The Best Pharmaceuticals for Children Act (BPCA) Overview

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Disclosure

• I have nothing to disclose.
• My presentation reflects my views only, not those of the NIH or the federal government.
History of Pediatric Drug Tragedies

• 1905: pediatric deaths from patent medicines
• 1906: Pure Food and Drug Act
  • Labels of food and drugs must truthfully identify contents (pure)
• 1936: sulfanilamide dissolved in diethylene glycol kills 107
• 1937: Federal Food, Drug, and Cosmetic Act
  • Drugs must be safe

• 1961: thalidomide causes limb deformities
• 1962: Kefauver-Harris Amendment
  • Drugs must be effective for their labeled indication
FDA Attempts to Add Pediatric Labeling

• 1994 Pediatric Rule
• 1997 FDA Modernization Act (FDAMA)
• 1998 Pediatric Rule (codified as PREA)
• 2002 Best Pharmaceuticals for Children Act (BPCA)
• 2003 Pediatric Research Equity Act (PREA)
Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA): Carrot and Stick

• 1994 Pediatric Rule
  • allows **extrapolation from adults to children**: If the course of the disease, mechanisms of action of drug are similar in children and adults, the efficacy can be extrapolated
  • requires safety, pharmacokinetic and pharmacodynamic studies in children

• 1997 FDA Modernization Act (FDAMA)
  • For drugs already approved and marketed
  • Provides 6 month **patent extension** in exchange for performing pediatric studies in response to FDA Written Request
    • Patent extension on the moiety
  • Generally originated by NDA holder
  • Results of the studies do NOT need to be positive

• 2002 BPCA: renewal of FDAMA + role for NIH
• 2003 PREA: mandate for pediatric studies for drugs under NDA review for the same indication
BPCA Provisions: NIH

• Section 409I
  • Generally applicable to drugs lacking patent exclusivity
  • NIH responsibility
    • Prioritization
    • Sponsorship of pediatric clinical trials
    • Submission of clinical trials data to FDA for consideration of label change
Pediatric Labeling Applicability: BPCA and PREA

Marketed, with exclusivity: BPCA/industry

NDA under review: PREA

Marketed, without exclusivity: BPCA/NIH
Elements needed to fulfill Written Request

• **Industry:** Medications of interest with existing marketing **exclusivity**

• **FDA:** Knowledge of basic **mechanism of disease** and mechanism of action of **drug**; **drug safety**; clinical trial **endpoints**; ability to **extrapolate** efficacy (if possible)
Written Request Process

Industry
- Drugs with remaining exclusivity
- Develops draft Written Request

Industry and FDA
- Negotiates terms of Written Request

FDA
- Issues Written Request
- Performs studies
- Submits data to FDA
- Reviews Data
- Makes exclusivity determination

Industry
Elements Needed to Fulfill Written Request

• Patient population meeting inclusion/exclusion criteria
• Pediatricians/pediatric subspecialists with capability to recruit/retain patients
• Physician equipoise
• Pediatric clinical pharmacologists to design the trials using agreed-upon efficacy and safety endpoints
• Pediatric formulation
• Trial design
  • Dose-finding study
  • Pharmacokinetic/safety +/- efficacy study
• Pediatric clinical trial infrastructure: nursing, pharmacy, patient- and family-friendly locale
• Compliance with Good Clinical Practice (GCP)
Commonly Used Medications in Obstetrics

**UTI**
- Cephalexin
- Ampicillin
- Nitrofurantoin
- TMP/SMX

**Depression**
- Citalopram
- Fluoxetine
- Sertraline
- Paroxetine

**Pre-eclampsia**
- Magnesium Sulfate

**Pre-term Labor**
- 17-α-OHP
- Terbutaline

**GDM**
- Insulin
- Glyburide
- Metformin

**Pregnancy-induced HTN**
- Nifedipine
- Labetalol
- Hydralazine
- Clonidine
- α-methylldopa

**Seizures**
- Lamotrigine
- Levetiracetam
### Population-Specific Conditions

#### Neonates
- Intraventricular hemorrhage
- Hypoxia-induced encephalopathy
- Bronchopulmonary dysplasia
- Necrotizing enterocolitis

#### Pregnant Women
- Pregnancy-induced hypertension
- Pre-eclampsia
- Preterm labor
- Post-partum hemorrhage
Maternal-fetal drug transfer

1. Embryogenesis/organogenesis
2. Fetal maturation
3. Fetal maturation and growth
What is unique to the pregnant and lactating population that is not covered by the pediatric knowledge?

• Two connected organisms with **continually changing maturity and physiology**

• Lack of **basic science** of **disease mechanisms** in pregnancy

• Need for basic science on **placental** and breast milk **drug transport**

• How safe is safe? What does safe mean?
  • For the embryo/fetus: Lack of **mechanistic approach to pre-clinical toxicology** and off-target effects of drugs
  • For the pregnant woman: **Is a drug safe if it is** safe for the embryo/fetus (does not increase the background rate of fetal malformations) **but ineffective** for the pregnant woman?

• Lack of **development of novel drug targets** applicable to pregnancy and lactation, including development of placental drug transport inhibitors