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
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Provisions Under FDASIA Have Mandated Neonatal Activities

- **SEC. 502. WRITTEN REQUESTS**
  
  “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.”

- **SEC. 508. REPORT**
  
  “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

25 products have neonatal PK/PD in the labeling

13 products approved for use in neonates
# 12 PopPK Reports Included Neonatal PK Data

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Neonates</th>
<th>Samples</th>
<th>Cov for CL</th>
<th>Cov for V</th>
<th>E-R?</th>
<th>Cov for PD</th>
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<tr>
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<td>WT</td>
<td>QTc</td>
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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.

Population Predicted EC50
Individual 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
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BACKUP