DISCLOSURES

Christopher M. Rubino, Pharm.D.

- Industry Potential Interest Conflicts
  - *Employer:* Employed by and have equity in ICPD, a company that provides pharmacometric services to industry
  - *Financial Interests or Benefits*: Achaogen, Actelion, AiCuris, Arsanis, Basilea, Cellceutix, Cempra, Cidara, Contrafect, Debiopharm, Genentech, Geom, GSK, Insmed, Kalyra, Medicines Company, Meiji Seika Pharma, Melinta, Merck, Nabriva, Nexcida, Northern Antibiotics, Novartis, Paratek, Raptor, Roche, Spero, Takeda, Theravance, Tetraphase, VenatoRx, Wockhardt, Zavante, Zogenix
  - *Speaker's Bureau*: None

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Using Pharmacometrics to Facilitate the Design and Analysis of Anti-Infective Drug Studies in Neonates

15 September 2016

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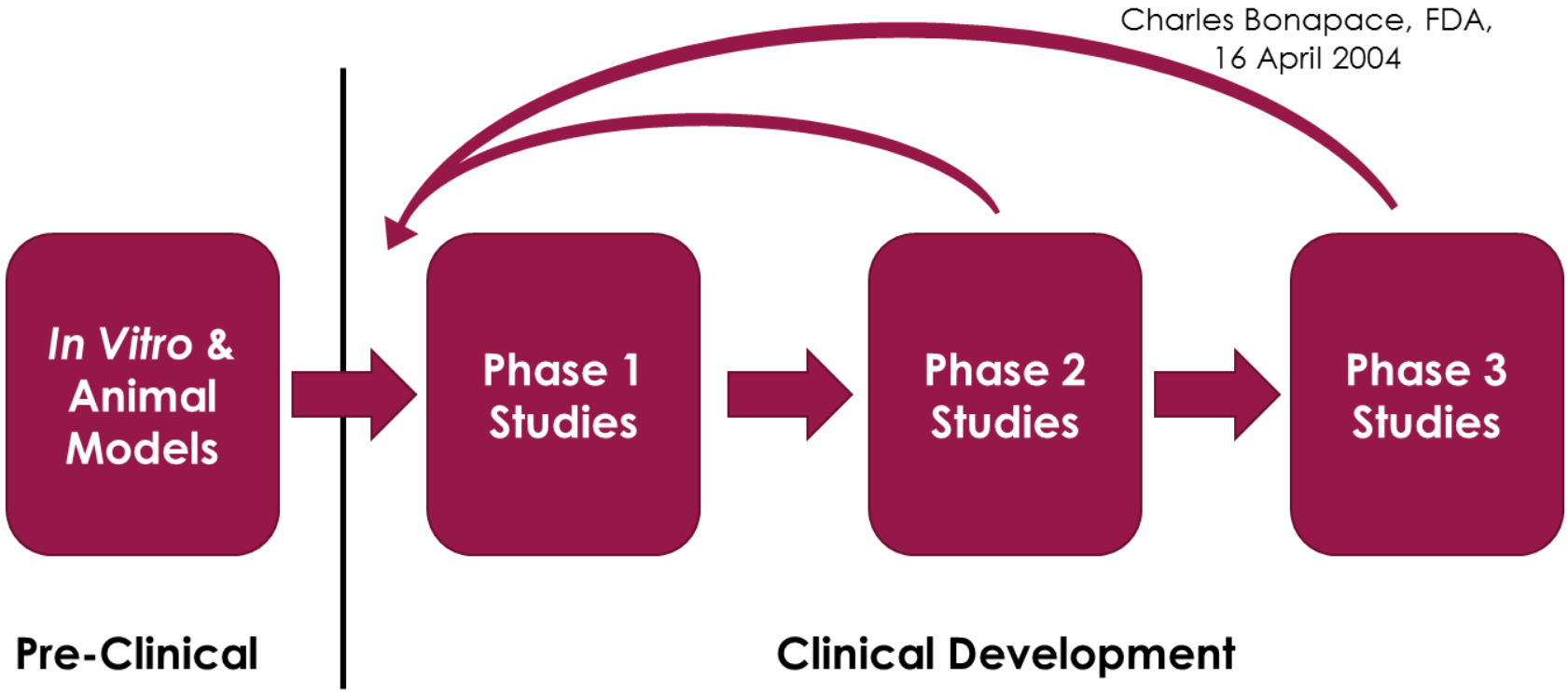
Institute for Clinical Pharmacodynamics, Inc.
Schenectady, New York

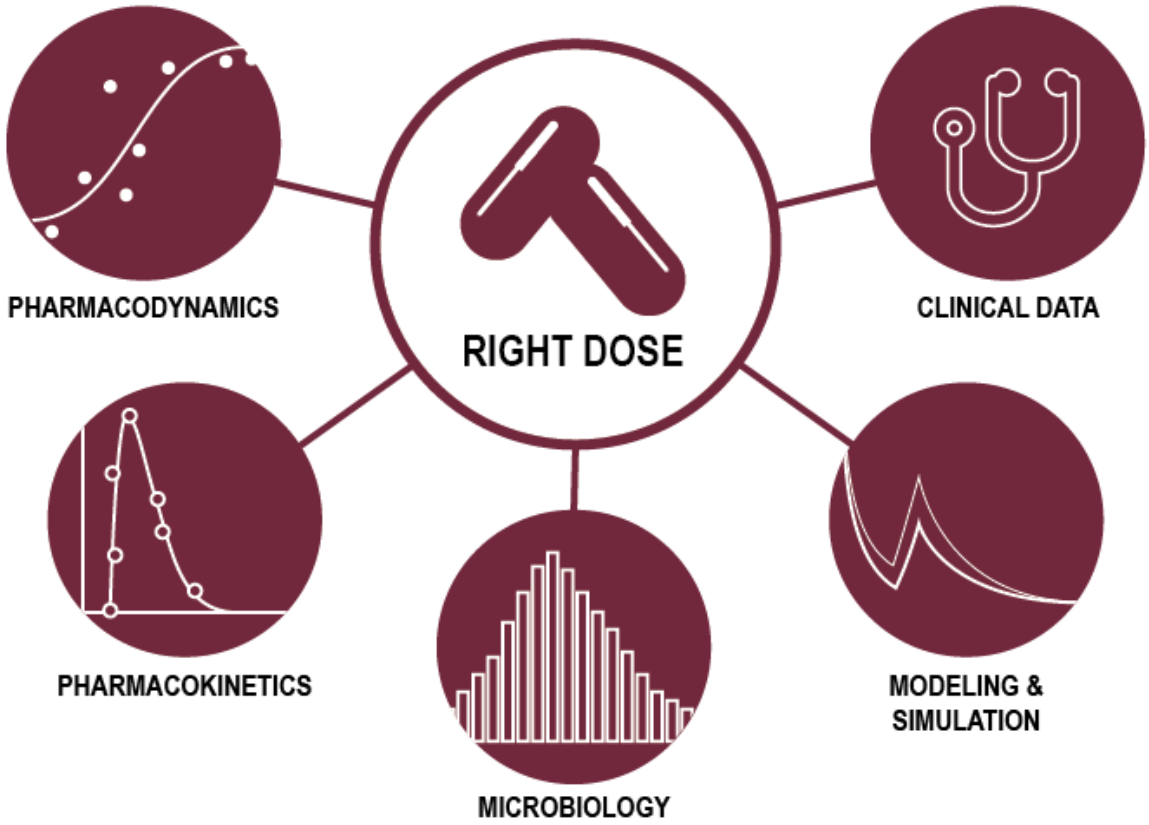
OUTLINE

- Overview of Pharmacometrics
  - Role of pharmacometrics in adult and pediatric drug development
  - Examples of pediatric applications
- Study Design Issues
  - Model-based approaches
  - Thoughts for discussion

Setting the Stage
Pharmacometrics in Adults

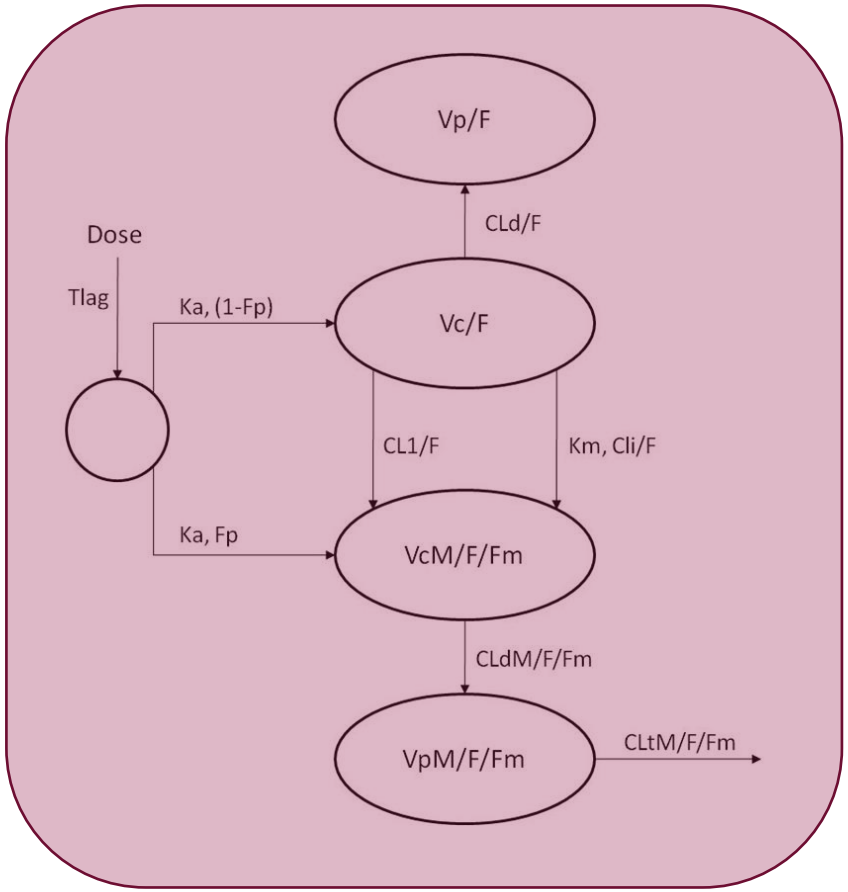


Setting the Stage
Pharmacometrics in Adults

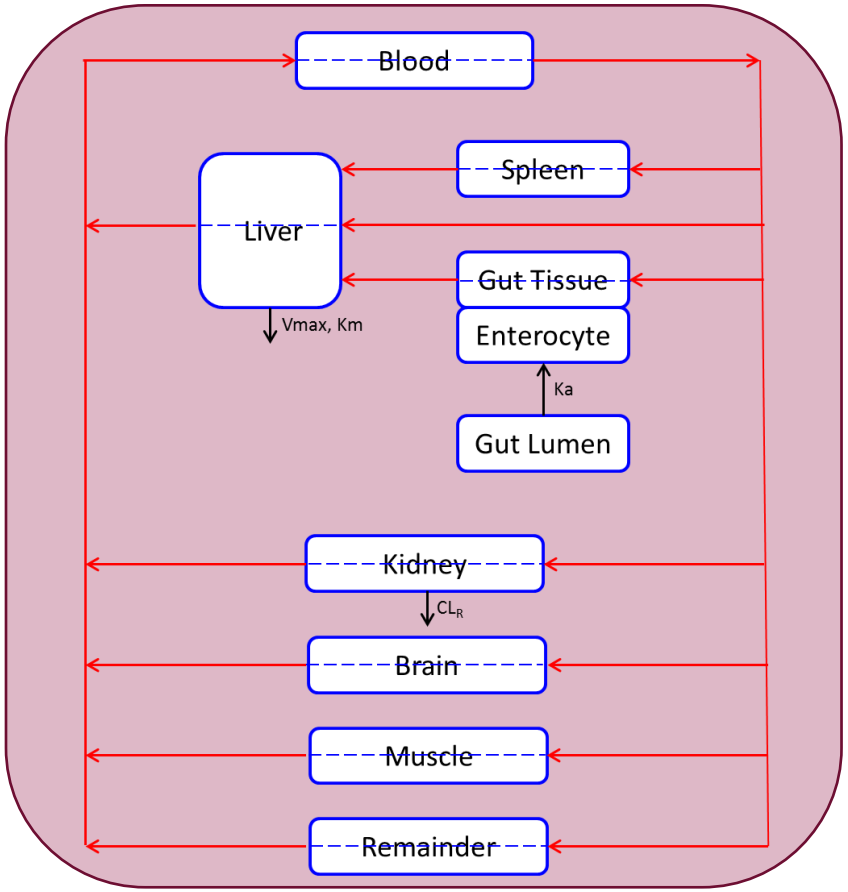


Potential Approaches

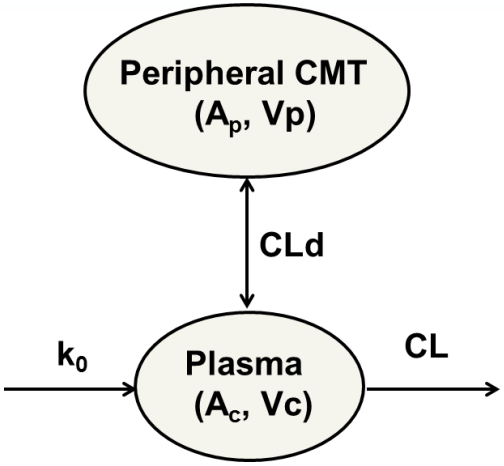
Top Down

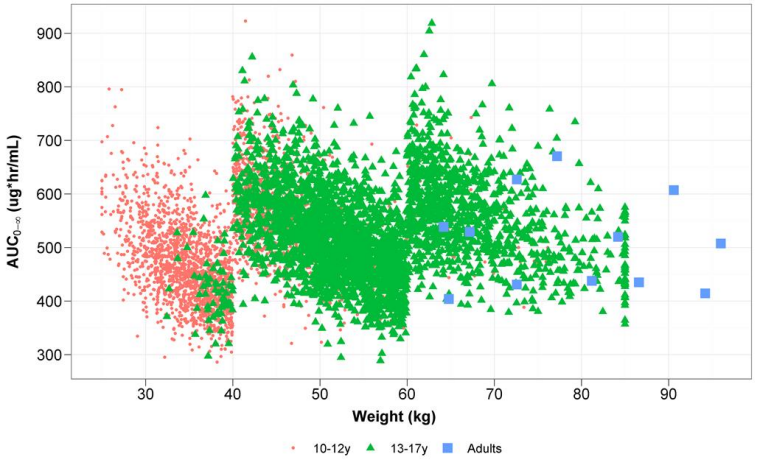


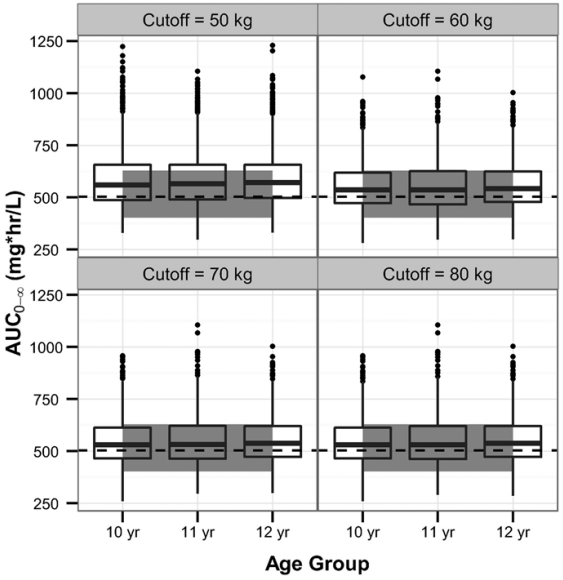
Bottom Up

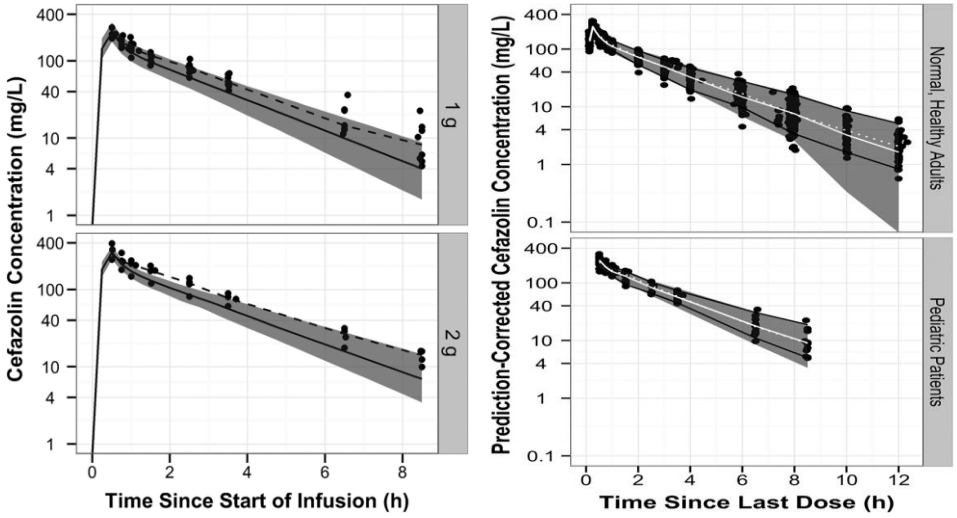


Pediatric Pharmacometrics Example
Top Down Approach



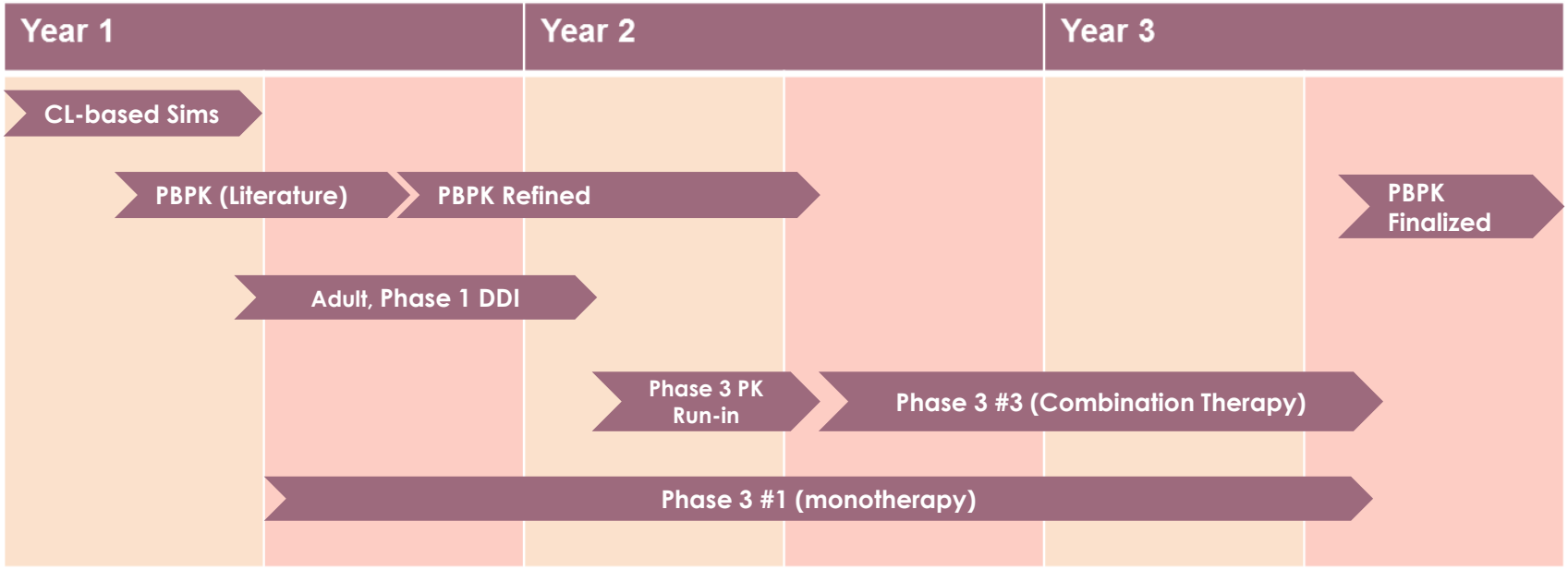


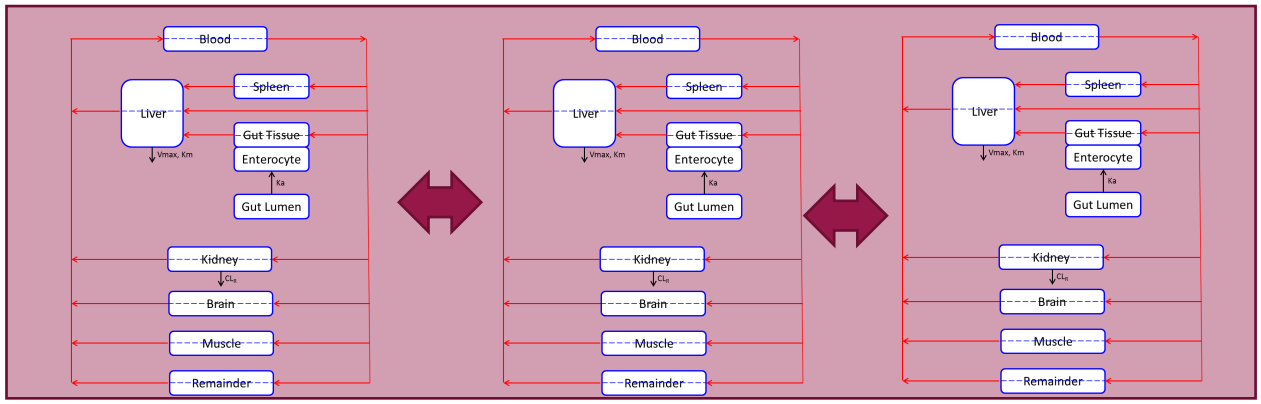




Schmitz MJ, Blumer JL, Cetnarowski W, Rubino CM. *Antimicrob Agents Chemother* 2015; 59(7): 4173-4180.

Pediatric Pharmacometrics Example
Bottom Up Approach





Study Design Considerations
Sample Size and Optimal Sampling

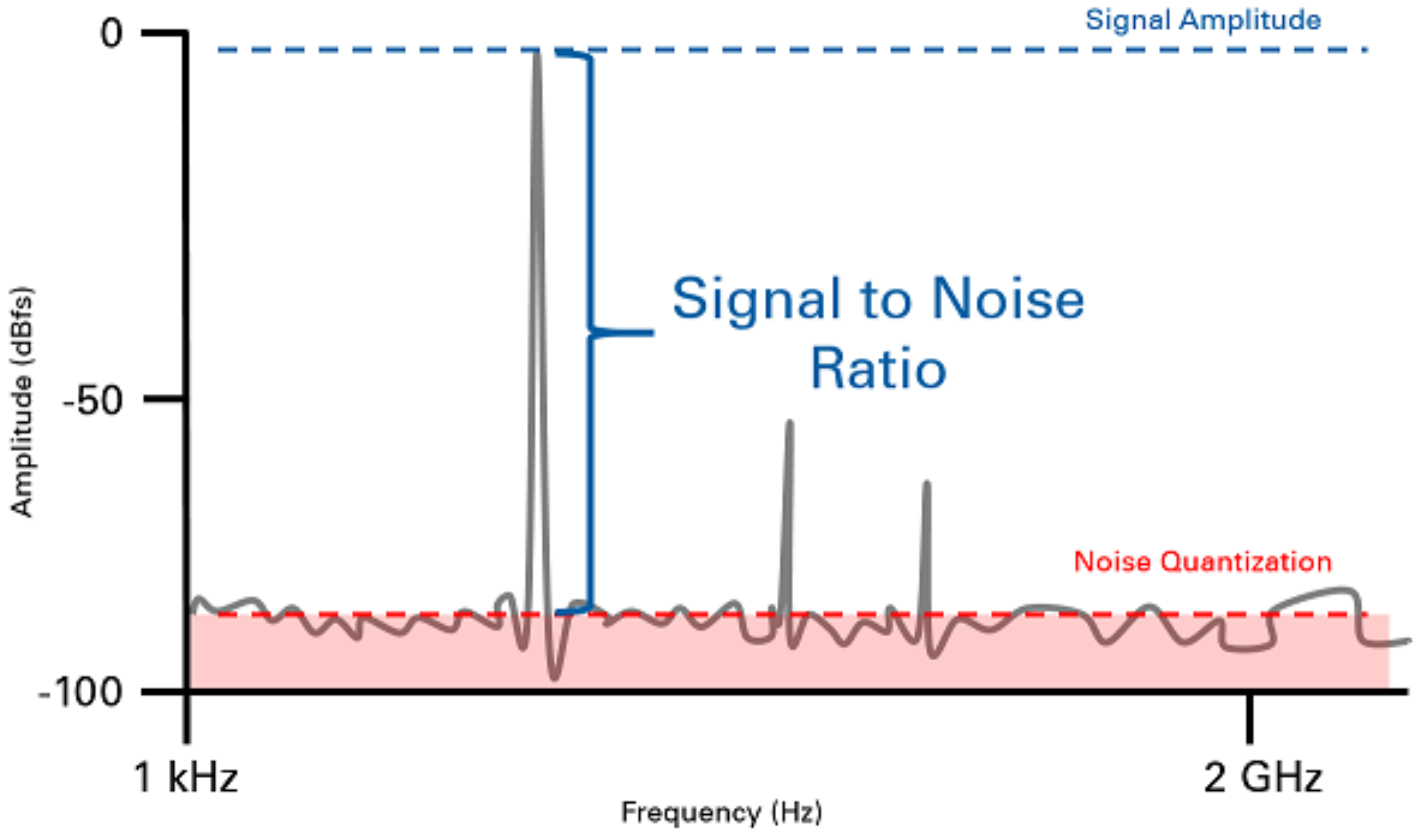
Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies

Yaning Wang, PhD, Pravin R. Jadhav, PhD, Mallika Lala, PhD, and Jogarao V. Gobburu, PhD

Keywords: *pediatric drug development; pharmacokinetics; regulatory requirement; precision*

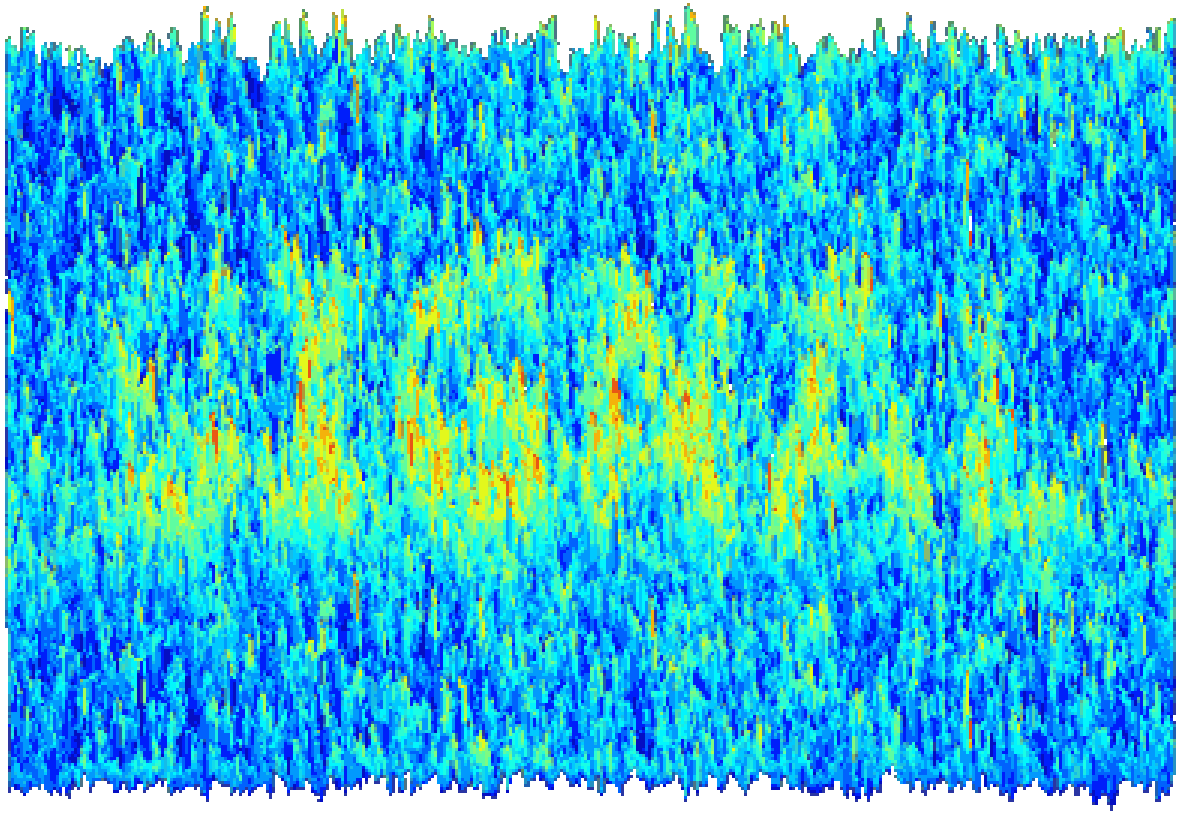
Journal of Clinical Pharmacology, 2012;52:1601-1606

"The Signal and The Noise"



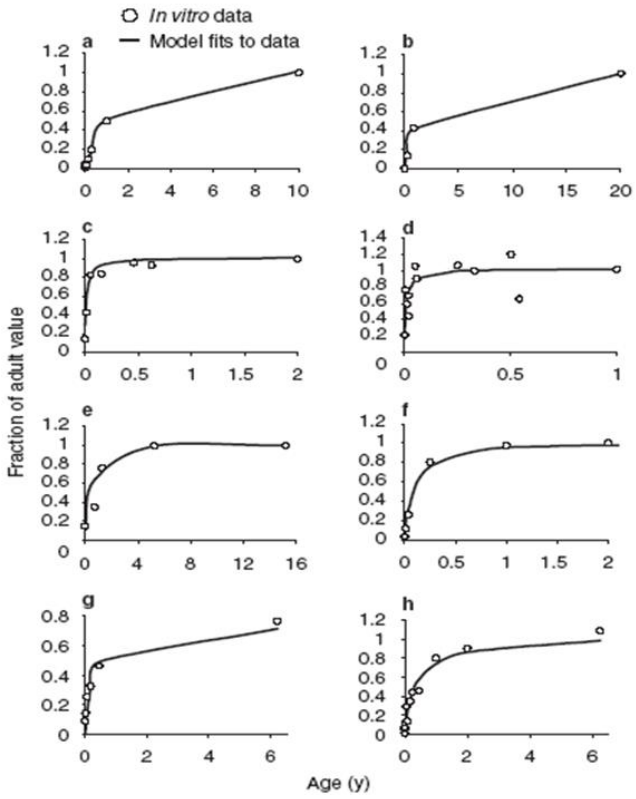
Understanding Frequency Performance Specifications. *National Instruments*, 25 April 2016. http://www.ni.com/white-paper/3359/en/. Accessed on 12 September 2016.

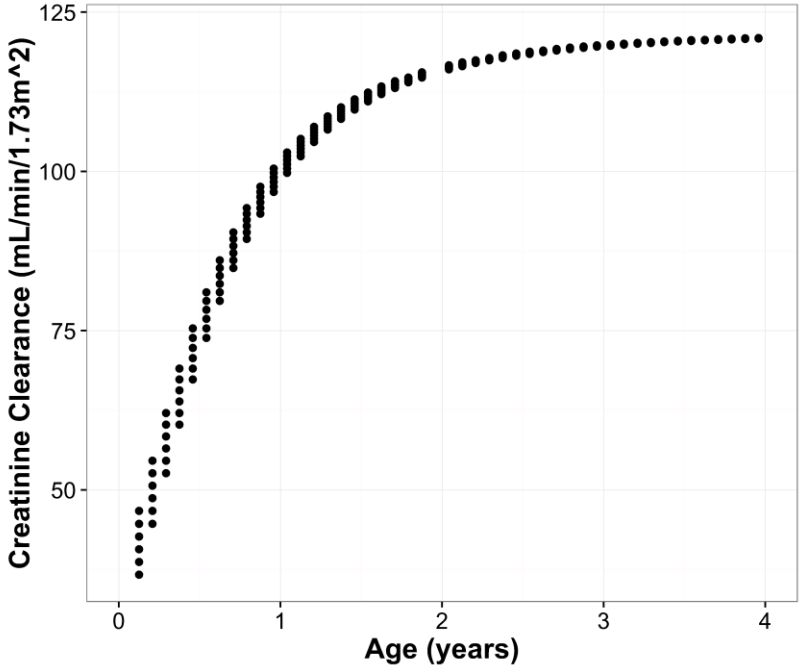
"The Signal and The Noise"



Principles of Design #58 – Signal-to-Noise Ratio. *doctordisruption*, 22 June 2014. http://www.doctordisruption.com/design/principles-of-design-58-signal-to-noise-ratio/ . Accessed on 12 September 2016.

The Signal is There…

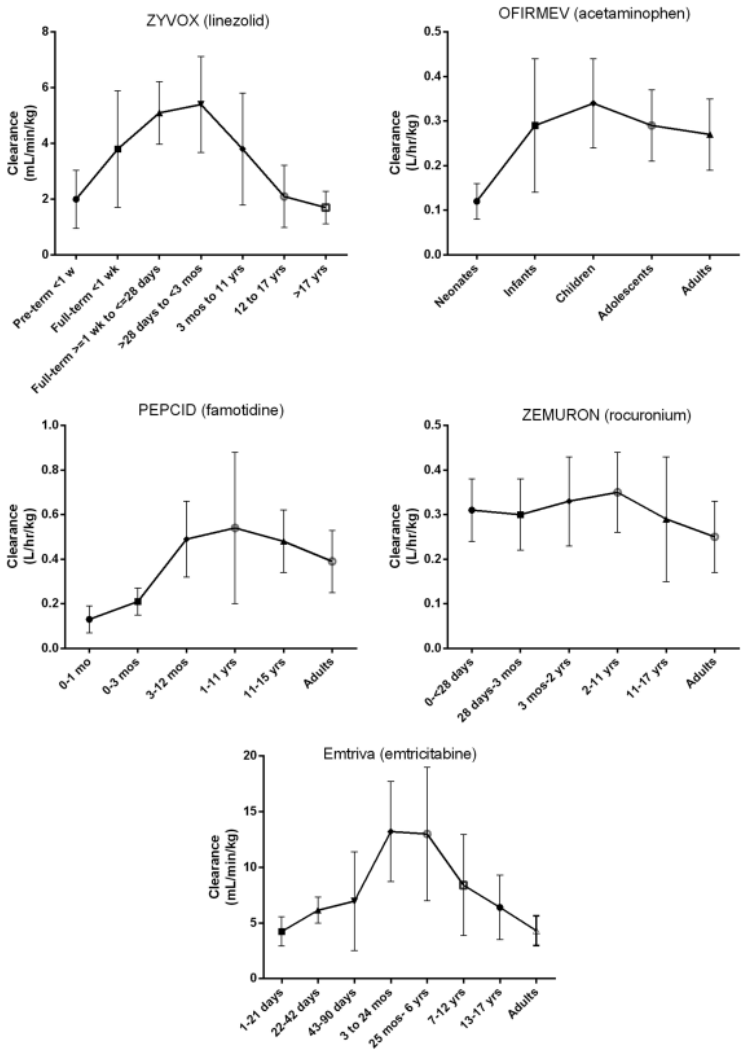




Johnson TN, et al. *Clinical Pharmacokinetics* 2006; 45(9):931-956

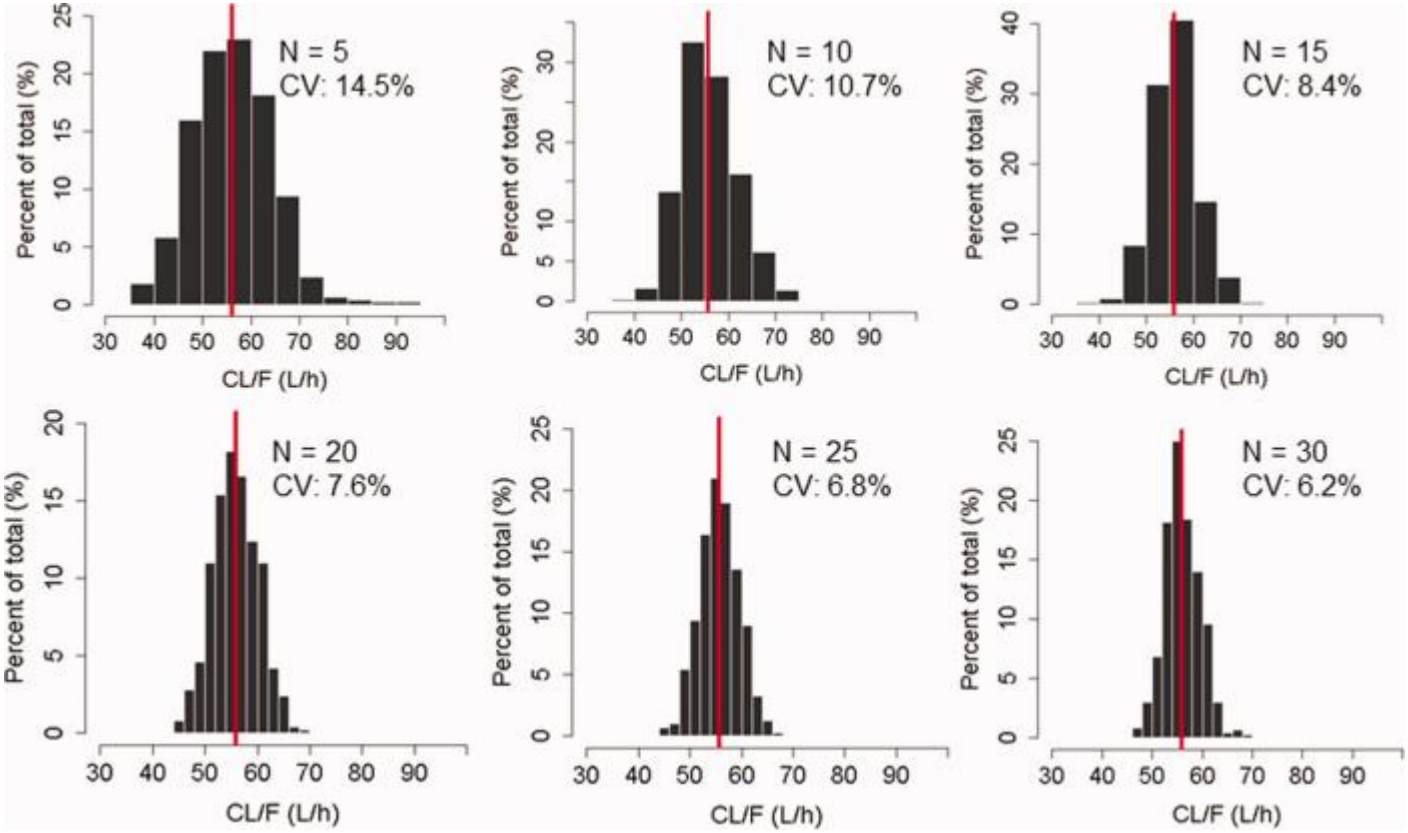
Rhodin MM, et al. *Pediatr Neph* 2009; 24:67-76

… But Kids Can Be Noisy



Wang J, et al. A Survey of Neonatal Pharmacokinetic and Pharmacodynamic Studies in Pediatric Drug Development. *Clin Pharmacol Ther* 2015; 98: 328-335.

Pharmacometrics Can Help
Top Down Approach



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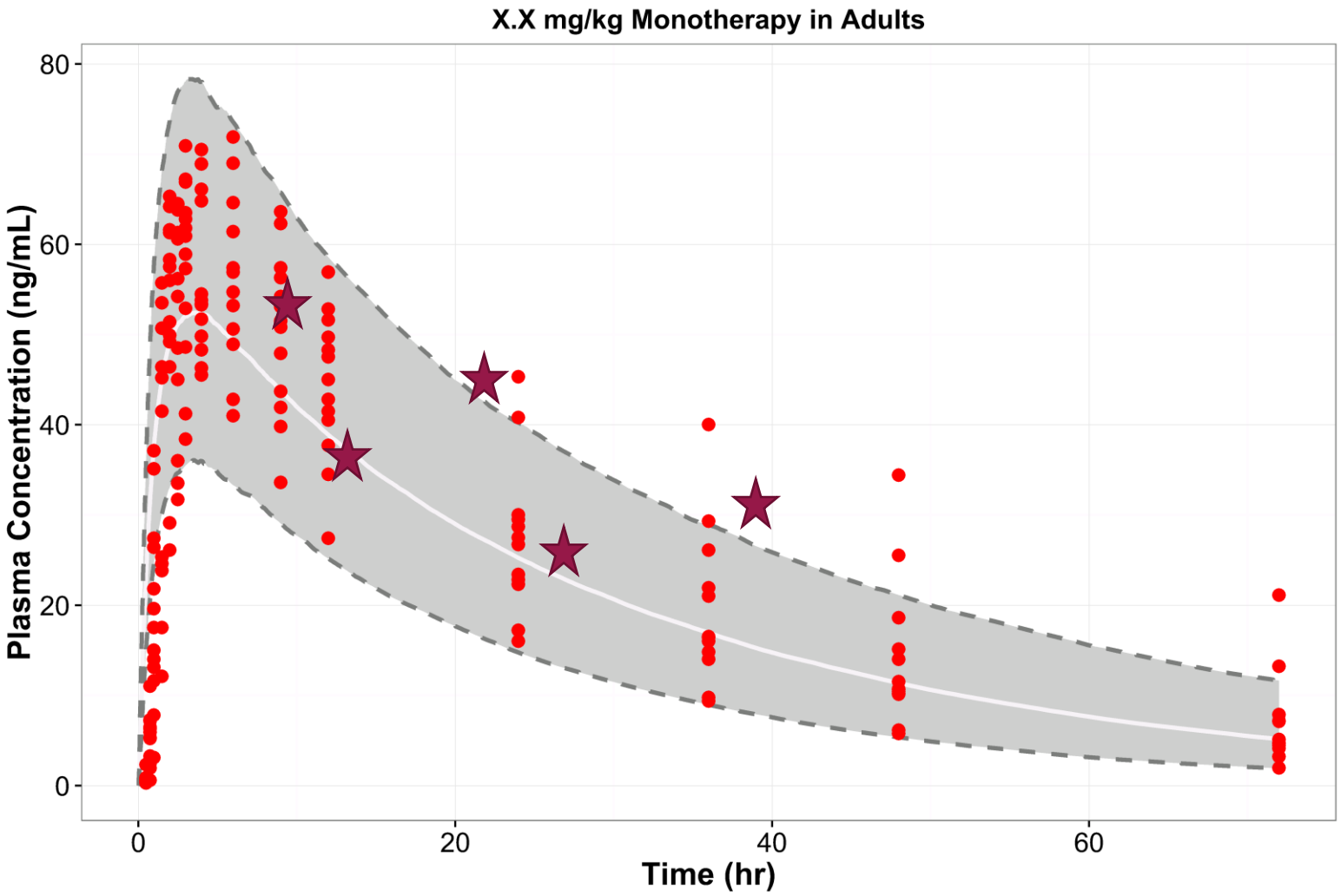
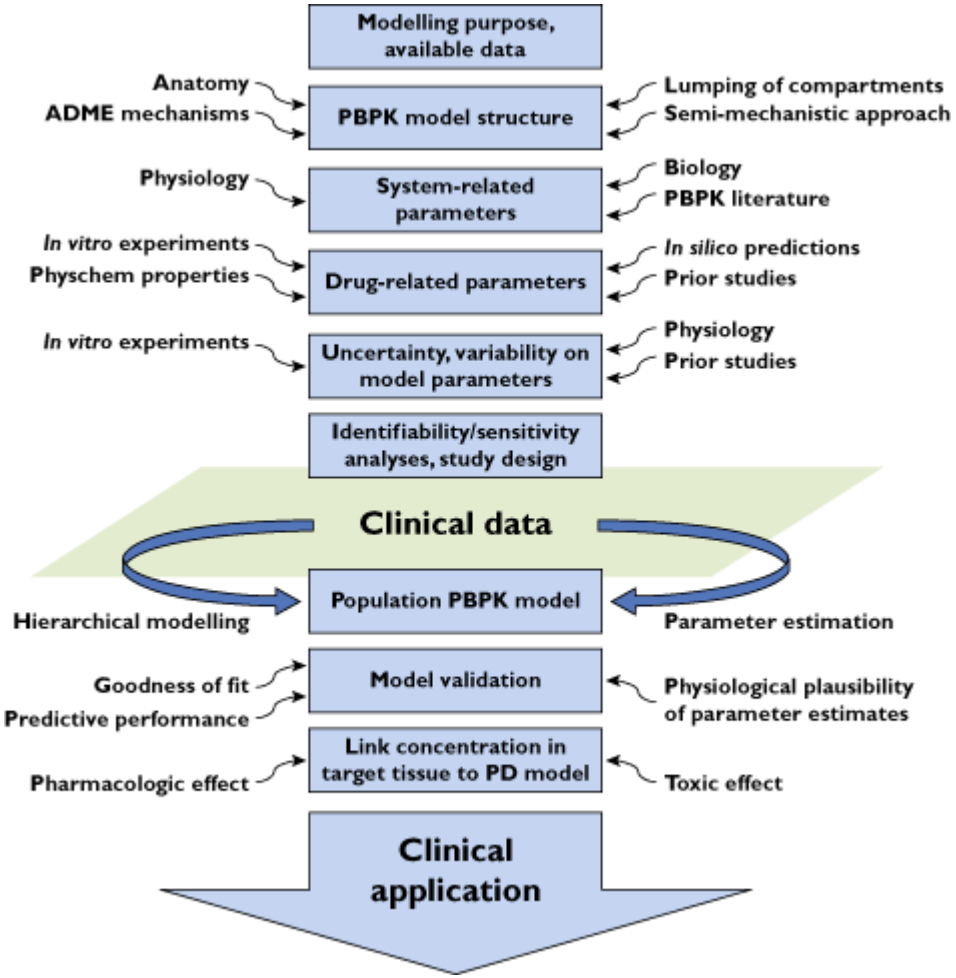
What About Bottom Up?
Qualifying PBPK Models

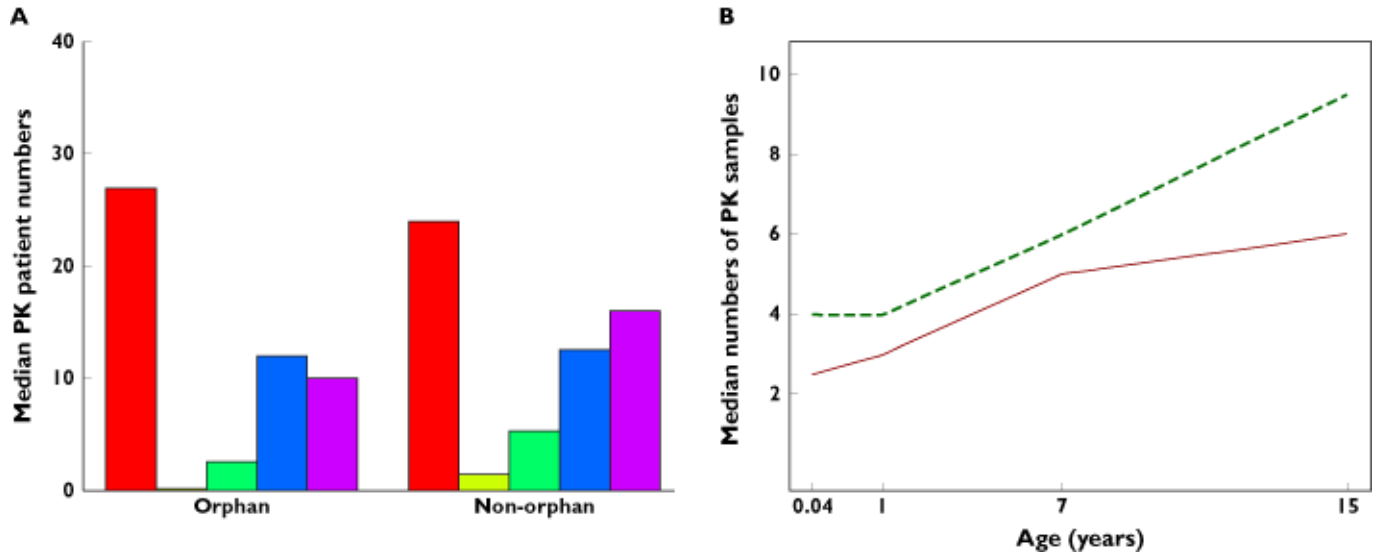


Hybrid Approach



Tsamandouras N, Rostami-Hodjegan A, Aarons L. Combining the 'bottom up' and 'top down' approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data. *Br J Clin Pharmacol* 2015; 79 (1): 48-55.

Reality Sometimes Gets in the Way



(A) Cumulative numbers of patients contributing PK information and (B) median numbers of PK samples per patient in 25 programmes conducting at least one PK trial, stratifying randomization into PK studies by age and stipulating intended sampling schedules. Numbers in each age group are based on programmes developing in that age group. Three (of 25) programmes obtain (some) PK samples from urine or saliva.
(A) Cumulative PK patient numbers. , total (red); , 0–27 days (light green); , 1–23 months (green); , 2–11 years (blue); , 12–17 years (purple) and (B) median numbers of PK samples per patient. , non-orphan (green, dashed); , orphan (red, solid)

Hampson LV, et al. Bridging the gap: a review of dose investigations in paediatric investigation plans. *Br J Clin Pharmacol* 2014; 78 (4): 898-907.

MEETING SUMMARY

Tripartite meeting held between the EMA, FDA and PMDA at the EMA, London, on 1-2 September 2016 to discuss regulatory approaches for the evaluation of antibacterial agents

"It may be appropriate to accept a **greater degree of uncertainty** regarding the benefit:risk balance when developing new antibacterial agents that can be used to treat patients with limited treatment options, e.g. it may be acceptable to conduct trials in smaller numbers of patients than would usually be required"

Il meglio è nemico del bene

(The better is enemy of the good)

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Thank you for your attention.