Pediatric PBPK Panel Discussion:
Clinical Pharmacology Studies in Neonates

Jian Wang, Ph.D; Gil Burckart, Pharm.D.

Pediatric Clinical Pharmacology Staff

FDA/CDER/OTS/OCP

May 5, 2014

Provisions Under FDASIA Have Mandated Neonatal Activities

- <u>SEC. 502. WRITTEN REQUESTS</u>

  "*If a request under this subparagraph does not request studies in neonates, such request shall include a statement describing the rationale for not requesting studies in neonates.*"
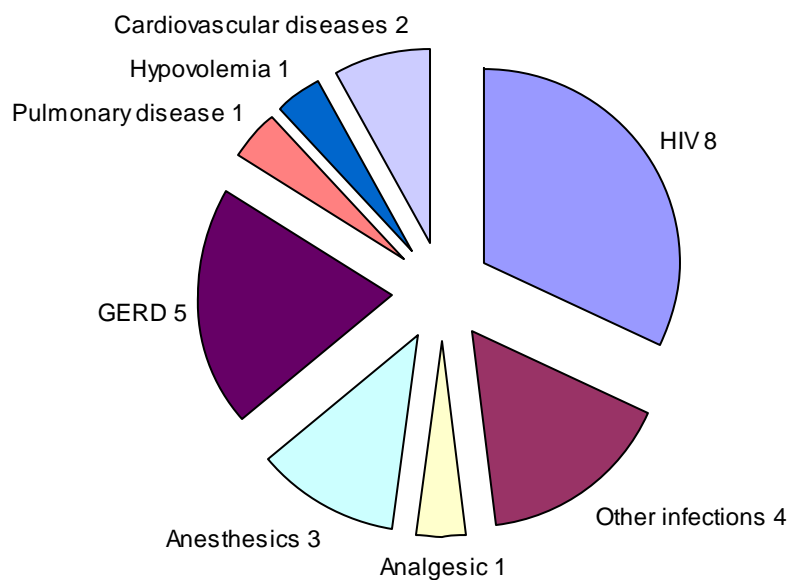
- <u>SEC. 508. REPORT</u>

  "*the efforts made by the Secretary to increase the number of studies conducted in the **neonatal population** (including efforts made to encourage the conduct of appropriate **studies in neonates** by companies with products that have sufficient safety and other information to make the conduct of the studies ethical and safe); and the results of such efforts.*"
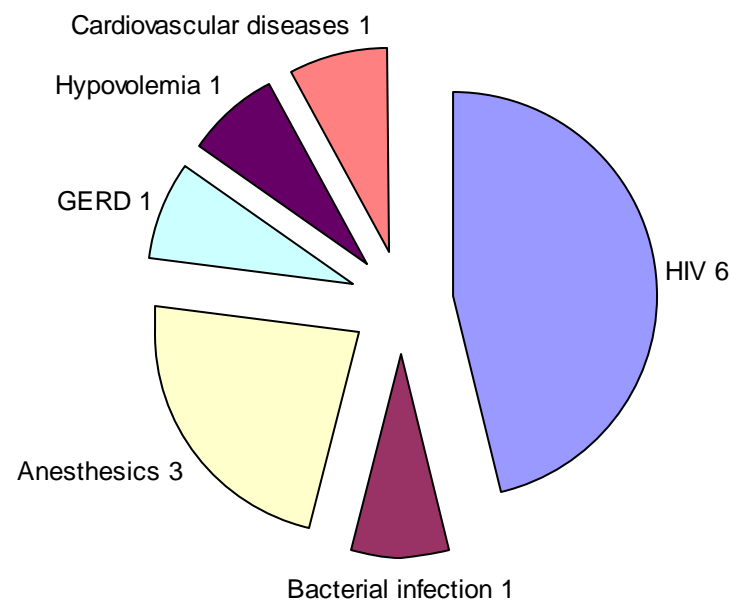
Drug Studies Including Neonatal Clinical Pharmacology between 1997 - 2012

- Pediatric PK studies included neonates:
  - **30** drugs with studies included neonates
  - **12** studies conducted population PK analyses
  - **~350** neonatal patients with PK data
  - **1 to 46** neonates per PK study

- Approval and Labeling:
  - **13** products approved for use in neonates
  - **24** products have neonatal PK information in the labeling
  - **3** products have neonatal PD information in the labeling

PK/PD Labeling or Approval for Neonates

Left pie chart labels:
- Cardiovascular diseases 2
- Hypovolemia 1
- Pulmonary disease 1
- GERD 5
- Anesthesics 3
- Analgesic 1
- Other infections 4
- HIV 8

25 products have neonatal PK/PD in the labeling

Right pie chart labels:
- Cardiovascular diseases 1
- Hypovolemia 1
- GERD 1
- Anesthesics 3
- Bacterial infection 1
- HIV 6

13 products approved for use in neonates

U.S. Food and Drug Administration
Protecting and Promoting Public Health

12 PopPK Reports Included Neonatal PK Data

Drugs	Neonates	Samples	Cov for CL	Cov for V	E-R?	Cov for PD
A	46	11	WT+ PMA	WT	Yes	No
B	1	5	PMA	-	-	-
C	2	9	WT+ Bilirubin	-	Yes	No
D	10	5	WT	-	Yes	PMA
E	20	9	WT+ PNA	WT	-	-
F	5	4	WT+ PNA	WT	Yes	No
G	14	4	-	WT+ PNA	-	-
H	-	-	WT+ PNA	-		
I	15	18	WT+ CrCL	WT	-	-
J	5	3	WT+ PNA	WT	-	-
K	13	3	WT +Age+Preterm+CYP	WT	No	No
L	2	4	WT (PCA for Ka)	WT	-	-
M	9	6	WT+PNA	WT	QTc	Age

Predict Neonatal Clearance from Prior Adult and Pediatric PK Data?
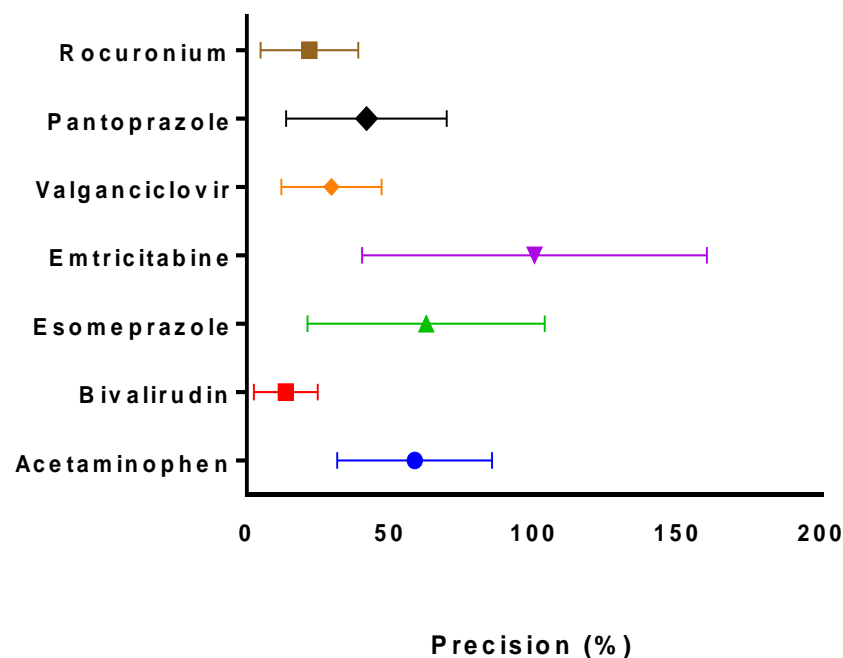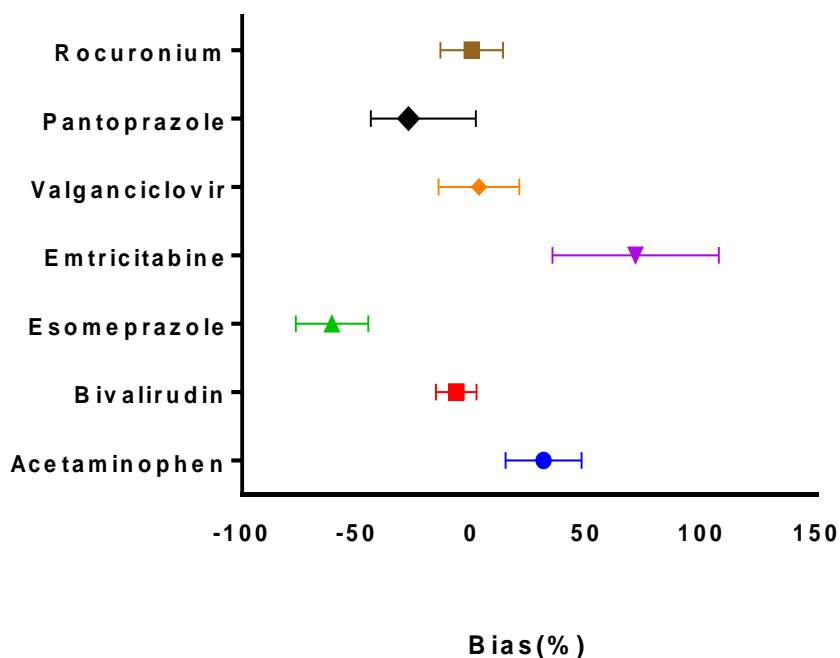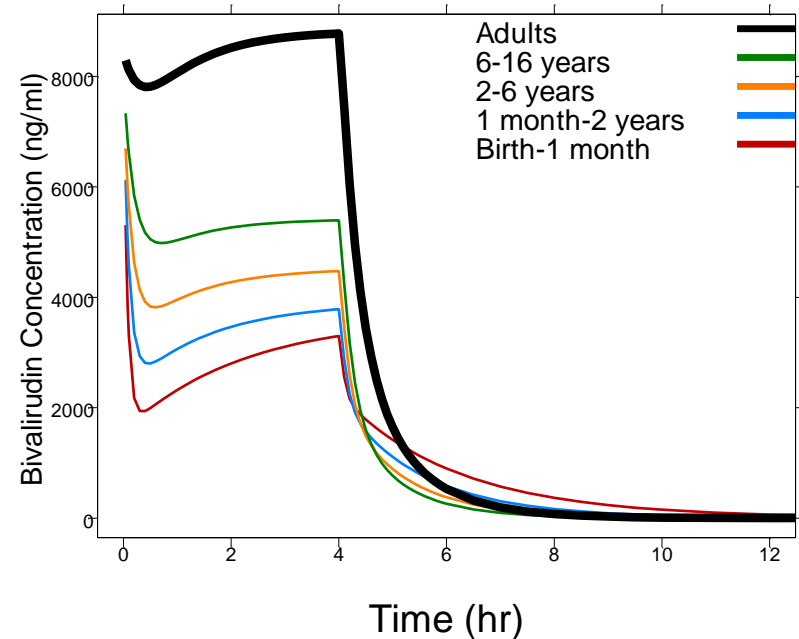

$$MPE = \frac{\sum P_{ei}}{N}$$

$$RMSE = \sqrt{\frac{\sum P_{ei}^2}{N}}$$
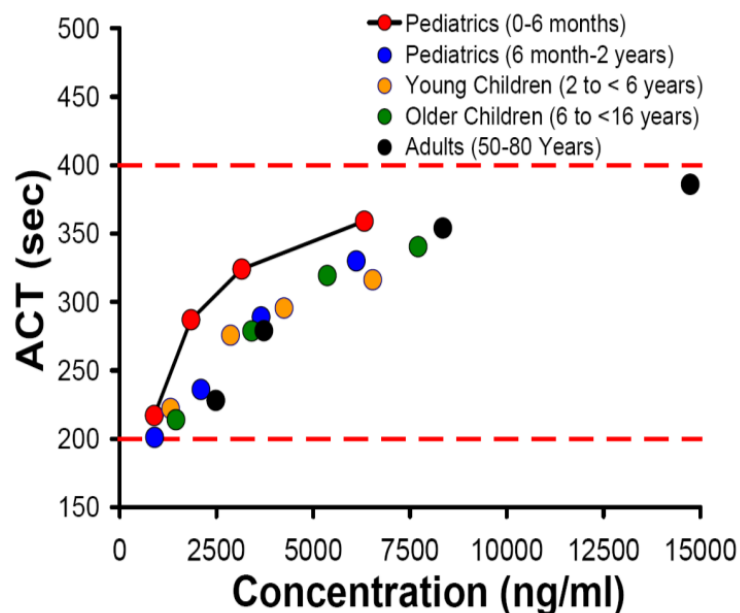
Neonates: Differences in PK
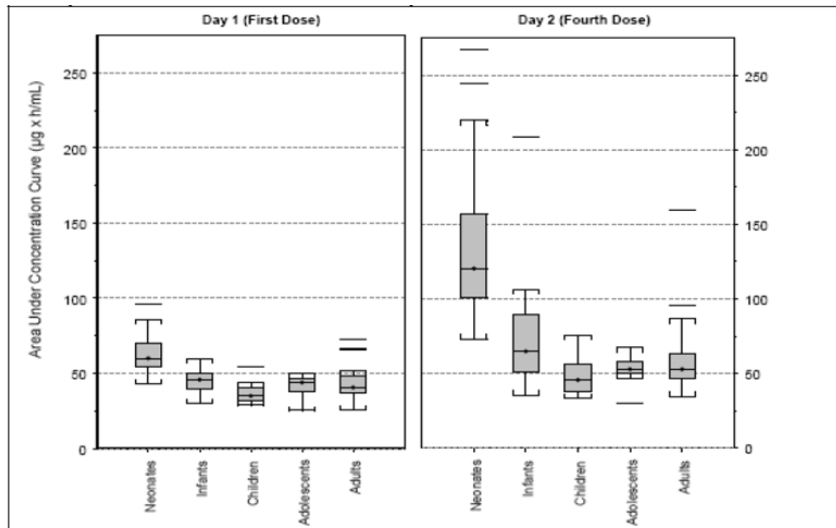
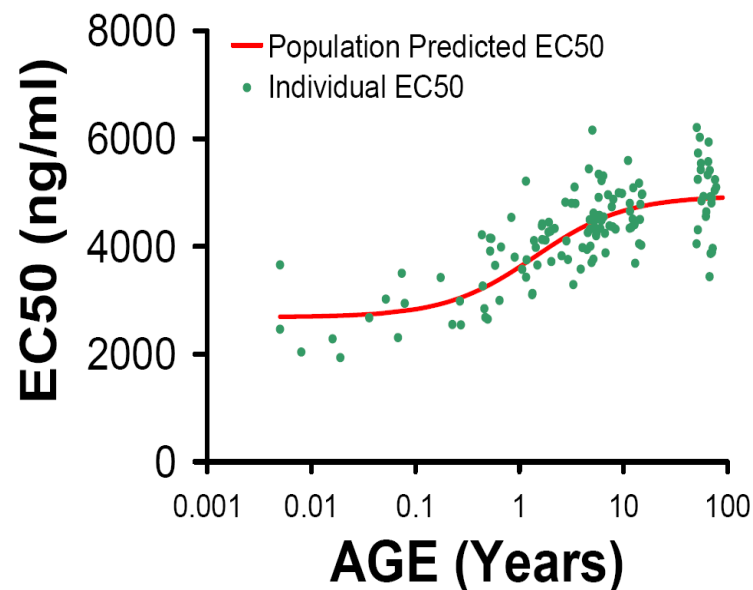Higher exposure and lower clearance in neonates (IV acetaminophen)

Neonates achieved lower exposure than older children at the same dose

FDA CP reviews for NDA22450 and NDA20873

Neonates: Differences in PD

Neonates had higher ACT at similar bivalirudin concentrations

Age explained 28% of the interindividual variability in EC50

FDA CP review for NDA20873

Summary

- Limited numbers of drugs that have been studied in neonates

- Considerable variability in drug PK

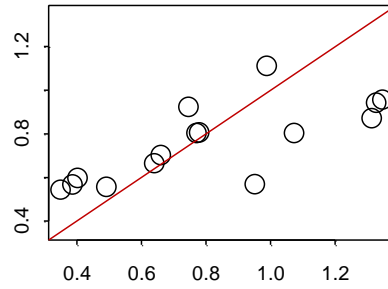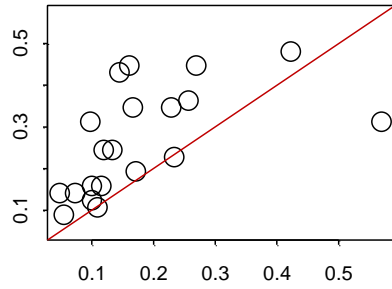- Small sample size
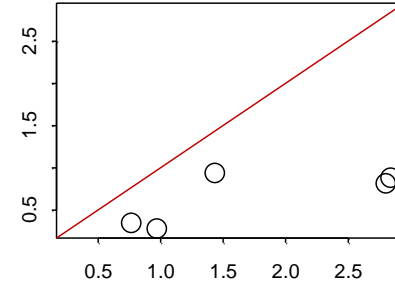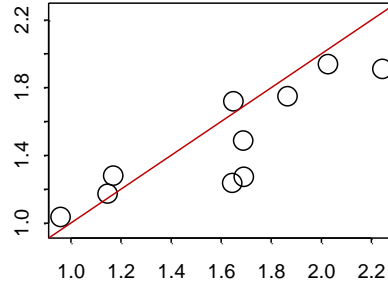
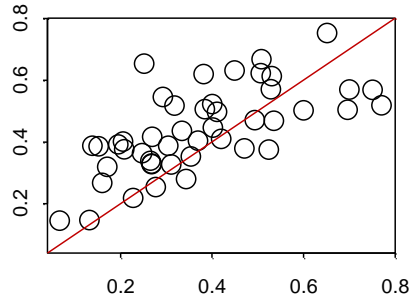- Lack of robust clinical/PD end points

Acknowledgements

- OCP reviewers

- PCPS

- Office of Pediatric Therapeutics

- Susie McCune

BACKUP

Predicted CL

Observed CL