The Best Pharmaceuticals for Children Act (BPCA) Overview

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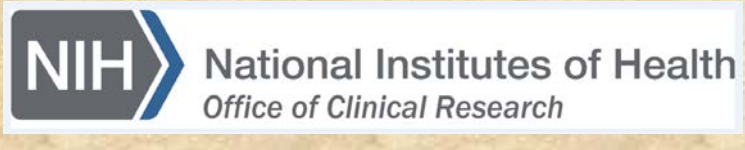


Disclosure

- 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

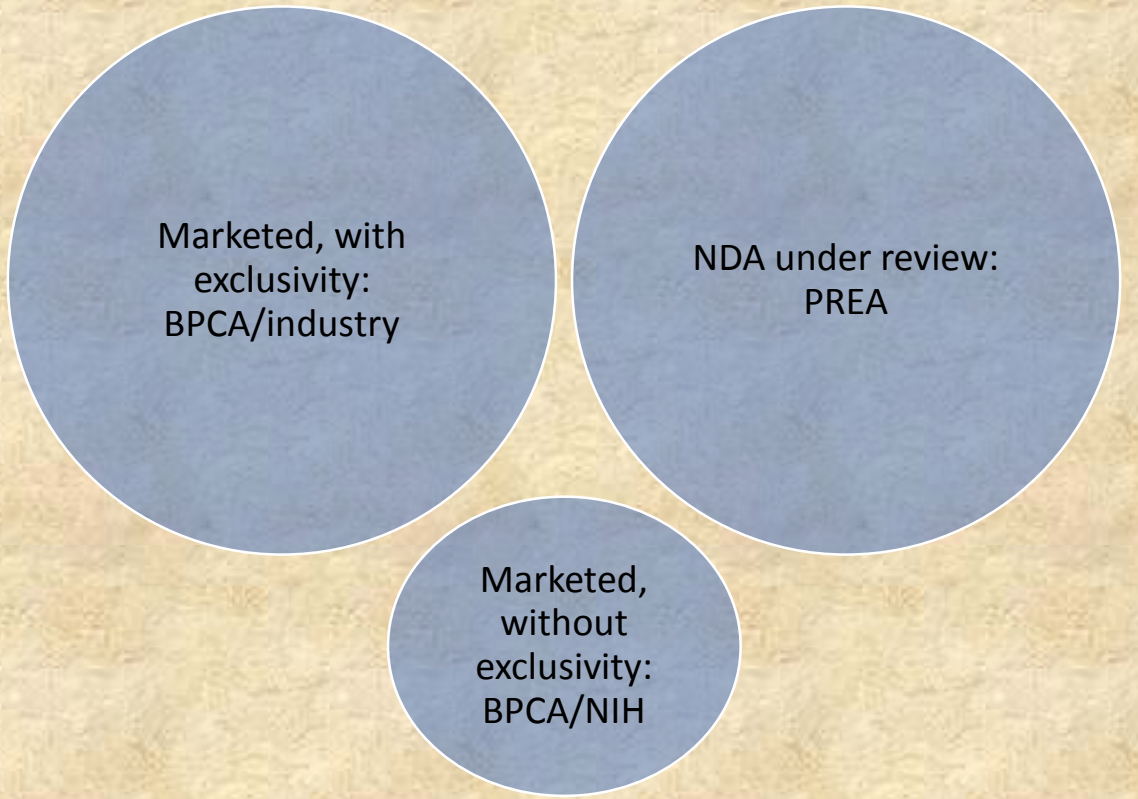
- 1997 FDA Modernization Act (FDAMA)
  - For drugs already approved and marketed
  - Provides 6 month **patent extension** in exchange for performing pediatric studies in response to FDA Written Request
    - Patent extension on the moiety
  - Generally originated by NDA holder
  - Results of the studies 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

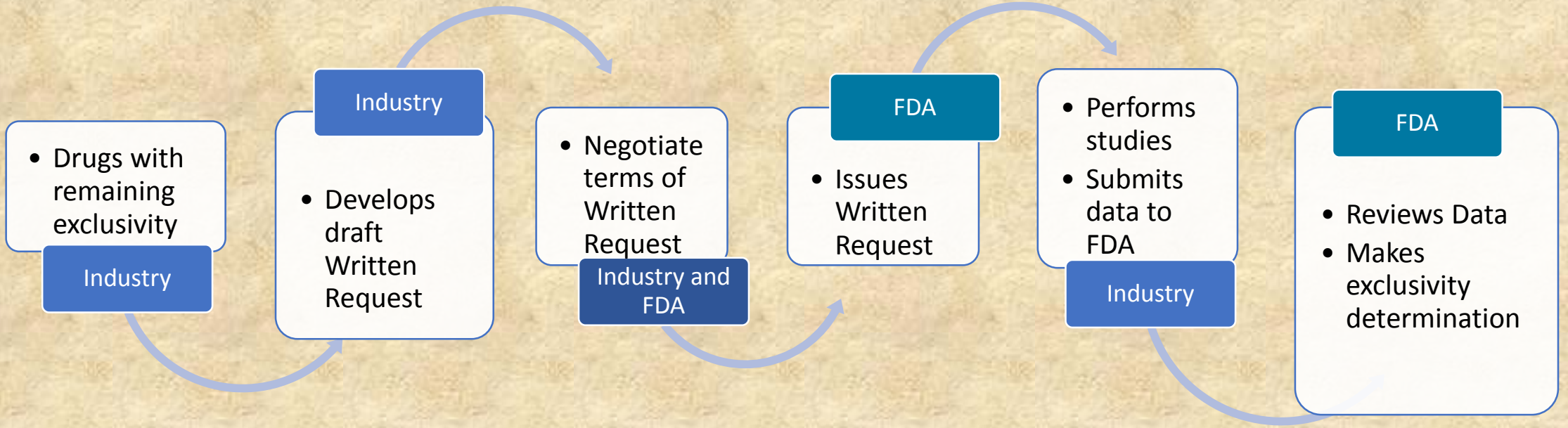
Pediatric Labeling Applicability: BPCA and PREA



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



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-methyldopa

Seizures
Lamotrigine
Levetiracetam

Population-Specific Conditions

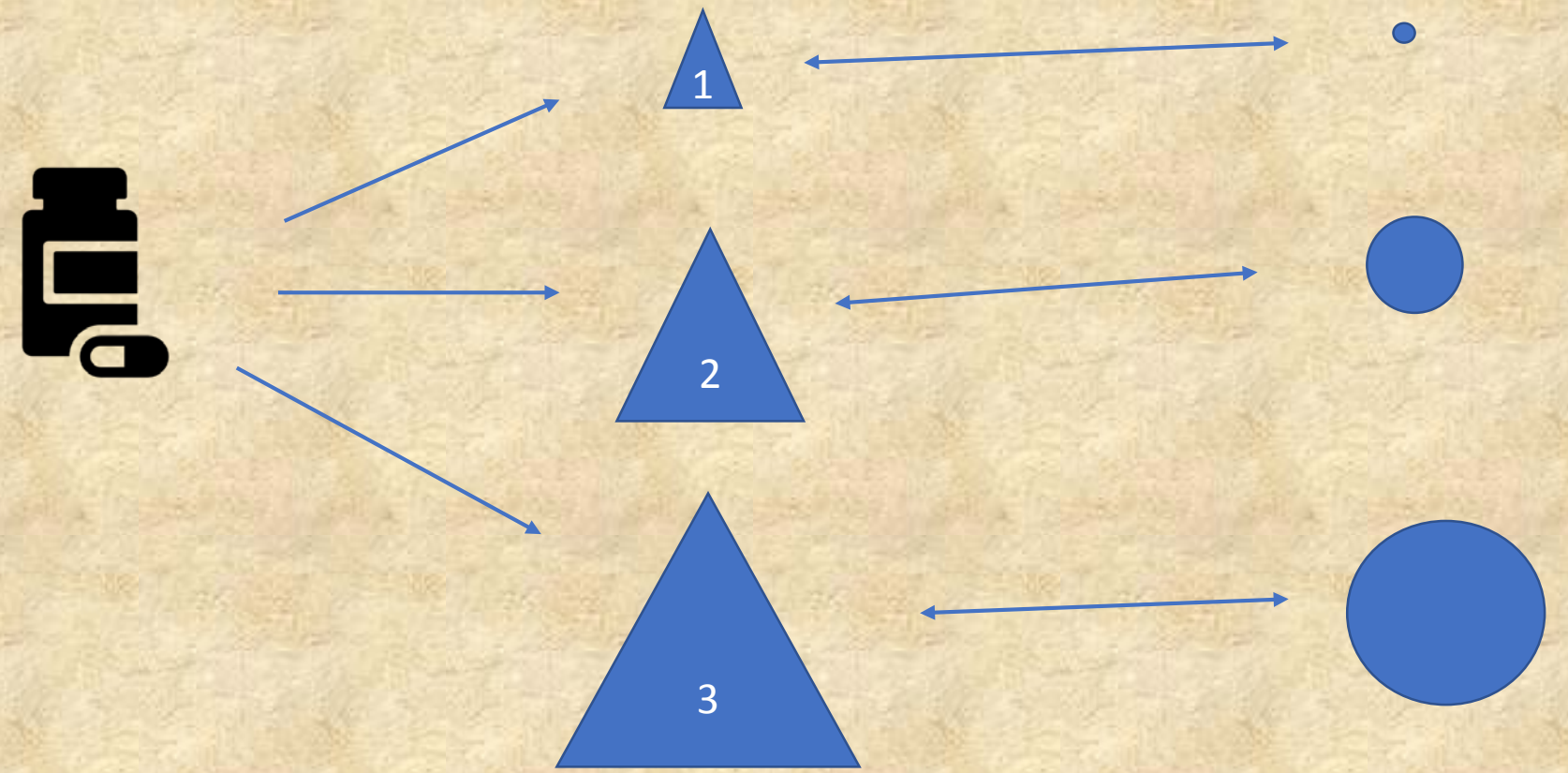
Neonates

- 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



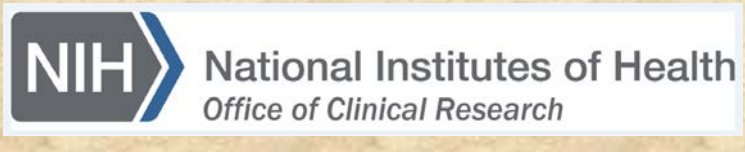
Embryogenesis/ organogenesis

Fetal maturation

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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