PPRU Pharmacometrics

Status of Pediatric Pharmacokinetic and Pharmacodynamic Studies at PPRU Inception

- 90% of drugs without complete pediatric labeling
- Industry approach to pediatric PK/PD studies
  - Not ethical
  - Not possible
  - Not interested
- Network Formation – 1994
  - Initial PK goals
    - Provide PK information
    - Provide labeling information
    - Provide training
- Pediatric Rule of 1994
  - Voluntary
  - Tepid industry response

Cycle-1 Industry Sponsored PPRU Pharmacokinetic Studies

- Pre-FDAMA - Limited
  - PPRU Network in role of children's advocate
  - Adolescents and older children
  - Therapeutic areas with prior Industry (and PPRU) experience
    - Infectious Diseases
    - General Pediatrics
  - Formulation development – nearly insurmountable barrier to studies
- PPRU involvement in industry studies highly variable
- Any "add-on science" required no significant cost to sponsor

Cycle-1 PPRU Investigator Initiated Pharmacokinetic/Pharmacodynamic Studies

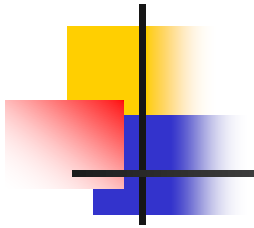
- PPRU Site composition similar with limited therapeutic interest areas
  - Nephrology, Critical Care, Infectious Diseases, Toxicology
- “Local” studies included in PPRU Network
  - Provide training opportunities
  - Foster interest in pharmacology studies within institution
- Inter-site collaborations
  - Mainly through industry sponsored studies
- Initiation of developmental pathway initiatives
  - CYP 3A
  - CYP 2D6
  - Renal Clearance

Cycle-1 PPRU Investigator Initiated Pharmacokinetic and Pharmacodynamic Studies

- All Centers had strong analytical capabilities including ability to work with small sample volumes
- PK studies predominately single dose without PD assessment
  - Non-compartmental analyses
  - Optimal sampling design
  - Mirror of industry approach in adults
- Computer tools relatively immature
  - PCNONLIN, NONMEM ver. V (FOCE recently release)
  - S-plus only command language
  - ACLS and Pharsight simulation software developed during first cycle
  - PD models limited - primarily effect compartment
  - Dynamic disease and mechanistic models not employed
- Integration of pharmacogenomics
  - Frowned upon by industry
  - Expensive

The PPRU Network Funding Cycles 2 & 3

- FDAMA, BPCA, PREA – starting in 1997 provided financial incentives for pediatric studies
- Industry Expanded Interest in Pediatrics
  - Modified adult studies / junior investigators
- FDA Guidance Documents for Pediatric PK studies and Population PK Studies
- PPRU Network expanded to 13 centers
- Limited local PPRU studies
- Development of collaboration among investigators with interest in pharmacometrics – PK/PD Modeling Committee



“ ... an alternate, and perhaps preferable, approach in many pediatric situations is the population PK approach”

- FDA Guidance for Pediatric Pharmacokinetic Studies

PPRU Pediatric Pharmacokinetic Studies – in Setting of FDAMA/BPCA

- Industry approach to pediatric PK studies
  - Increased use population study designs
    - Adult format for pediatric studies despite different objectives
    - Pediatrics lack multitude of intensive studies to support structural of models
    - Very limited data collected often with uninformative sample design
    - Analysis based on adult template – ignoring co-linearity of covariates, their impact on multiple PK parameters and non-linear developmental patterns of drug disposition.
  - PPRU expertise integral for population PK study design and analysis to develop useful PK models.

PK/PD in PPRU Investigator Initiated Trials

- Focus towards therapeutic areas where understanding pediatric pharmacology is lacking and particularly important for effective therapy
  - eg. neonatology, transplantation, pain, critically ill subjects

PPRU Pharmacometrics Impact on PPRU Trial Design

- Maximizing generation of knowledge from studies
  - Work with PPRU trial specialists to develop creative study designs – adaptive, real time assessments, scavenged samples, simulation assisted
  - Measurement drug concentrations in urine, tissue, saliva and free drug concentrations and drug binding to characterize activity at site – (included in 10 recent studies)

PPRU Pharmacometrics Impact on PPRU Trial Design (2)

- Maximizing generation of knowledge from studies
  - Measurement of drug metabolites for mechanistic understanding PK and ontogeny of metabolism
  - Ability and willingness to develop assays and optimize for minimal volume (over 250 methods available with PPRU)
  - Work with other PPRU investigators on assessment of biomarkers

PPRU PK/PD in Model-Based Pediatric Therapeutics Development

- Integration of existing data
- Use of Modeling and Simulation
  - To maximize information gained and trial success
  - To improve communication between pharmacologists, statisticians and clinicians
- Compiling pediatric data across studies
  - From literature, PPRU studies and PPRU investigators
- Iterative developmental models of drug disposition

Pediatrics in Model Based Drug Development (MBDD)

- Pediatric labeling does not require two phase III studies
- Modeling successes touted by FDA are come from pediatric examples
- Model based designs for pediatric studies proposed at 4/2008 FDA Clinical Pharmacology Advisory Committee Meeting.
- PPRU playing key role in approach
  - PPRU studies as examples
  - FDA Advisory Committee involvement

Modeling and Simulation (MS) Frequently Used in PPRU Study Design

- Childhood Absence Epilepsy
- Acetaminophen protein adduct
- Actinomycin
- Azythromycin
- Daptomycin
- Fexofenadine
- Pleconaril
- Ibuprofen for PDA
- Inositol
- Lorazepam for Sedation
- Lorazepam for Status
- Meropenem
- Morphine in infants

PPRU Pharmacometrics Group