# Impact of Legislation on Pediatric Therapeutic Development: Regulatory Perspective

Prabha Viswanathan, MD
Deputy Director, Office of Pediatric Therapeutics
Office of Clinical Policy and Programs | Office of the Commissioner | FDA

National Academies of Sciences, Engineering, and Medicine

Committee on Developing a Framework to Address Legal, Ethical, Regulatory, and Policy Issues for Research Specific to Pregnant and Lactating Persons

September 27, 2023

# Disclaimers

- This presentation reflects my views and should not be construed to represent FDA's views or policies
- I have no financial conflicts of interest related to this presentation
- This presentation may include discussion of off-label use of medical products


# Overview

- Review of Pediatric Legislation:
  - Best Pharmaceuticals for Children Act (BPCA)
  - Pediatric Research Equity Act (PREA)
- Achievements in Pediatric Labeling
- Ongoing Challenges
- Parallels with Pregnant and Lactating Persons (PLP)

# Historical Milestones and Legislation in Pediatrics

**1902** — National Institutes of Health enacts the Biologics Control Act following the death of 22 children from tainted anti-toxins

**1938** — FD&C Act: enacted after the deaths of over 100 people, many of whom were children, following use of the Elixir Sulfanilamide; all marketed drugs must be safe for use as directed

**1962** — The FD&C Act amended: Drugs not tested in children should not be used in children

Following the thalidomide tragedies in Europe, the Kefauver–Harris amendments to the FD&C Act requiring that all approved drugs demonstrate both safety and effectiveness

**1974** — AAP Committee on Drugs issues guidelines for evaluating drugs for pediatric use

**1979** — FDA requires sponsors to conduct pediatric clinical trials before including pediatric information in the labeling

**1990** — Institute of Medicine holds workshop regarding the lack of labeling for pediatric drugs

**1992** — Agency proposed pediatric labeling and extrapolation

**1994** — Pediatric Plan to encourage voluntary development of pediatric data

**1997** — The pediatric exclusivity provision, FDAMA: provides 6-month market exclusivity incentive to sponsors who, in response to a FDA pediatric written request, conduct pediatric studies for drugs with potential use in children

**1998** — Pediatric Rule (mandatory): newly approved products are required to include pediatric assessments if the drug is likely to be used in a "substantial number of pediatric patients" (50,000) or if it may provide a "meaningful therapeutic benefit" unless requirement is waived or deferred

**2002** — FDAMA reauthorized as the BPCA 2002. Maintains the 6-month market exclusivity added to the remaining patent life of the active moiety. Biological products are not eligible

Pediatric Rule declared invalid by the Federal Court for the District of Columbia. The court determined that the rule exceeded the FDA's existing statutory authority

**2003** — PREA reinstates the FDA's 1998 pediatric rule. Requires each new drug or biological product application contain data adequate to assess the safety and effectiveness of the drug for its claimed adult indication and to support safe and effective dosing formulations for each pediatric subgroup.

Products with orphan designation are exempted

**2007** — Reauthorization of BPCA & PREA for 5 years under the FDAAA: Pediatric Review Committee (PeRC) formed for consults on pediatric plans/assessments and reviews all requests for deferrals, waivers, and pediatric plans. Studies submitted will result in pediatric labeling information

**2012** — FDASIA legislation BPCA and PREA are permanent

**2017** — FDARA implemented for oncology products

**2019** — Molecular Target list posted publicly in August

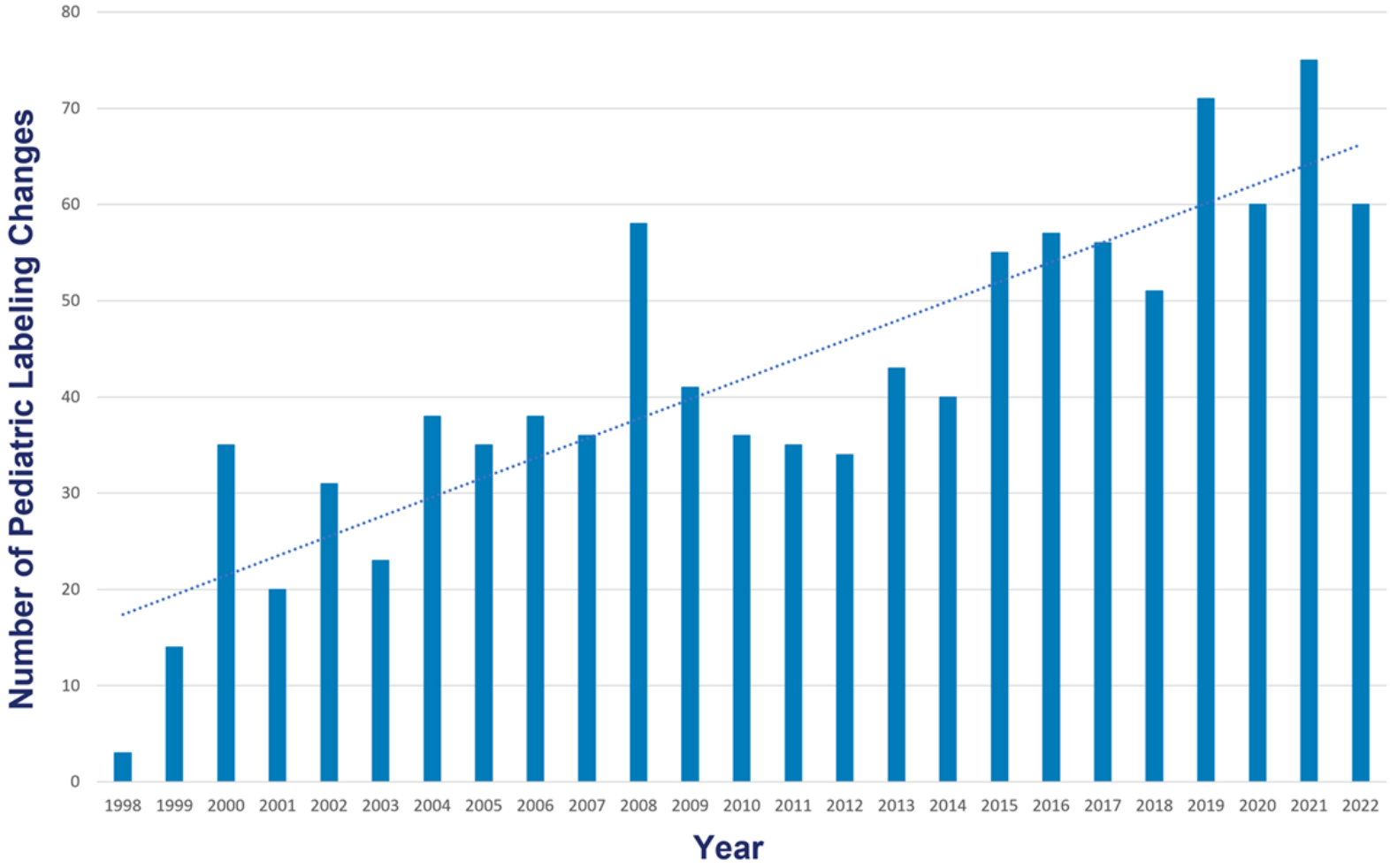
# ACHIEVEMENTS IN PEDIATRIC LABELING

# Do These Programs Work?

- Prior to 1997, more than 80 percent of approved drugs had no pediatric-specific labeling information.[1]
- Since then, over 1,000 pediatric labeling changes have been completed based on studies conducted pursuant to PREA or BPCA.[2]
  - Through 2021, 544 changes included expanded indications to include pediatric age groups not previously included.[3]
  - Through May 2023, 293 drugs have earned pediatric exclusivity (for 280 moieties).[4]

[1] BPCA and PREA Status Report to Congress July 1, 2015- June 30, 2020. Accessed September 17, 2023
[2] Pediatric Labeling Changes | FDA. Accessed September 17, 2023
[3] Pediatric Tracking Requirements Under FDAAA | FDA. Accessed September 17, 2023
[4] Pediatric Exclusivity Granted | FDA. Accessed September 17, 2023

# Pediatric Labeling Changes: 1998-2022

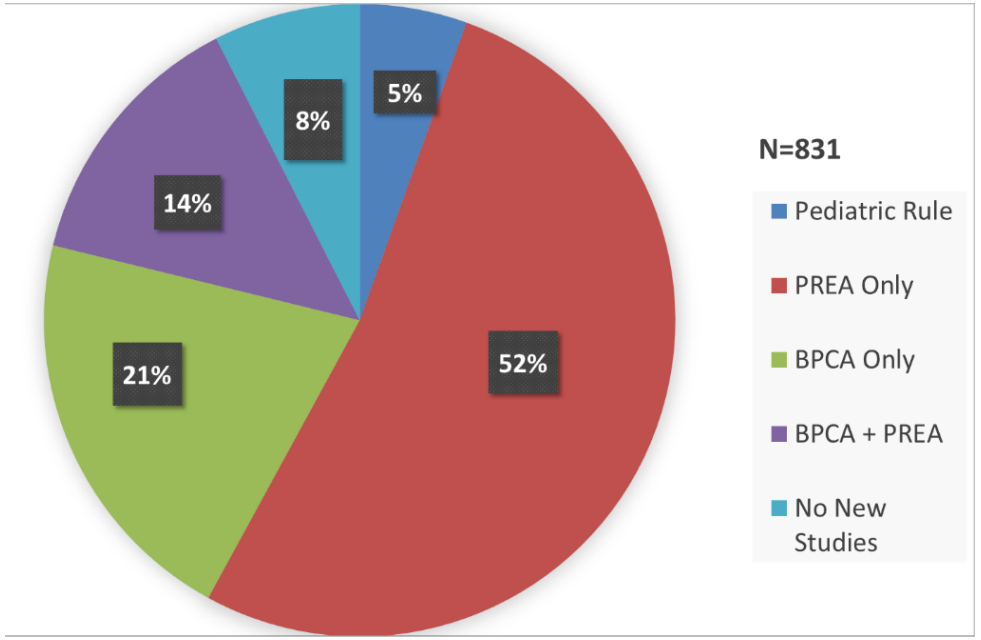



**Increasing number of pediatric labeling changes for drugs and biologics pursuant to the Pediatric Research Equity Act, Best Pharmaceuticals for Children Act, and Pediatric Rule**

# Pediatric Labeling for Medical Products

- 1,093 pediatric labeling changes through July 2023[1]
  - Pediatric Rule: 49 labeling changes
  - BPCA: 210 labeling changes
    - 409i (off patent BPCA) changes through NICHD[2]
  - PREA + BPCA: 178 labeling changes
  - PREA: 638 labeling changes

**Pediatric Labeling Changes From 1998-2019** [3]




[1] Pediatric Labeling Changes | FDA. Accessed September 17, 2023
[2] NIH Funded Pediatric Labeling Changes for drugs studied under the 409i process | FDA
[3] BPCA and PREA Status Report to Congress July 1, 2015- June 30, 2020. Accessed September 17, 2023

# ONGOING CHALLENGES

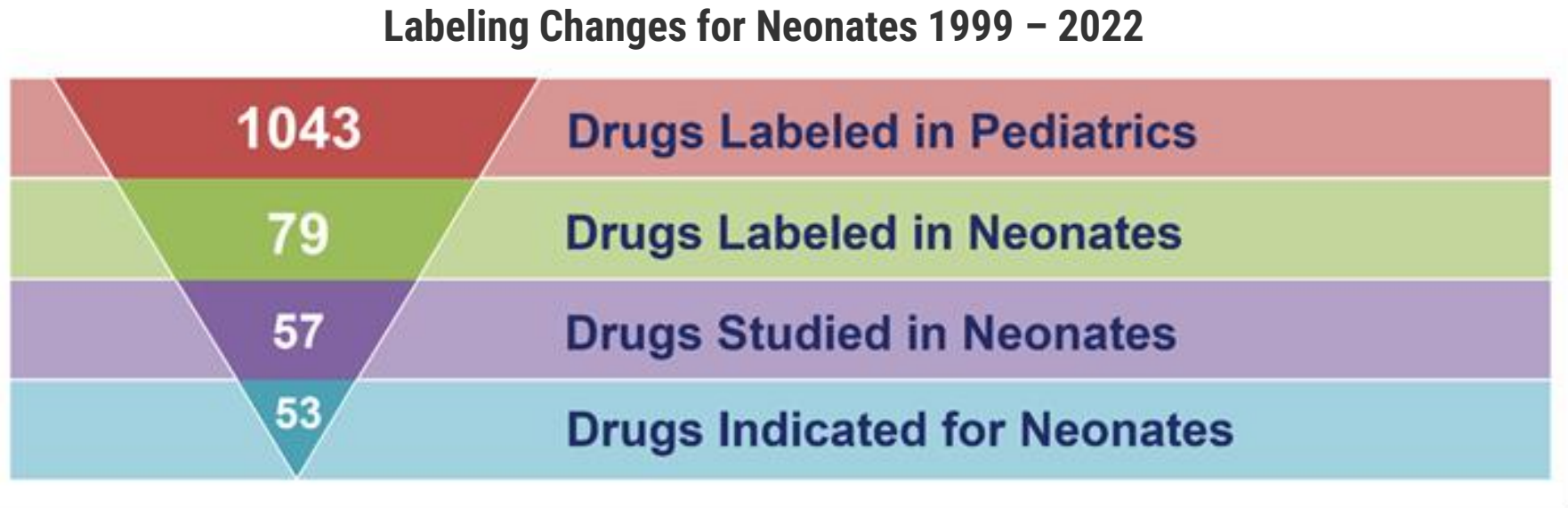
# Delays in Pediatric Labeling

- Gap of several years between approval for adults and any pediatric labeling for most medical products approved from 2017-2020
  - Average delay of 6.25 years (range 0.6-17.1 years) for new drugs
  - Average delay of 4.8 years (range 1-10.1 years) for new biologics
- Contributing factors:
  - Staggered pediatric enrollment by age groups
  - Delays in age-appropriate formulation development
  - Recruitment and enrollment challenges

BPCA and PREA Status Report to Congress July 1, 2015 – June 30, 2020

# Drug Development for Neonates

- Gaps in product labeling for neonates and preterm infants
- BPCA and PREA does not always address neonatal-specific conditions
- FDA encourages and supports studies in neonates through other mechanisms




Medical Products for Newborns | FDA

# PREA Exemption for Orphan Drugs

- The Orphan Drug Act does not require evaluation of orphan drugs in any specific populations affected by a rare disease
- PREA does not apply to drugs for an indication for which orphan designation has been granted*
- Need for additional pediatric labeling for over one-third of approved products for orphan indications that are relevant to the pediatric population
  - No pediatric information in some cases; in other cases, labeling does not address the full age range of affected pediatric patients
- Removal of the orphan exemption under PREA would improve the availability of approved therapies for pediatric patients with rare diseases

* Exception: some oncology drugs

Source: 2019 report to Congress on the pediatric labeling of orphan drugs

# Research to Accelerate Cures and Equity (RACE) for Children Act

- Amended PREA provisions requiring Sponsors to submit reports on pediatric investigations for cancer drugs that act on a molecular target that is substantially relevant to pediatric cancers[1]
- This requirement is not impacted by orphan drug designation
- Became effective in August 2020
- Insufficient time has passed to assess whether this will translate to more drugs being approved to treat pediatric cancer[2]
  - There has been an upward trend in the number of planned pediatric studies

[1] FDA Pediatric Oncology, accessed September 2, 2023.
[2] Pediatric Cancer Studies: Early Results of the Research to Accelerate Cures and Equity for Children Act. US Government Accountability Office, January 2023.

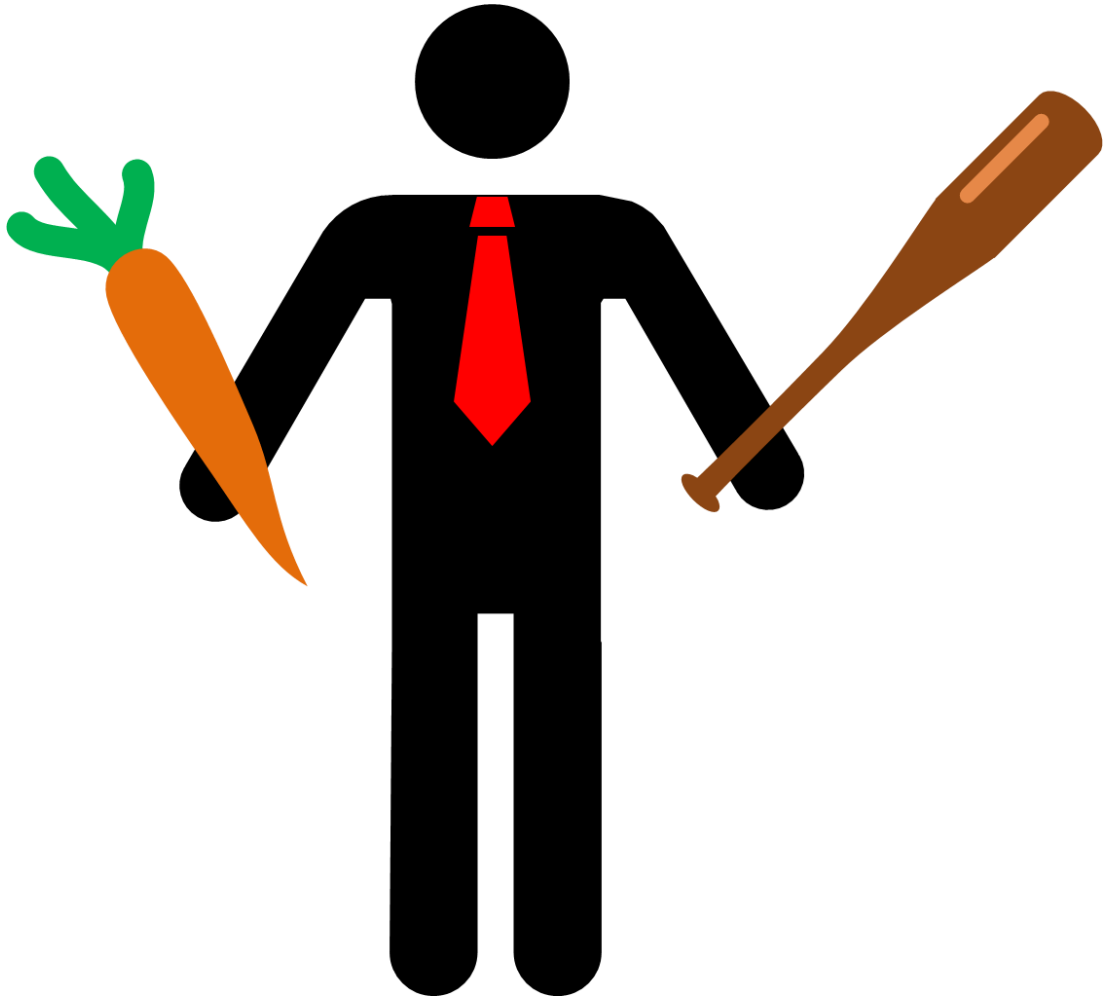
# TRANSLATING LESSONS LEARNED FROM PEDIATRICS TO PLP

# Similar Challenges

- Delays in evidence generation after marketing authorization for non-pregnant adults
- Logistical factors
  - IRB/Ethics committee approvals, trial insurance/liability
- Lack of data to guide dosing, efficacy, safety in special populations
- Complex benefit/risk considerations for clinical trials
  - Ethical and scientific considerations
  - Eased by having robust safety and efficacy data from non-pregnant adult populations
- Many factors complicate efforts to treat conditions unique to the population (e.g., bronchopulmonary dysplasia, preeclampsia)

# Carrot and Stick Model

- Mandates (like PREA) could be effective to get labeling for PLP for the same indication approved for non-pregnant adults
- Incentives (like BPCA) could propel development for other indications unique to pregnancy or lactation



# Conclusions

- There has been a steady rise in pediatric labeling since BPCA and PREA were enacted
  - Mandated studies under PREA drive this trend
- Some populations are not benefiting as much as others by existing pediatric legislation
- There are many parallels between medical product development for children and PLP
- The mandate/incentive model could be effective in improving data generation for PLP

# Acknowledgements


- Division of Pediatric and Maternal Health:
  - John Alexander
  - Lynne Yao
- Office of Pediatric Therapeutics
  - Debbie Avant
  - Melanie Bhatnagar
  - Dionna Green
  - Cindy Tworek

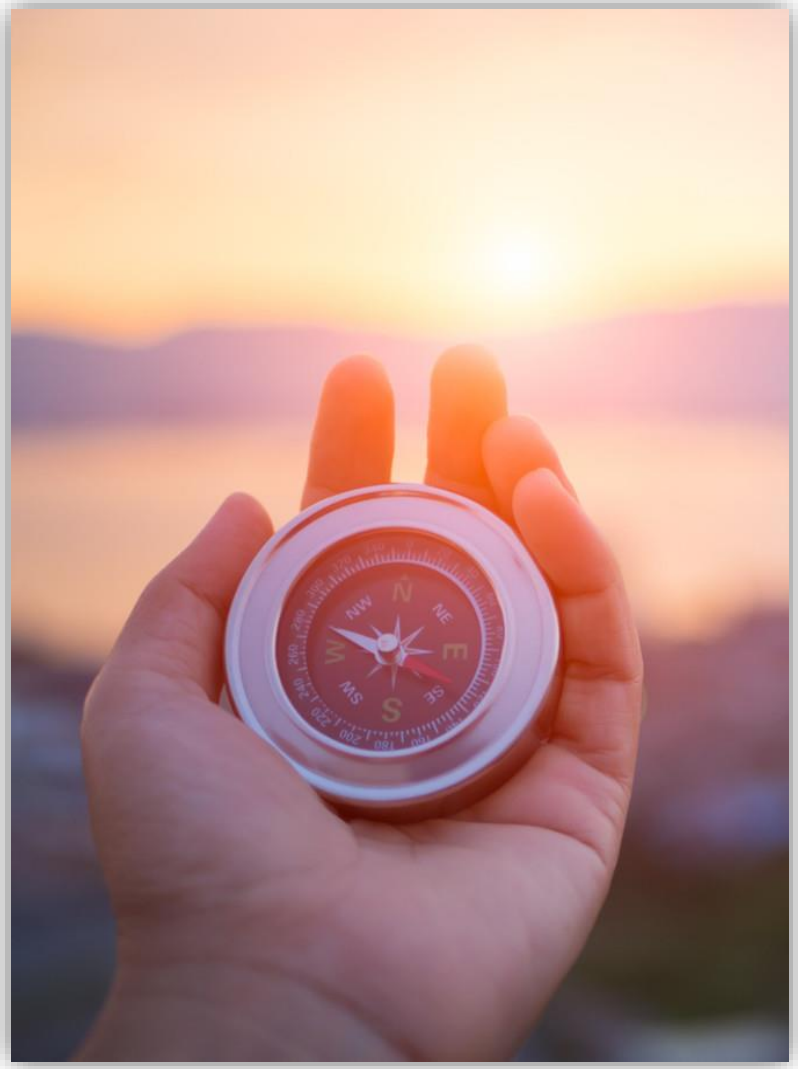


FDA
U.S. FOOD & DRUG
ADMINISTRATION

# SUPPLEMENTAL INFORMATION

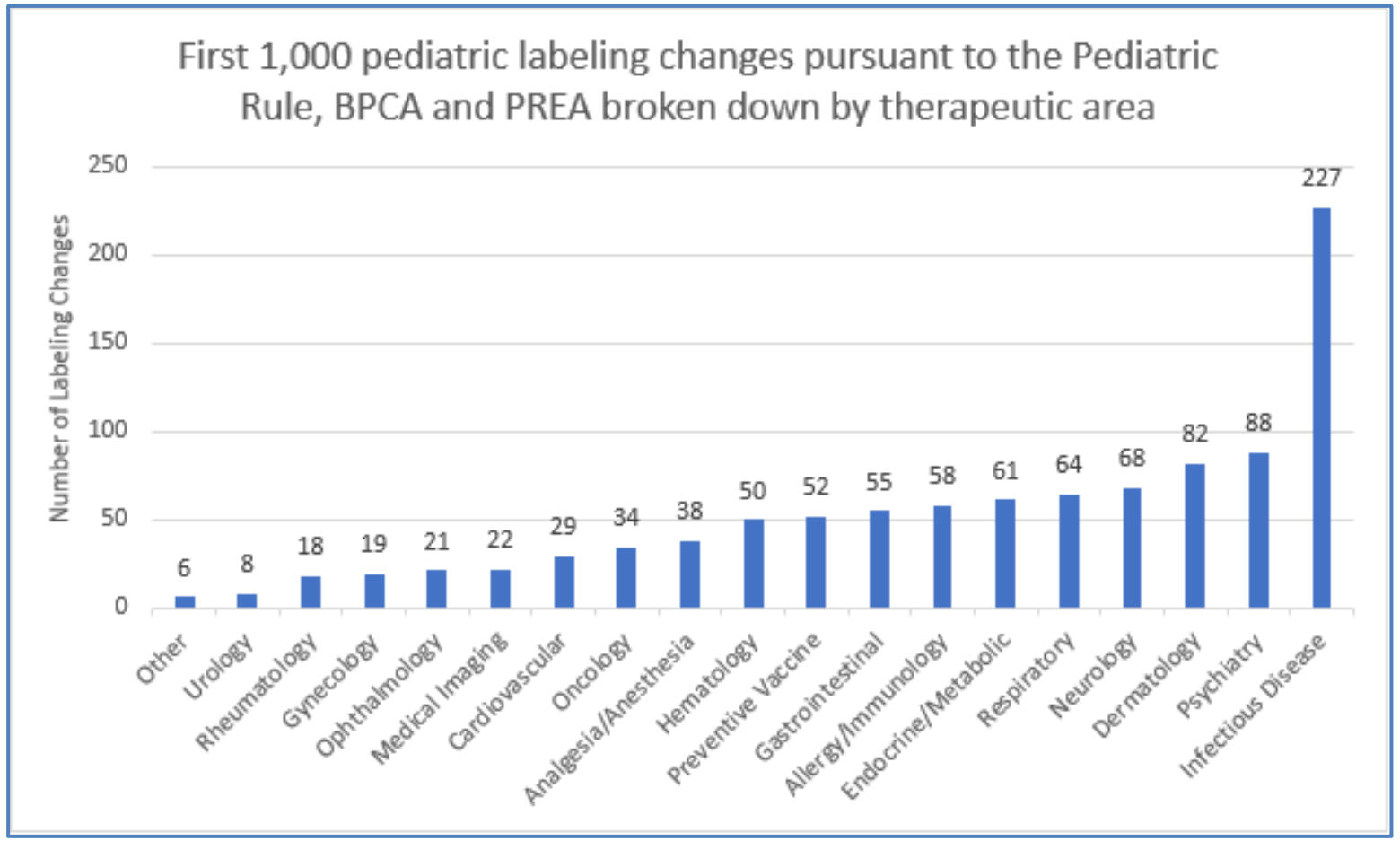
# General Principles

- Pediatric patients should have access to products that have been appropriately evaluated
- Product development programs should include pediatric studies when pediatric use is anticipated
- The timing and approach to pediatric clinical development should be discussed with regulatory authorities at an early stage and periodically during the product development process
- Pediatric clinical trials should be well-designed to collect interpretable data



Pediatric Study Plans | FDA ; Ethical Considerations for Clinical Investigations of Medical Products Involving Children | FDA ; E11 (R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population | FDA . Accessed September 17, 2023.

# First 1,000 Pediatric Labeling Changes by Therapeutic Area




**Labeling Changes by Indication**

- HIV: 82
- ADHD: 42
- Acne Vulgaris: 23
- Atopic Dermatitis: 17
- Major Depressive Disorder: 16
- Hepatitis C: 16
- Influenza: 13
- Bipolar Disorder: 13
- Plaque Psoriasis: 12

Labeling changes pursuant to PREA, BPCA, and the Pediatric Rule

# Rare Pediatric Disease Priority Review Voucher Program

- Program to encourage treatment for rare pediatric diseases (RPD)
- As of September 2021, FDA granted over 480 RPD designations for over 220 unique pediatric diseases
  - RPD designation is needed to be eligible for a priority review voucher when the product is approved
- FDA awarded 32 rare pediatric disease priority review vouchers
  - 25/32 products approved were the first approved therapy for the disease
  - Examples:
    - The first ever FDA-approved gene therapy (Kymriah, tisagenlecleucel) for a form of acute lymphoblastic leukemia
    - Targeted therapies for biallelic RPE65 mutation-associated retinal dystrophy, spinal muscular atrophy, Duchenne muscular dystrophy, and others