing (DR4)
  - ✓ No consensus among clinicians on the use of any standard vancomycin dosing regimen in term and preterm neonates
    - o Comparative evaluation in clinical trial hampered by logistic and ethical constraints
  - ✓ Little information on dosing in premature vs. term neonates
    - o Growing demand based on more sophisticated NICUs
  - ✓ Initial dosing frequently followed by *a posteriori* individualization based on Sawchuk-Zaske method or Bayesian forecasting
  - ✓ Comparative clinical study nearly impossible due to logistic and ethical constraints of studies in neonates
- **Objectives**
  - ✓ To evaluate the four standard dosing regimens in silico for their ability to achieve target vancomycin concentrations

Step 1: PopPK Analysis

Establish pharmacostatistic vancomycin disposition model based on local population

- Retrospective, non-interventional clinical study
  - ✓ LeBonheur Children's Medical Center, Memphis, TN
- Inclusion criteria:
  - ✓ Full term and premature neonates with PMA ≤44 wks
  - ✓ At least one vanc serum concentration level
  - ✓ Documented vanc dose, dosing schedule, and time of blood draw
- Exclusion criteria:
  - ✓ Concurrent nephrotoxic drugs (i.e., amphotericin B, cisplatin)
  - ✓ Extracorporeal membrane oxygenation or hemodialysis
- Covariates tested:
  - ✓ Gestational age (GA), postnatal age (PNA), postmentrual age (PMA), weight, serum creatinine, blood urea nitrogen, and urine output.

N	Male/ Female	Preterm/Term	Weight	GA	PNA	SCR
134	54%/ 46%	66%/ 34%	0.64-5.3 kg	23-41 wks	1-121 days	0.2-2.5 mg/dL



Step 1: PopPK Analysis

Nonlinear Mixed Effects Modeling

Parameter	Model		Estimate (%RSE)
CL (L/hr)	$\theta_1*(WT/2.5)^{0.75}*(SCR/0.42)^{\theta 3}*(PMA/37)^{\theta 4}$	θ_1	0.18 (3.5)
		θ_3	0.7 (9.0)
		θ_4	1.41 (15.4)
V (L)	$\theta_2*(WT/2.5)$	θ_2	1.7 (7.3)
BSV CL	Between subject variability in Clearance		25% (18.7)
BSV V	Between subject variability in Volume of Distribution		22% (51.7)
Residual error	Proportional: 16.4% (36.7%)	Additive: 1.5 µg/ml (37.5%)	

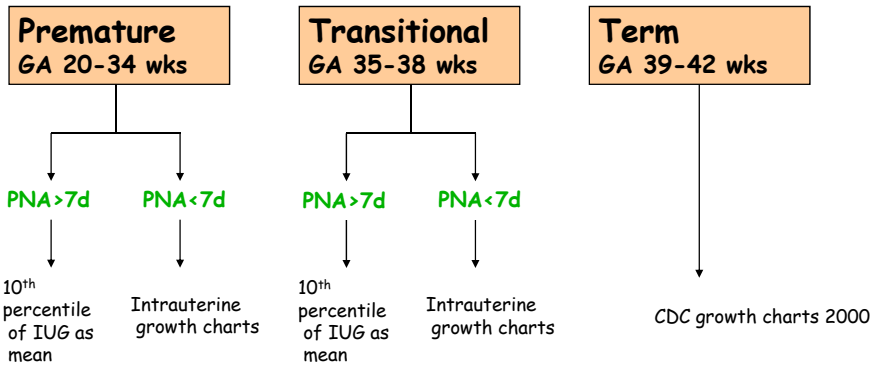
- ✓ Parameters allometrically scaled for weight using exponent of ¾ for CL and 1 for Vd
- ✓ SCR and PMA explained 53% of the BSV in CL

Step 2: Simulations of DRs

- Monte-Carlo simulations based on PopPK model
  - ✓ Each dosing regimen was treated as a different scenario having
    - 200 replicates per scenarios
    - 100 subjects per replicate
  - ✓ Multivariate age-weight distributions
    - Term Neonates: CDC growth charts
    - Preterm neonates: intra-uterine and postnatal growth charts
  - ✓ Covariance between PNA and SCR based on original dataset
- Outcome metrics
  - Trough concentrations 0.5 hr prior to next dose
  - Percentage of subjects having trough concentration between 5-15 µg/ml

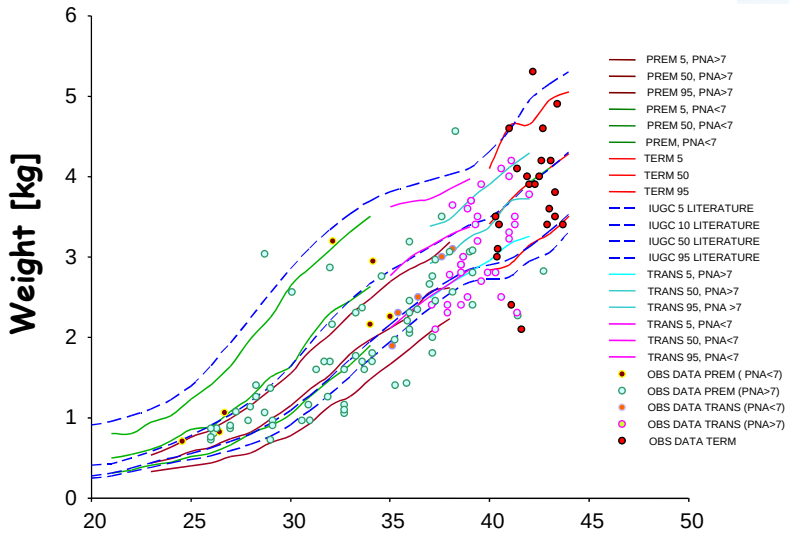
Multivariate Covariate Distribution

Physiologically reasonable covariate vectors



Alexander et al., 'A United States reference for fetal growth', Obstetrics & Gynecology 1996, 87, 163-8

Virtual Patient Population



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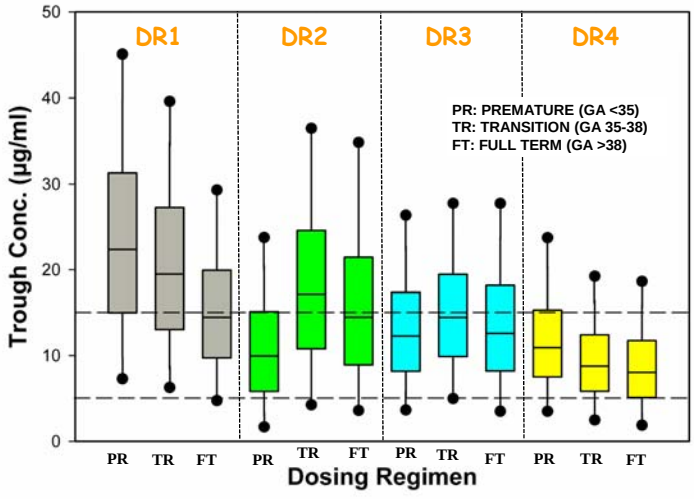
In silico Comparison of DRs

Box plot for dosing regimens (DR-1 to DR-4) stratified based on gestational age



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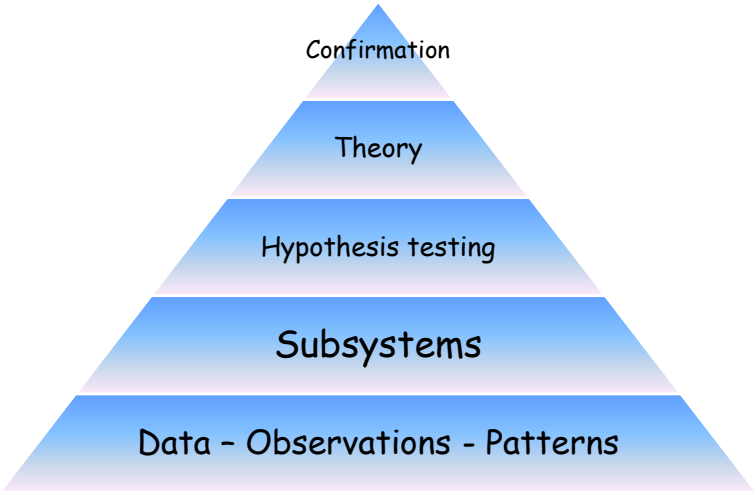
Bottom Up Approaches

Inductive or Synthetic Approaches

- **Synthesize individual pieces of information to form broader generalizations and theories**
  - Observations
  - Data
  - Patterns
- **Individual elements are linked together to form larger subsystems based on Systems Biology**
  - ✓ Subsystems are linked via many levels to from a complete top-level model
  - ✓ Assumption-rich approach
  - ✓ Hypotheses are driven by observed patterns and interdependencies
  - ✓ Predictions possible without experimental (clinical) data

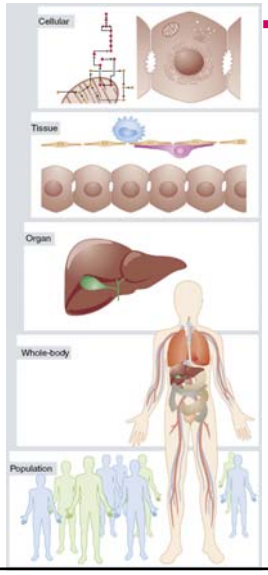
Bottom Up Approaches

Inductive Reasoning



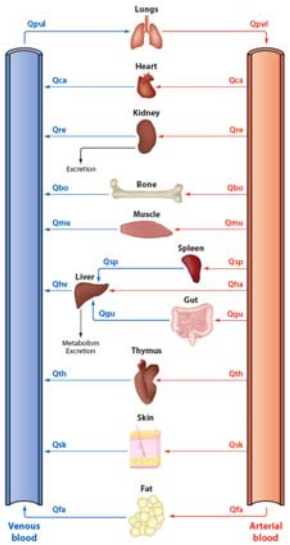
Bottom Up Approaches

Example: Physiologic PK Modeling



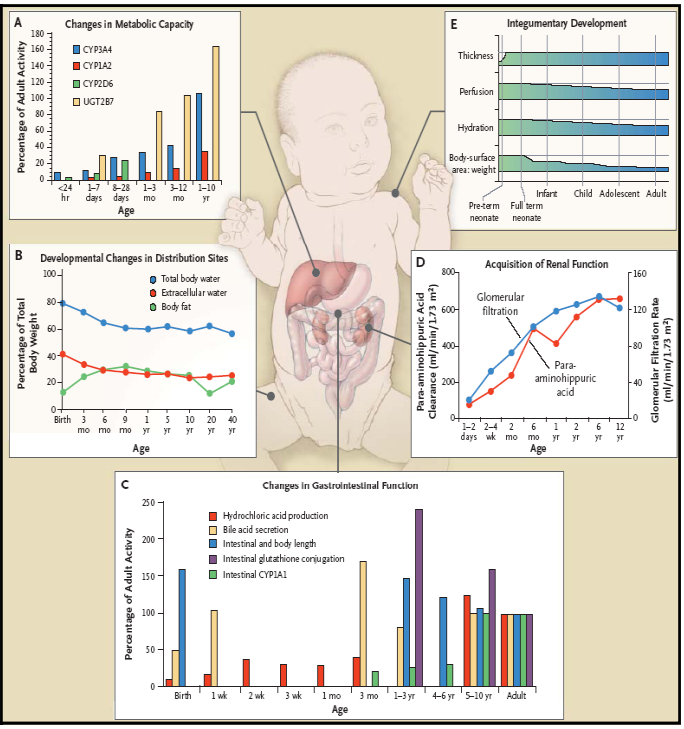
- **Integration of information from multipl sources**
  - ✓Types of data:
    - o Anatomical&Physiological
    - o Pathophysiological
    - o Drug-specific
    - o Molecular
  - ✓Relevant organ & tissue function individually considered
  - ✓Based on 'typical' parameters for specific subpopulation
  - ✓Uncertainty may be implemented

Kuepfer, Mol Syst Biol 2010, 6, 409
Rowland et al., Annu Rev Pharmacol Toxicol 2011, 51, 45-73



Developmental Changes in Physiologic Factors Affecting Drug Disposition

Kearns et al.
N Engl J Med 2003, 349:1157-67



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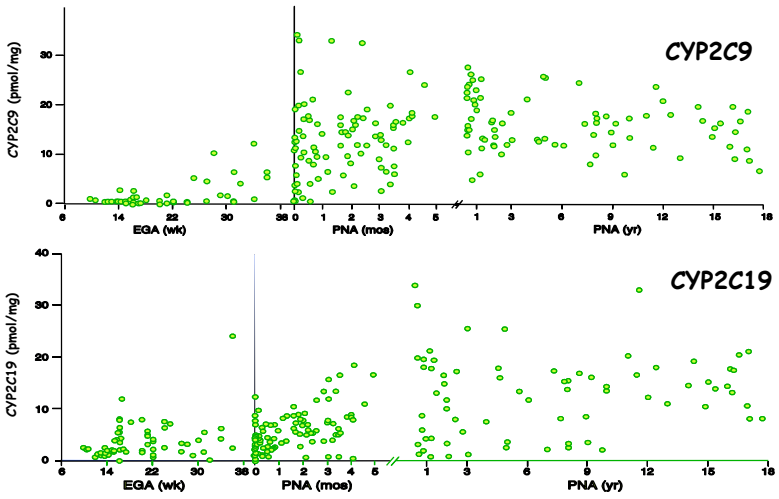
Ontogeny of Hepatic DME (I)

CYP2C

Koukouritaki et al., J Pharmacol Exp Ther 2004, 308:965-74



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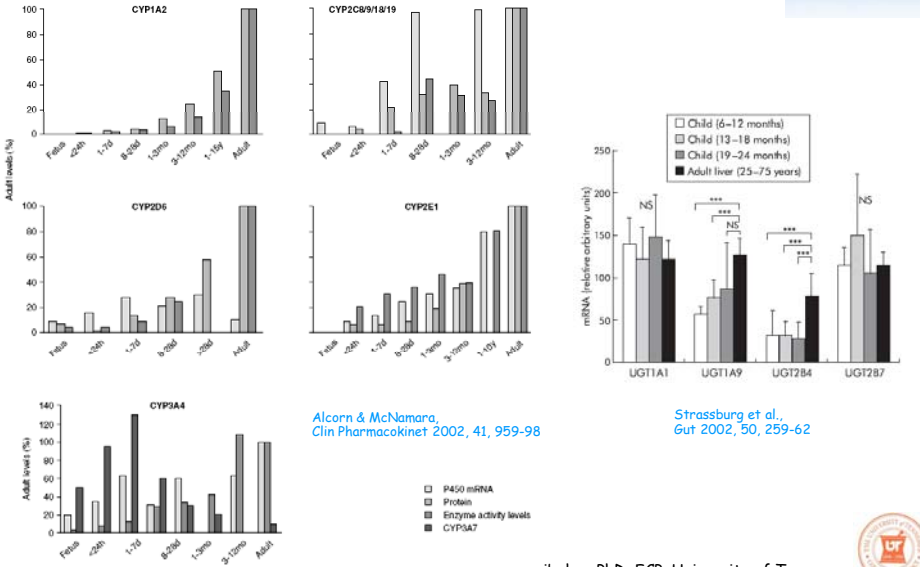
Ontogeny of Hepatic DME (II)

Hepatic Phase I & Phase II Enzymes



Alcorn & McNamara, Clin Pharmacokinet 2002, 41, 959-98

Strassburg et al., Gut 2002, 50, 259-62

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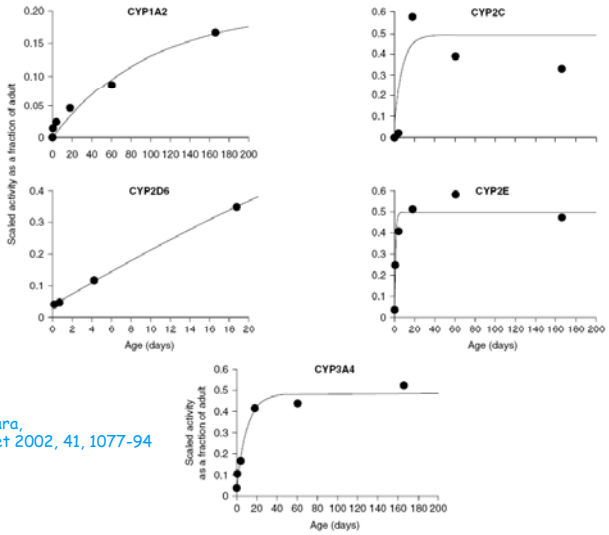
Ontogeny of Hepatic DME (III)

Modeling of Developmental Trajectories



Alcorn & McNamara,
Clin Pharmacokinet 2002, 41, 1077-94

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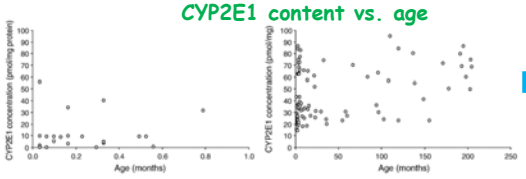
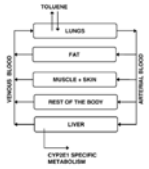
Example: CYP2E1 & Toluene Clearance

CYP2E1 content vs. age

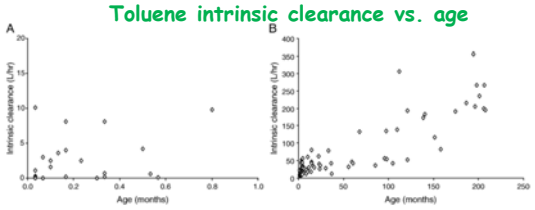




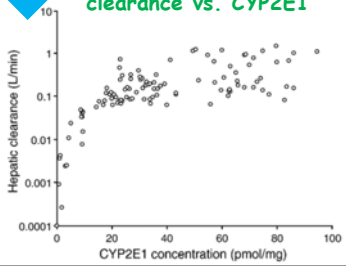
PBPK-model

$$CL_{int-child} = \left(\frac{CL_{int-adult}}{[CYP2E1]_{adult} \times V_{liver-adult}}\right) \times [CYP2E1]_{child} \times V_{liver-child}$$

Toluene intrinsic clearance vs. age



Toluene hepatic clearance vs. CYP2E1



Nong et al., Toxicol Appl Pharmacol 2006, 214, 78-87

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The *In Silico* Child

Dual Direction Up & Down Approach

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The *In Silico* Child

Dual Direction Up & Down Approach

- Usually not sufficient data available to describe full bottom up model system
  - ✓ Dependence on assumptions with associated uncertainty
- Incorporation of bottom up subsystem components in top down methodology to explain residual variability
  - ✓ Multi-scale models based on systems biology
- Combination of both methodologies is the most promising approach to give birth to the *In Silico* Child

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Example #1

Inhalational Anthrax in Children

Levofloxacin therapy

- **Rare bacterial infection with *B. anthracis***
  - ✓ Inhaled spores germinate in lower respiratory tract, leading to toxin-mediated necrotizing pneumonia with respiratory failure and death
  - ✓ Bioterrorism threat
  - ✓ Efficacy studies not feasible
- **Fluoroquinolones as empirical therapy**
  - ✓ Despite usually limited use in children due to lesions in the cartilage of juvenile animals
  - ✓ Potentially life-saving treatment outweighs risks
- **Development of an optimized pediatric dosing regimen for children from 6 months to 17 years**
  - ✓ Based on exposure in animal experiments that prevents progression of pulmonary anthrax after inhalation exposure
  - ✓ Extrapolating adult data to children
    - o No difference in C-R relationship
    - o Beneficial and adverse drug effects similar between children and adults
    - o Only adjustment for PK differences

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Inhalational Anthrax in Children

Levofloxacin Population Pharmacokinetics

- PK characteristics
  - Linear PK
  - 99% oral bioavailability
  - Renal excretion as major elimination pathway (fe = .87)
- Development pharmacology
  - Disposition as function of body size
  - Maturation of renal function within first 2-3 yrs
- Available PK data
  - 90 pediatric patients (7 mg/kg) and 47 healthy adults (500 or 750 mg)

✓ $CL \sim BW^{0.43} \times (Age/[Age+A_{50}])$; A_{50}=0.34 yr
Allometrically weight-adjusted clearance with maturation function for renal elimination
Renal function maturation: 60% for 6-month old; 75% for 1-yr old
Strictly limited to lower age range of 6 months

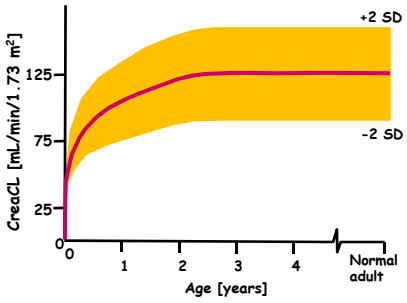
✓ $V \sim BW$

33 Li et al., Antimicrob Agents Chemother 2010, 54, 375-9 © Bernd Meibohm, PhD, FCP, University of Tennessee

Inhalational Anthrax in Children

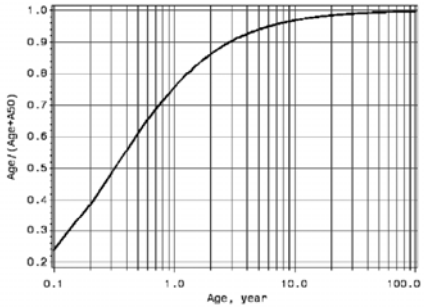
Maturation of Renal Excretion Function

Creatinine Clearance vs. Postnatal Age



Holliday et al., Pediatric Nephrology, Williams & Wilkins 1994

Estimated based on Levofloxacin PopPK Analysis



Li et al., Antimicrob Agents Chemother 2010, 54, 375-9

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Inhalational Anthrax in Children

Pediatric Dosing Recommendations

- **Simulation of exposures**
  - ✓ To match adult exposures for 500 mg QD with AUC_{24}, $C_{ss,max}$, $C_{ss,min}$
  - ✓ 15 mg/kg QD in children matches adult 500 mg QD
  - ✓ $C_{max,ss}$ exceeds adult values: 7.5 mg/kg BID dosing
  - ✓ For children >50 kg: 500 mg QD (adult dose)

Age	PK parameter		
	$AUC_{0\text{-}24,ss}$ (μg.h.ml)	$C_{max,ss}$ (μg/ml)	$C_{min,ss}$ (μg/ml)
6 mo to < 2 yr	51.7 (26.8–75)	5.6 (3.2–7.3)	0.6 (0.26–1.2)
2 to <5 yr	50 (41.7–65.2)	5.4 (4.2–6.6)	0.6 (0.25–1.1)
5 to <10 yr	55.6 (46.9–83.3)	5.4 (3.7–7.1)	0.9 (0.38–1.6)
10 to 18 yr	55.7 (42.0–83.5)	6.3 (4.6–8.1)	0.6 (0.2–1.4)
Adult[b]	47.7 (41.8–55.1)	5.5 (5.0–6.8)	0.4 (0.3–0.55)

[a] Data are presented as the median (10th percentile to 90th percentile). The dosage regimen was 7.5 mg/kg b.i.d (not exceeding 250 mg/dose), 500 mg q.d. for children more than 50 kg.

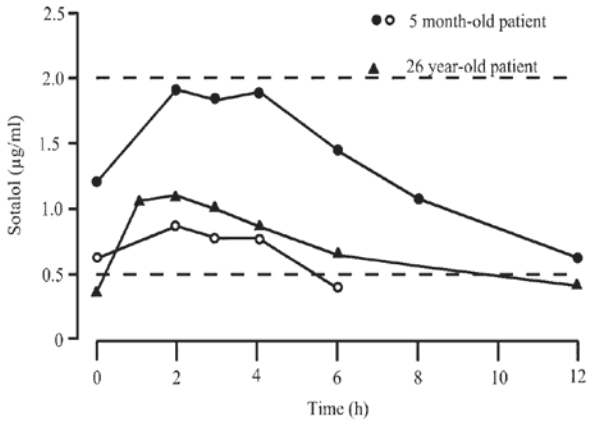
- **Final recommendation**
  - ✓ 8 mg/kg BID (500 mg QD for children >50 kg)

35 Li et al., Antimicrob Agents Chemother 2010, 54, 375-9 © Bernd Meibohm, PhD, FCP, University of Tennessee

Example #2

Sotalol in Pediatric Supraventricular Tachycardia

Sotalol Plasma Concentrations in a 5 month-old (5.5 mg/kg; open circles; 7.8 mg/kg; closed circles) and a 26 yr-old Patient (2 mg/kg)



Läer et al., Eur J Clin Pharmacol 2001, 57, 181-2

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Sotalol in Pediatric Patients

Pharmacokinetic Properties

- BCS class 1 (hydrophilic; secondary amine)
- Oral bioavailability 90-100 %
- Linear PK
- No plasma protein binding
- Elimination
  - ✓ Terminal half-life: ~12 hr (adults)
  - ✓ 80-90% renal excretion in unchanged form
  - ✓ Essentially no metabolism
  - ✓ Renal CL > GFR (~1.5 x) and reduced by cimetidine coadministration ➔ filtration and secretion

Study Population

	N (%)	Mean (SD)	Range
Age [yrs]	82	3.0 (4.2)	0.03 - 13.7
Newborns	14 (17)	0.050 (0.015)	0.03 - 0.07
Infants	38 (46)	0.53 (0.43)	0.09 - 1.7
Children	30 (37)	7.6 (3.7)	2.1 - 13.7
Sex (male)	51 (62)		
Weight [kg]		14.3 (15.8)	2.2 - 84.3
Height [cm]		84 (36)	35 - 178
BSA [m^2]		0.55 (0.41)	0.17 - 2.04
SCr [mg/dL]		0.44 (0.15)	0.2 - 1.0
GFR [mL/min]		42.8 (45.6)	3.1 - 232
NGFR [mL/min/1.73m^2]		103 (45.5)	31.5 - 217

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Sotalol in Pediatric Patients

- Age-Specific Pharmacokinetics
  - $CL \sim BW^{0.75} \times (1+S \times Age^{0.142})$; S=1 for Age <1 yr; else S=0
    Allometrically weight-adjusted oral clearance is reduced within the first months of life, probably due to maturation of renal elimination processes, including glomerular filtration and transporter-mediated active tubular secretion.
  - $V \sim BW \times (1+S \times Age^{-0.101})$; S=1 for Age <1 yr; else S=0
    Weight-adjusted volume of distribution is increased for the first months of life, probably due to higher percentage of total and extracellular body water at early age.
- Age-Specific Pharmacodynamics
  - $\Delta QTc \sim 1+S \times Age^{-0.296}$; S=1 for Age <1 yr; else S=0
    Increase in QTc per unit drug concentration is higher in young compared to older pediatric patients

Läer et al., J Am Coll Cardiol 2005, 46, 1322-30

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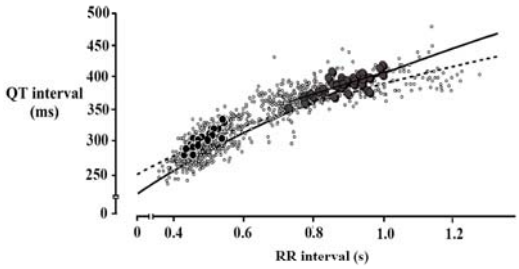
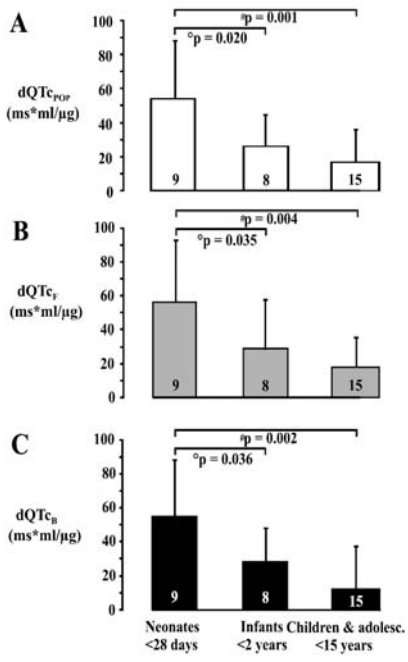
Sotalol - Pharmacodynamics

Age-dependent ΔQTc





✓ Independent of methodology for heart rate correction of QT interval

Läer et al., J Am Coll Cardiol 2005, 46, 1322-30

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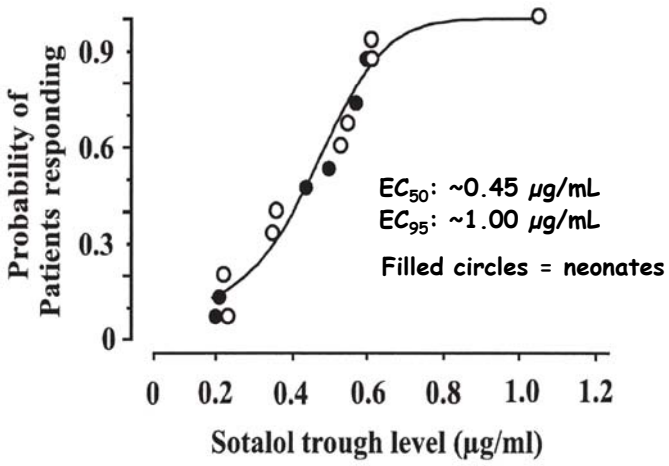
Sotalol – Pediatric C/R



Läer et al., J Am Coll Cardiol 2005, 46, 1322-30

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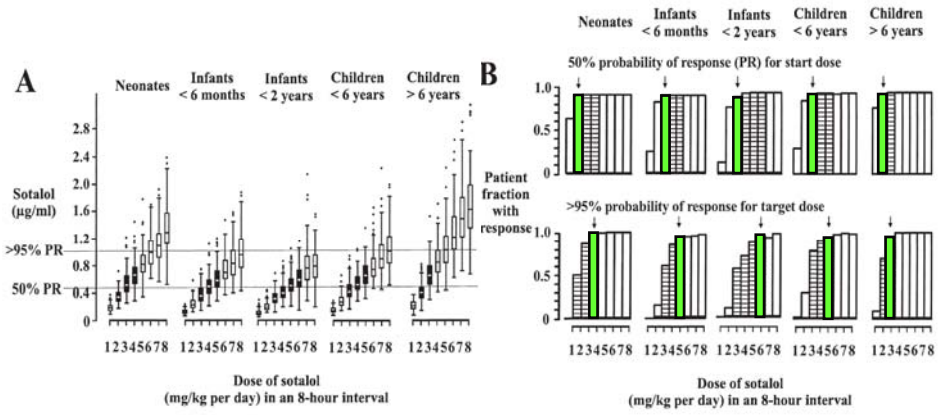
Age-Specific Pediatric Dosage Recommendations

Based on Exposure-Response Relationship

Group	(Start/Target) (mg/kg/day)
Neonates	2/4
Infants <6 months	3/5
Infants <2 yrs	3/6
Children <6 yrs	3/5
Children >6 yrs	2/3



Läer et al., J Am Coll Cardiol 2005, 46, 1322-30

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The Future

The *In Silico* Child in Drug Development & Clinical Practice

- Integrated M&S using all available sources of information
  - ✓ Molecular & Mechanistic Information
  - ✓ Anatomy, Physiology and Pathophysiology
  - ✓ Ontogeny
  - ✓ Clinical observations and their between-subject variability
  - ✓ Historic data
  - ✓ Comparator compounds
  - ✓ Class effects
  - ✓ Species & subpopulations
- Methodologies
  - ✓ Bottom up & Top Down
  - ✓ Bayesian priors
  - ✓ Individual vs. population
  - ✓ Monte Carlo simulations as core
  - ✓ Easy user interface for widespread acceptance
  - ✓ Education, education, education…

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The In Silico Child: Using Simulation to Guide Pediatric Drug Development and Manage Pediatric Pharmacotherapy

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