# Specific Populations in Clinical Trials

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# Objectives

- Review the inclusion specific populations in drug development
  - Children
  - Pregnant and lactating individuals
- Discuss enhancing diversity in clinical trials

# Specific Populations

- FDA labeling regulations include requirements for content and format of human prescription drug and biological product labeling under the Physician Labeling Rule (PLR)*
- Includes section 8:  Use in Specific Populations
  - Section 8.1:  Pregnancy
  - Section 8.2:  Lactation
  - Section 8.3:  Female and males of reproductive potential
  - Section 8.4:  Pediatric use
- Other definitions of “specific” populations will not be discussed

*21 CFR 201.56(d) and 201.57

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# Inclusion of Pediatric Patients in Clinical Trials

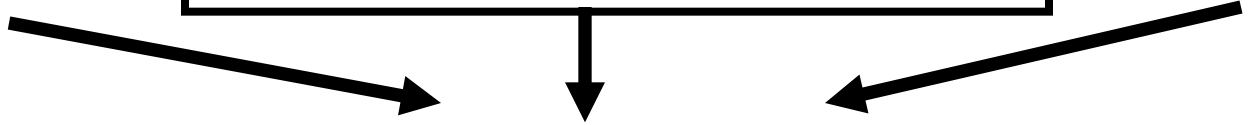
# Pediatric Product Development: The Historical Problem

Acknowledged different drug responses, toxicity, and metabolism in adults versus children

Discouraged the study of drugs in children

- Concerns related to ethical issues
- Fears of harming children
- Perceived increased liability of testing drugs in children

Lacked an incentive for drug companies to conduct pediatric trials



## Choices for Pediatric Practitioners

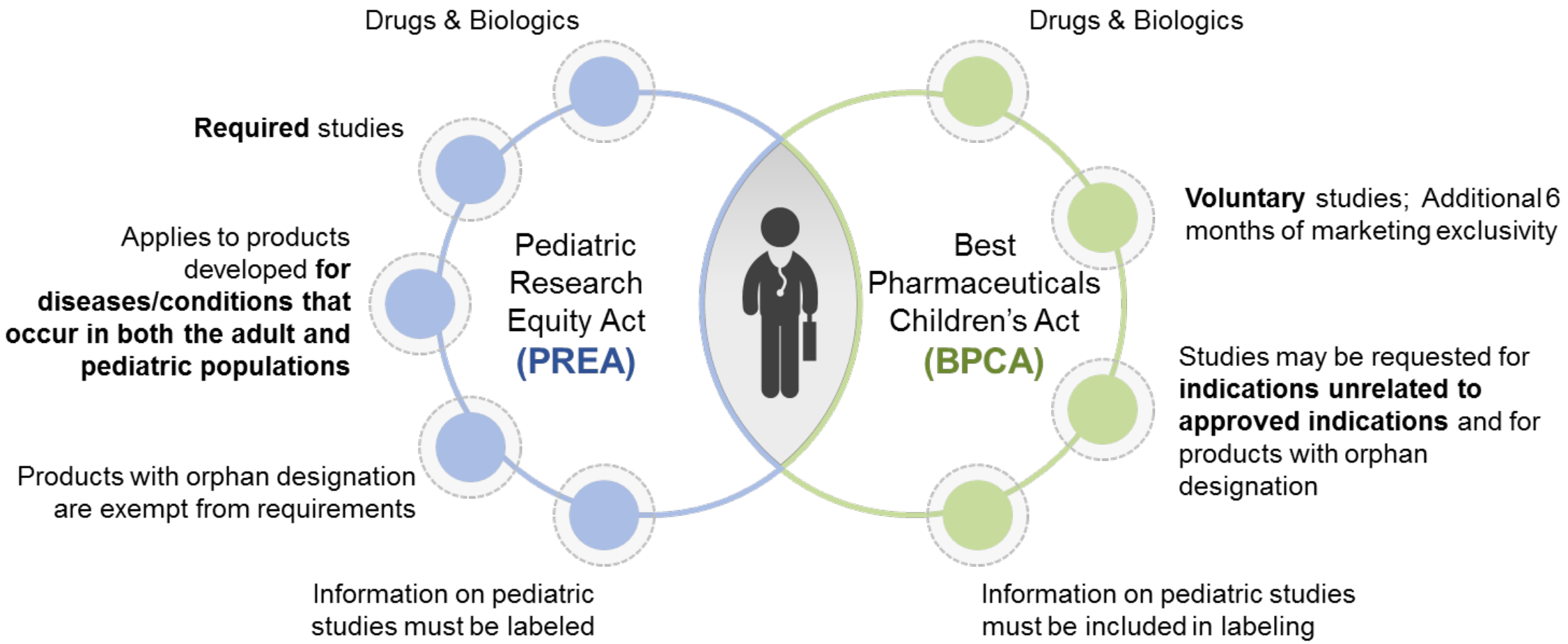
- Not treat children with potentially beneficial medications because they are not approved for use in children
- Treat with medications based on adult studies with limited or anecdotal pediatric experience (off-label use)

# Pediatric Drug Development
# 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
- Incorporation of regulatory standards into pediatric clinical research strengthens the quality of the research

From FDA guidance to industry titled *E11(R1)- Clinical Investigation of Medicinal Products in the Pediatric Population,* December 2017

# Pediatric Drug Development Laws



# U.S. Evidentiary Standard for Approval

- For approval, pediatric product development is held to same evidentiary standard as adult product development:
- A product approved for children must:
  - Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)
  - Clinical benefit:
    - The impact of treatment on how patient feels, functions or survives
    - Improvement or delay in progression of clinically meaningful aspects of the disease
- Evidence of effectiveness [PHS Act, 505(d)]
  - Evidence consisting of adequate and well –controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling
- Adequate safety information must be included in the application to allow for appropriate risk benefit analysis [FD&C 505(d)(1)]

# Special Considerations for Pediatric Product Development

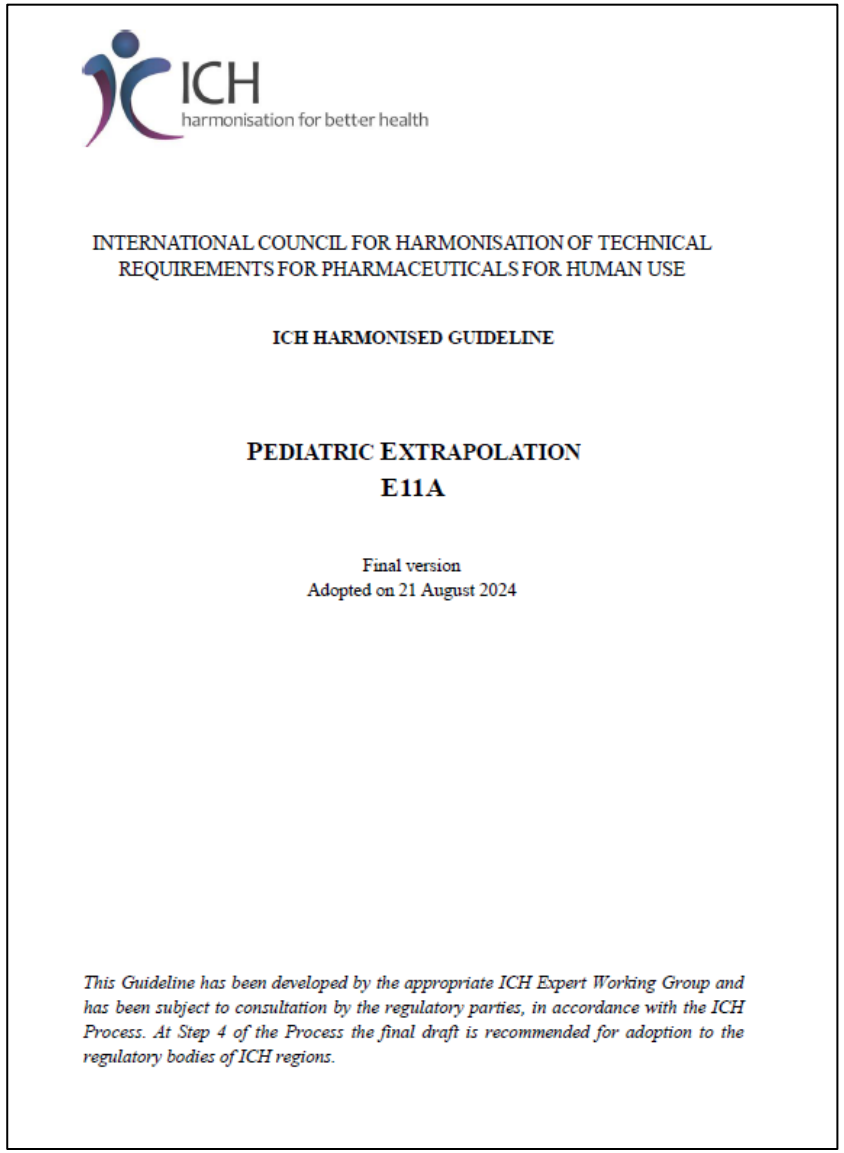
- Ethical considerations
  - Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults)
  - Absent a prospect of direct therapeutic benefit, the risks to which a child would be exposed in a clinical trial must be “low”
  - Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care
- Feasibility considerations
  - The prevalence and/or incidence of a condition is generally much lower compared to adult populations

# Special Considerations for Pediatric Product Development

- Pediatric Formulation Development
  - Should permit accurate dosing and enhance patient compliance
  - Different oral dosage forms may be needed for pediatric patients of different ages
- Animal Toxicology Studies
  - Need to consider whether juvenile toxicology studies are necessary
  - ICH S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals; https://www.fda.gov/media/148478/download
- Study Design Considerations
  - Dose selection
  - Endpoint selection and choice of control
  - Safety considerations
- Timing of Studies
  - Will depend on the disease, the product, the safety considerations and the availability of alternative treatments
- Use of Pediatric Extrapolation
- Recommend review of ICH E11 and ICH E11(R1): Clinical Investigation of Medicinal Products in the Pediatric Population; https://www.fda.gov/media/101398/download and https://www.fda.gov/media/101398/download

# Pediatric Extrapolation

- An approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric [target] and reference (adult or other pediatric) population
- Can increase the efficiency and success of pediatric product development
- Must be considered carefully and supported by available data
- Both efficacy and safety extrapolation can be considered
- Requires multidisciplinary expertise (clinical, clinical pharmacology, biostatistics)
- Final guidance published in August 2024 https://database.ich.org/sites/default/files/ICH_E11A_Guideline_Step4_2024_0821.pdf



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

PEDIATRIC EXTRAPOLATION
E11A

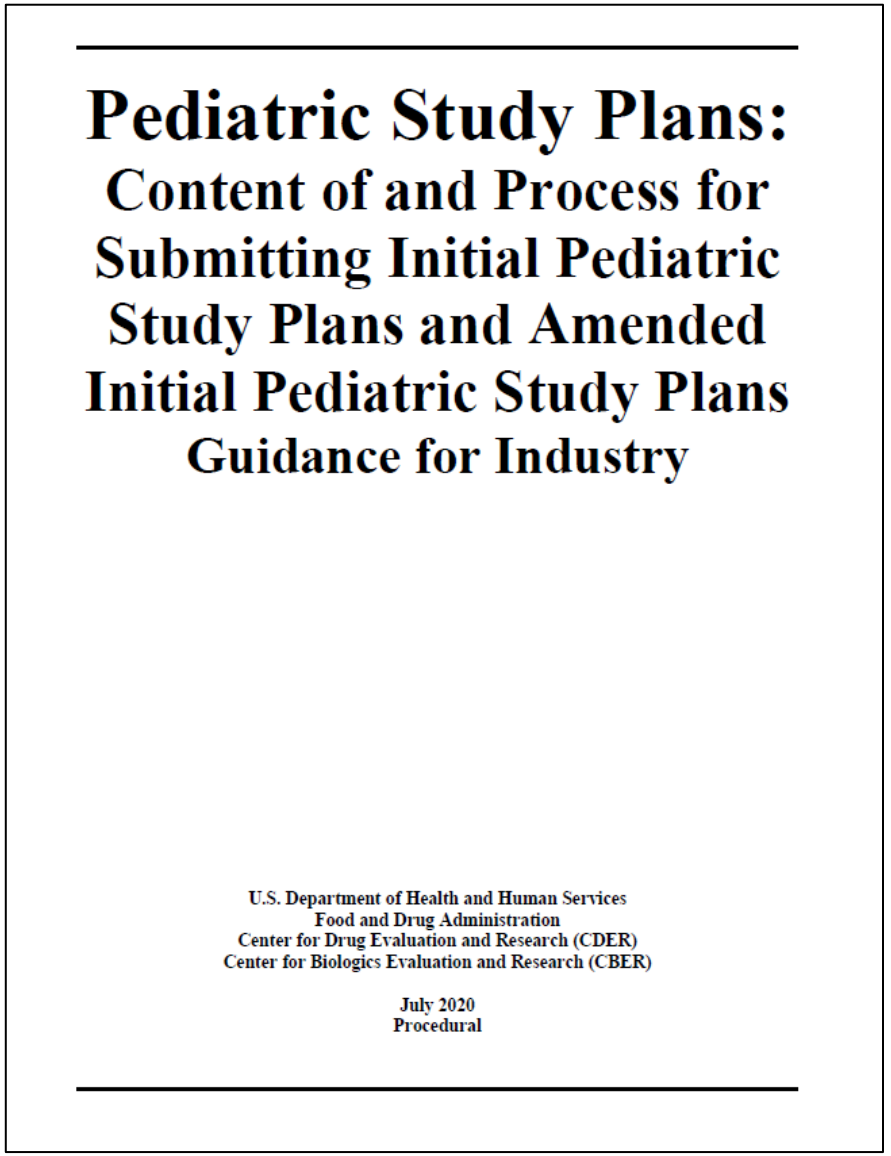
Final version
Adopted on 21 August 2024

*This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.*

# Initial Pediatric Study Plan (iPSP)

- Final guidance published in 2020
- Encourage sponsors to identify pediatric studies as early as possible in product development
- When appropriate, conduct pediatric studies prior to the submission of the NDA or BLA
- Provides detailed information including:
  - Required timelines for submission
  - Required content for submission
  - Sample template for submission

https://www.fda.gov/media/86340/download

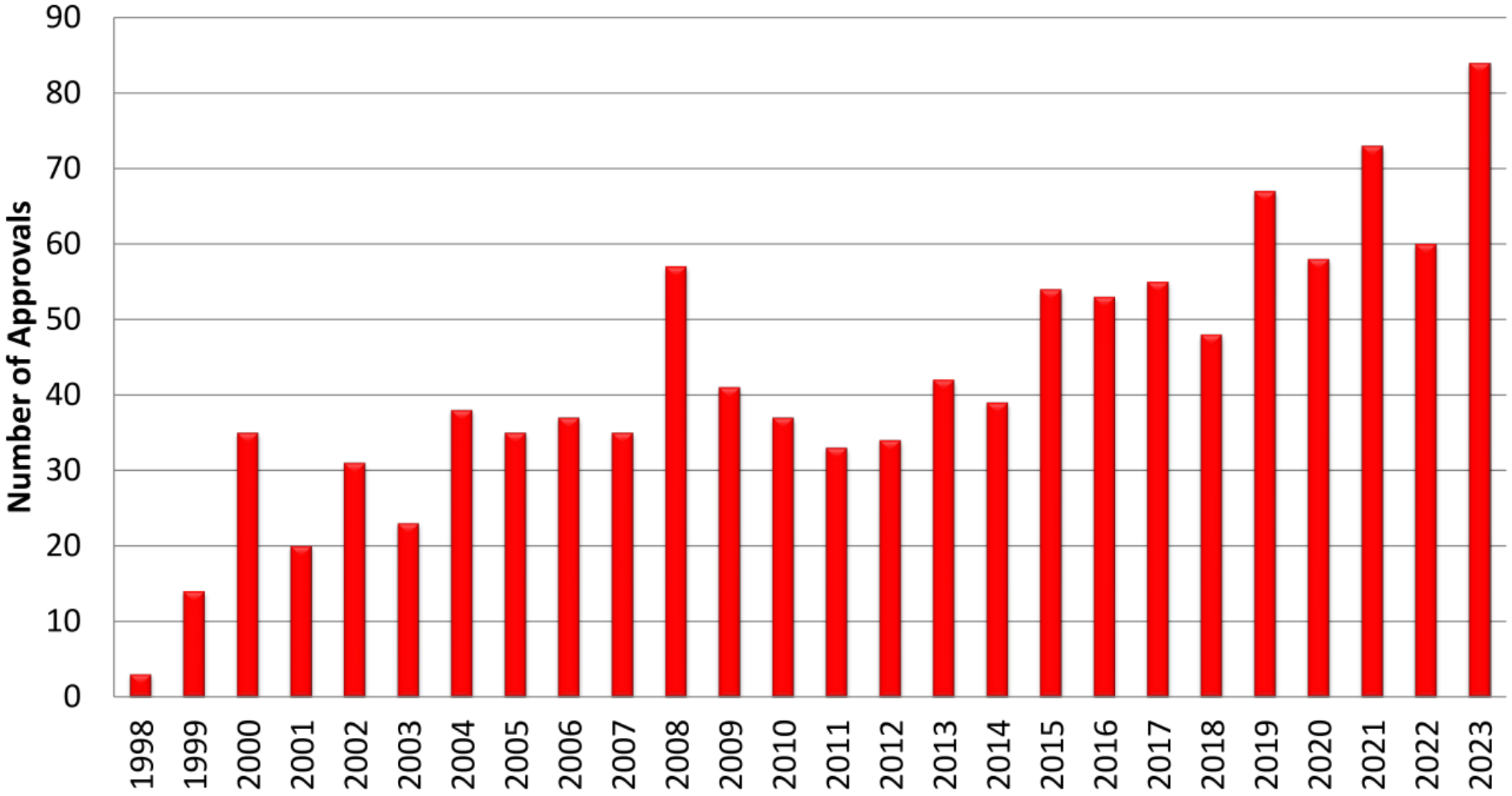


**Pediatric Study Plans:**
**Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans**
**Guidance for Industry**

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2020
Procedural

# Pediatric Labeling Changes 1998-2023



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# Inclusion of Pregnant and Lactating Individuals in Clinical Trials

# Background

- There are approximately 5.5 million pregnancies in the U.S. each year
  - Pregnant individuals may need treatment for chronic or acute conditions
- Pregnant individuals have historically been automatically excluded from drug development trials
- Most drugs are approved with only nonclinical reproductive toxicology data
- Data are needed to inform labeling and clinical care

# Background

- Like children, pregnant and lactating individuals should have access to medicines that have been appropriately evaluated
- Unlike children, medicines for specific indications approved in adults are also approved in pregnant adults unless specifically contraindicated
- But. . .
  - Altered physiology in pregnancy may impact dosing and safety of medicines
  - Little to no human data exist to support safety and dosing prior to approval in most cases
  - Prescribers and their pregnant patients are left to make benefit/risk decisions without data

# A Paradigm Shift

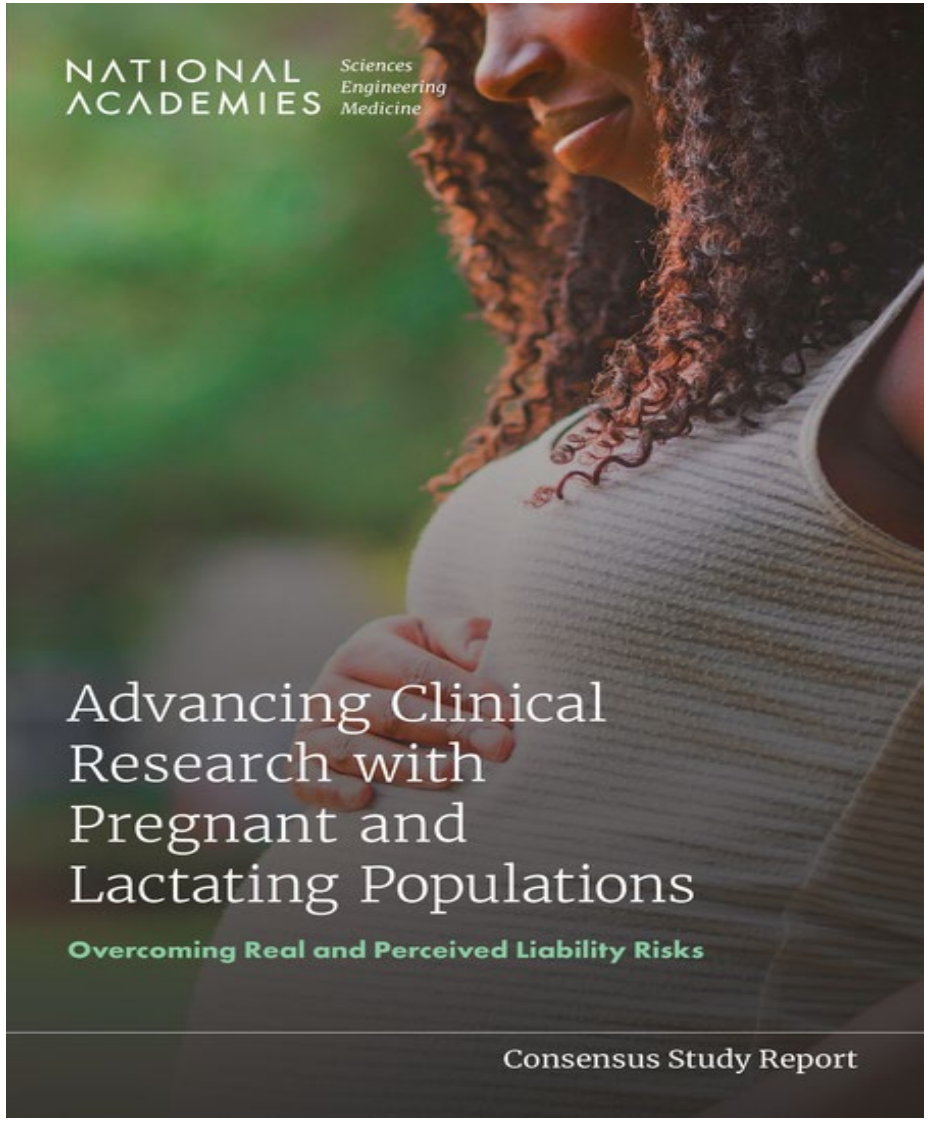
- There is increasing awareness and interest among stakeholders on the need to include pregnant and lactating individuals in clinical trials
- Regulatory advances are occurring
  - Common Rule: has removed reference to pregnant women as “vulnerable”
  - FDA is working to harmonize its regulations with the Common Rule

# Considerations for Inclusion of Pregnant Individuals in Clinical trials

- Adequate nonclinical studies (including studies on pregnant animals) have been completed
- In the pre-marketing setting:
  - The clinical trial holds out the prospect of direct benefit to the pregnant woman and/or fetus that is not otherwise available outside the research setting or cannot be obtained by any other means (e.g., the pregnant woman may not have responded to other approved treatments or there may not be any treatment options)
- In the post-marketing setting:
  - There is an established safety database in nonpregnant women from clinical trials or preliminary safety data from the medical literature and/or other sources regarding use in pregnant women and one of the following:
    - Efficacy cannot be extrapolated and/or
    - Safety cannot be assessed by other study methods
- Also, for individuals who become pregnant during the clinical trial:
  - Should unblind and consider continuation after reconsent process and collection of safety and PK information

Guidance for Industry: Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials
https://www.fda.gov/files/drugs/published/Pregnant-Women--Scientific-and-Ethical-Considerations-for-Inclusion-in-Clinical-Trials.pdf

# Recent NASEM Report




- Published 4-10-2024
- Key Findings:
  - Lack of evidence of liability related to including pregnant and lactating women in clinical trials
  - Potential liability related to use of approved medical products during pregnancy
  - Liability may be prevented by conducting clinical trials in pregnant women

https://nap.nationalacademies.org/catalog/27595/advancing-clinical-research-with-pregnant-and-lactating-populations-overcoming-real

# ICH-E21 Guideline: Inclusion of Pregnant and Breastfeeding Individuals in Clinical Trials

- Goal: provide a globally accepted framework and best practices to enable inclusion and/or retention of pregnant and breastfeeding individuals in clinical trials
- Will cover principles and practices to enable the collection of safety, efficacy, and/or pharmacokinetic data in pregnant and breastfeeding individuals to better inform clinical decision-making in medicinal product use (e.g., improve product labeling)

https://www.ich.org/page/efficacy-guidelines

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# Enhancing Diversity in Clinical Trials

# Diversity in Clinical Trials

"The U.S. population has become increasingly diverse, and ensuring meaningful representation of racial and ethnic minorities in clinical trials for regulated medical products is fundamental to public health"

--FDA Commissioner Robert M. Califf, M.D.

- FDA working to ensure public health of the whole public
- Trials should reflect the population most likely to use the drug
- Certain groups continue to be underrepresented in many clinical trials.

# FDA Efforts to Ensure Diversity in Clinical Trials

- Guidances
  - Draft Guidance: Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies; June 2024 https://www.fda.gov/media/179593/download
  - Final Guidance: Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs; November 2020 https://www.fda.gov/media/127712/download
- Workshops
  - Virtual Public Workshop to Enhance Clinical Study Diversity; November 2023
  - ADEPT-9: Enhancing Diversity in Therapeutics Development for Pediatric Patients, September 2024

  https://www.fda.gov/drugs/news-events-human-drugs/adept-9-public-workshop-enhancing-diversity-therapeutics-development-pediatric-patients-09062024#event-information

# Diversity and Decentralized Clinical Trials

- A clinical trial where some or all the trial-related activities occur at a location separate from the investigator's location
- Potential benefits
  - Patient convenience (avoiding travel to sites, time off work, etc.)
  - Improved participation and diversity
  - Potentially improves enrollment (rare or sporadic diseases)
- Challenges
  - Increased need for innovative training and tracking strategies
  - Compliance issues

# Summary

- Children, pregnant, and lactating individuals should have access to medicines with information to support their safe and effective use
  - When drugs are approved for specific indications in adults, this includes pregnant and lactating individuals unless specifically contraindicated
  - When drugs are approved for adults, pediatric populations are not automatically approved
- Drug development should be designed to include specific populations when use is expected in these populations
- Early planning needed to ensure adequate participation of specific populations
- The Health of the Child Begins with the Health of the Mother
- Children, pregnant and lactating individuals are protected through research not from research
- U.S. population has become increasing diverse and clinical trials should reflect the population most likely to use the drug

# Challenge Question

- Specific populations that should be considered for enrollment in clinical trials during drug development include:
  - A: Pediatric populations
  - B: Pregnant and lactating populations
  - D: All of the above
  - E: None of the above

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# Thank You