FDA

Interested Parties Meeting for Pediatrics

Provide your feedback on implementation of the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA)

September 15, 2025

9:00 a.m. to 4:30 p.m. ET

FDA Great Room
White Oak Campus
Silver Spring, MD

Virtual option available

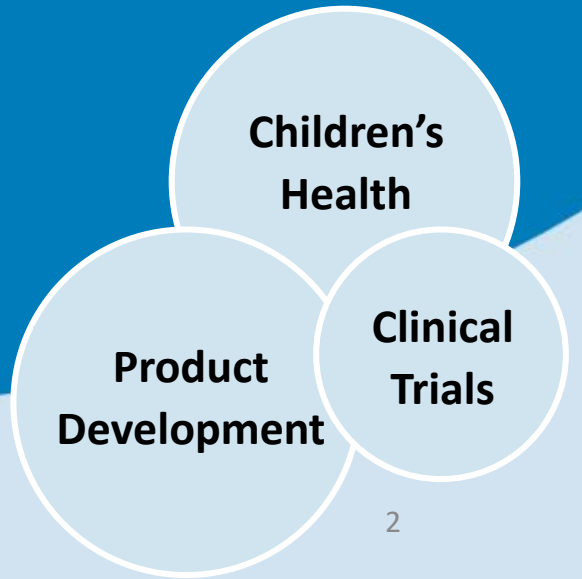
Submit comments to the public docket number FDA-2024-N-5784 until 11:59 p.m. Eastern Time, September 30, 2025

Visit https://www.regulations.gov

U.S. FOOD & DRUG ADMINISTRATION

Advancing Medicines for Children:

FDA Overview of BPCA and PREA Implementation Successes & Opportunities for Improvement



Interested Parties Meeting for Pediatrics
FDA Great Room Conference Center

September 15, 2025

Outline

FDA Overview of the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) Implementation Successes and Opportunities for Improvement:

I. Reflections on the last 20+ years since passage of BPCA and PREA

II. Overview of BPCA and PREA

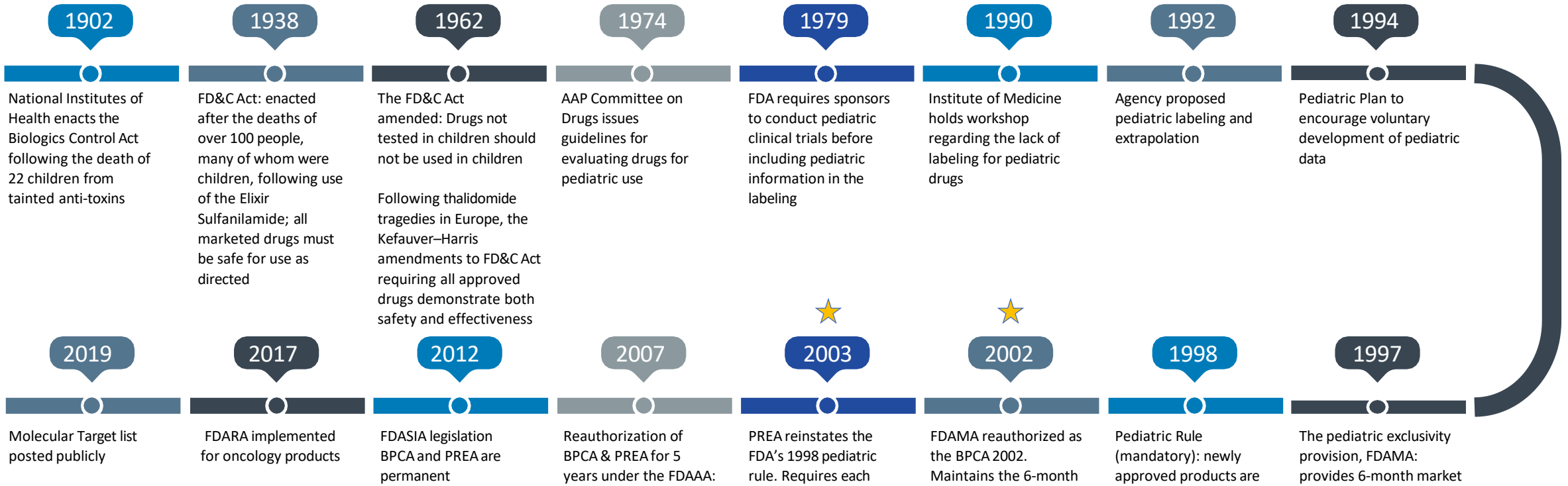
III. Successes in developing safe and effective medicines for children

IV. Opportunities for improvement

V. FDA's work to address interested parties' feedback from 2019 interested parties meeting

VI. Overview of the day's agenda

Reflections on the Last 20+ Years



Historical Milestones and Legislation in Pediatrics

Reflections on the Last 20+ Years

Guiding principles …

- Children should have access to products that have been appropriately evaluated for pediatric use
- Product development programs should include pediatric studies when use by children is anticipated
- The timing and approach to pediatric clinical development should be discussed early in product development
- Pediatric clinical trials should be well-designed to collect interpretable data (pediatric product development held to same evidentiary standard as adult product development)
- Clinical trial participation should not compromise the well-being of pediatric subjects

Reflections on the Last 20+ Years

We've come a long way…

FDA Update

Number of drugs, biologics with pediatric use information reaches 1,000

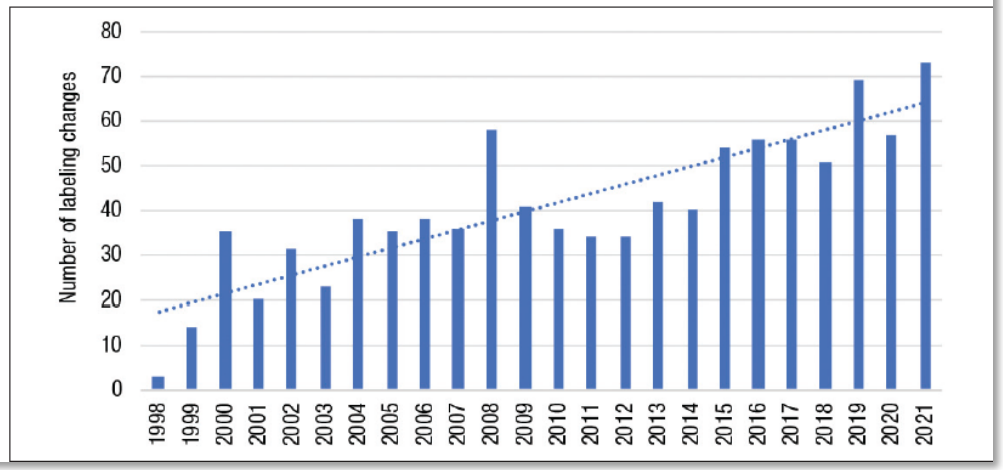
from the **Food and Drug Administration**

The Food and Drug Administration (FDA) has announced a historic milestone as more than 1,000 drugs and biologics have undergone labeling changes to include pediatric use information.

The changes stem from laws and regulations that have encouraged or required pharmaceutical companies to evaluate their products for use in children.

Prior to passage of the first law incentivizing pediatric studies in 1997, more than 80% of approved drugs had no pediatric-specific labeling information. After decades of advocacy by the AAP, FDA and other stakeholders to address inadequate pediatric labeling, Congress passed the Best Pharmaceuticals for Children Act (BPCA) of 2002 and the Pediatric

Figure 1. Number of pediatric labeling changes that occurred pursuant to PREA, BPCA and the Pediatric Rule from 1998-2021



Reflections on the Last 20+ Years

Collective work of all interested parties…

Academia ▪ Advocacy Organizations ▪ Biotechnology Companies ▪ Chemists ▪ Clinical Investigators ▪ Clinical Research Organizations ▪ Epidemiologists ▪ Ethicists ▪ Families ▪ Government ▪ Healthcare Professionals ▪ Institutional Review Boards ▪ Law Makers ▪ Parents ▪ Pediatric Patients ▪ Professional Societies ▪ Pharmaceutical Industry ▪ Pharmacologists ▪ Policymakers ▪ Regulators ▪ Researchers ▪ Scientists ▪ Statisticians ▪ … and more

Reflections on the Last 20+ Years

Thousands of children have participated in clinical trials

BPCA AND PREA – 20+ Years

Overview of BPCA and PREA

- Best Pharmaceuticals for Children Act (BPCA)
  - Provides a financial incentive to companies to voluntarily conduct pediatric studies by way of a Written Request (WR)
  - FDA and the National Institutes of Health (NIH) partner to obtain information to support labeling of off-patent products used in pediatric patients (Section 409I of the Public Health Service Act)
- Pediatric Research Equity Act (PREA)
  - Requires companies to assess safety and effectiveness of certain new drugs/biologics in pediatric patients (Pediatric Assessment)

Overview of BPCA and PREA

Best Pharmaceuticals for Children Act (BPCA)

- Voluntary studies
- 6 months additional exclusivity
- Studies may expand indication(s)
- Studies may be requested for orphan indications

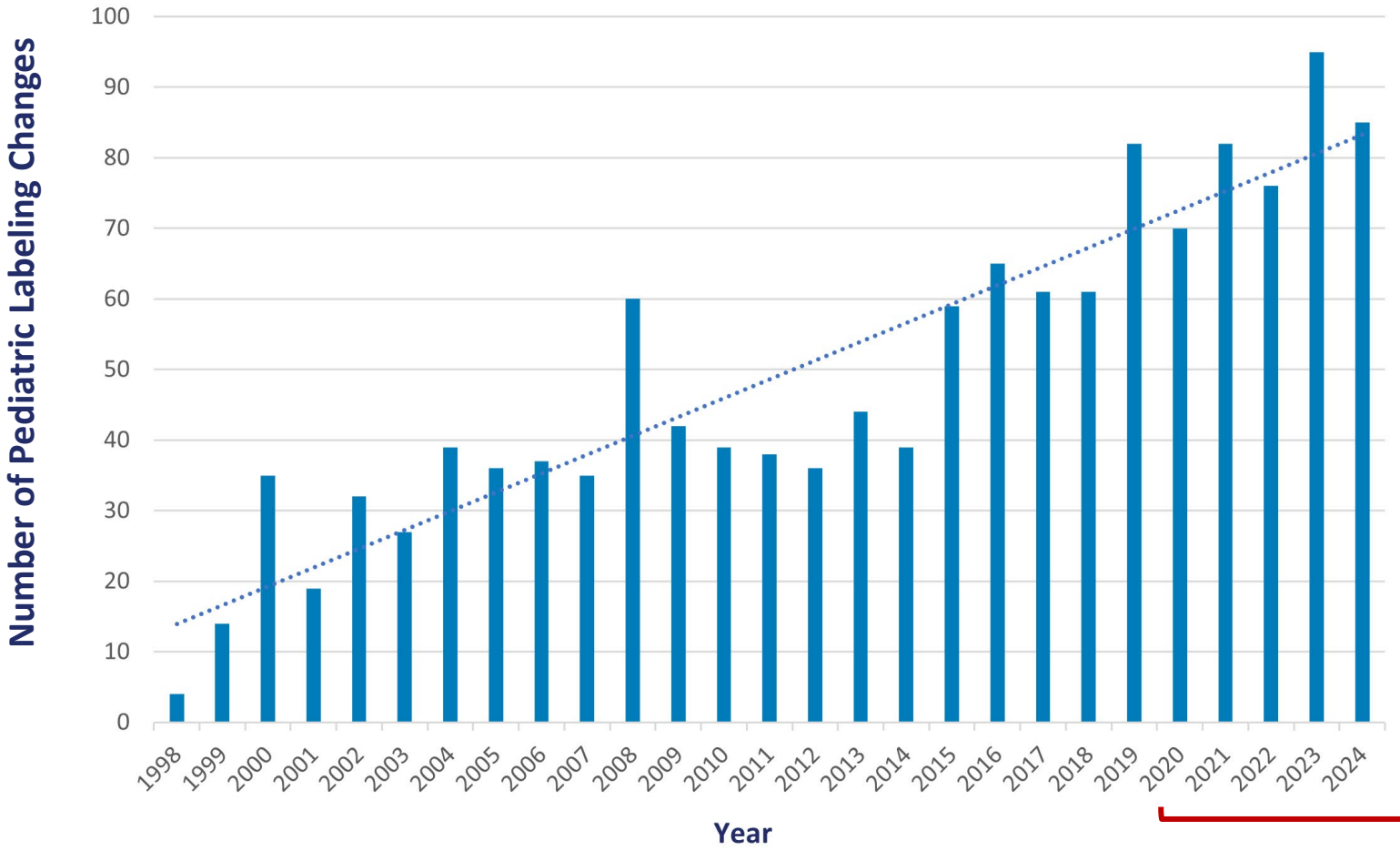
- Drugs and Biologics
- Pediatric studies must be labeled

Pediatric Research Equity Act (PREA)

- Mandatory studies
- No reward
- Studies may be required only for approved indication(s)
- Orphan indications exempt (except for molecularly targeted oncology drugs relevant to pediatric cancers)

Pediatric Labeling Changes

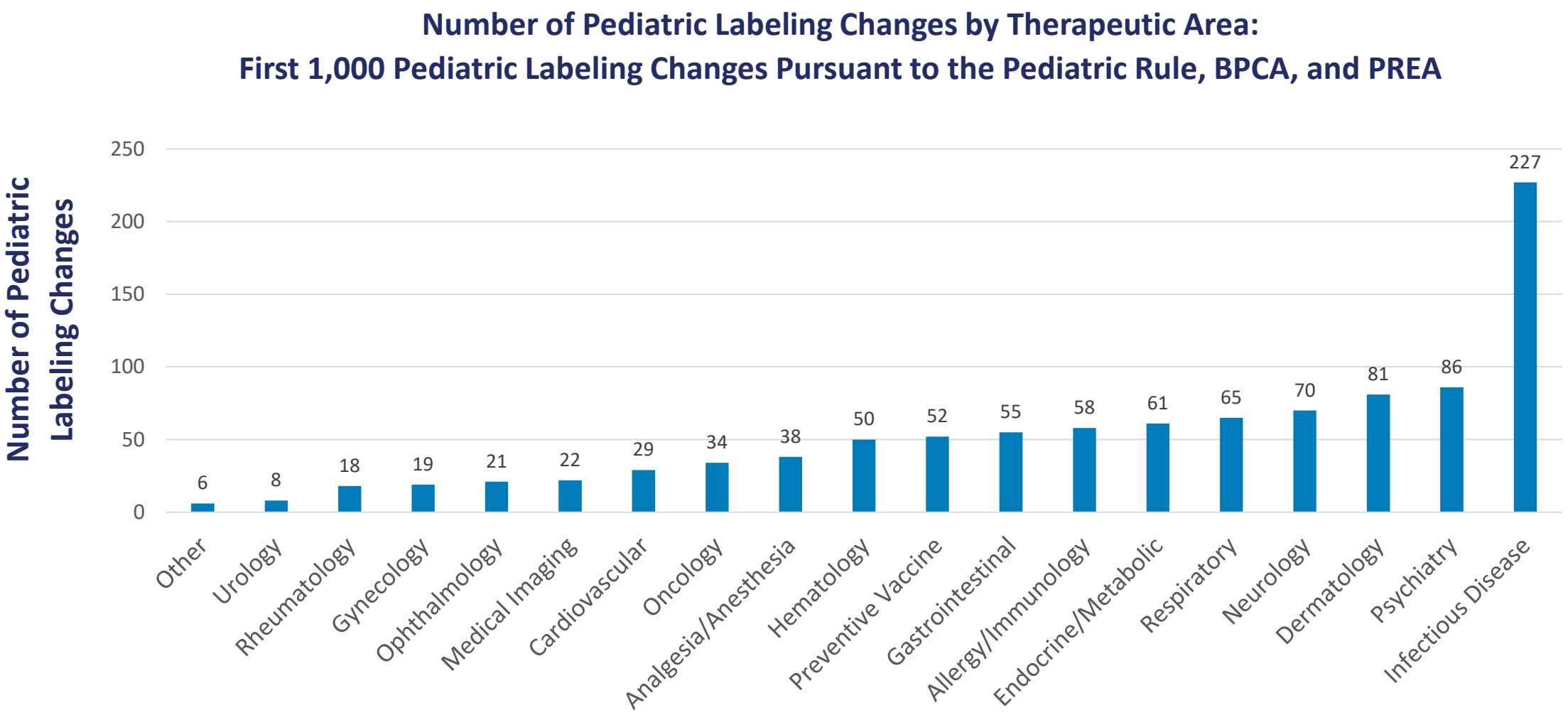
Increasing number of pediatric labeling changes for drugs and biologics pursuant to the Pediatric Research Equity Act, Best Pharmaceuticals for Children Act, and Pediatric Rule



Current reporting period: July 1, 2020 – June 30, 2025]

Pediatric Labeling Changes | FDA

Pediatric Labeling Changes



Pediatric Labeling Change Examples

[Current reporting period:
July 1, 2020, through June 30, 2025]

FDA NEWS RELEASE

FDA Approves New Drug to Prevent RSV in Babies and Toddlers

For Immediate Release: July 17, 2023

Español

Today, the U.S. Food and Drug Administration a
the prevention of Respiratory Syncytial Virus (R
neonates and infants born during or entering th
24 months of age who remain vulnerable to sev
RSV season.

**"RSV can cause serious disease in infants a
number of emergency department and phys
Farley, M.D., M.P.H., director of the Office of
for Drug Evaluation and Research. "Today's
products to help reduce the impact of RSV c
health care system."**

FDA NEWS RELEASE

FDA Approves First Nasal Spray for Treatment of Anaphylaxis

For Immediate Release: August 09, 2024

Español

Today, the U.S. Food and Drug Administration approved neffy (epi
for the emergency treatment of allergic reactions (Type I), includin
threatening (anaphylaxis), in adult and pediatric patients who weig
(about 66 pounds).

**"Today's approval provides the first epinephrine product for t
anaphylaxis that is not administered by injection. Anaphylaxi
and some people, particularly children, may delay or avoid tr
injections," said Kelly Stone, MD, PhD, Associate Director of
Pulmonology, Allergy and Critical Care in the FDA's Center fo
Research. "The availability of epinephrine nasal spray may re
treatment of anaphylaxis. As a result, neffy provides an impo
and addresses an unmet need."**

New studies show diabetes drug not proven to improve blood sugar control in pediatric patients

[12/4/2020] The U.S. Food and Drug Administration has approved labeling changes stating that Januvia (sitagliptin), Janumet (sitagliptin and metformin hydrochloride), and Janumet XR (sitagliptin and metformin hydrochloride extended-release) are not proven to improve glycemic (blood sugar) control in pediatric patients age 10 to 17 with type 2 diabetes . The drugs are approved to improve blood sugar control in adults age 18 and older with type 2 diabetes.

The labeling changes are based on results from three double-blind, placebo-controlled studies. These studies evaluated sitagliptin's effectiveness and safety over 54 weeks among 410 patients aged 10 to 17 with inadequately controlled type 2 diabetes. At the beginning of the clinical trials, patients in study 1 were not receiving oral antihyperglycemic therapies (drugs that lower blood sugar); patients in studies 2 and 3 were taking maximally tolerated metformin therapy, a type of oral antihyperglycemic therapy, and 12% to 15% of patients were taking insulin.

www.fda.gov/pediatrics

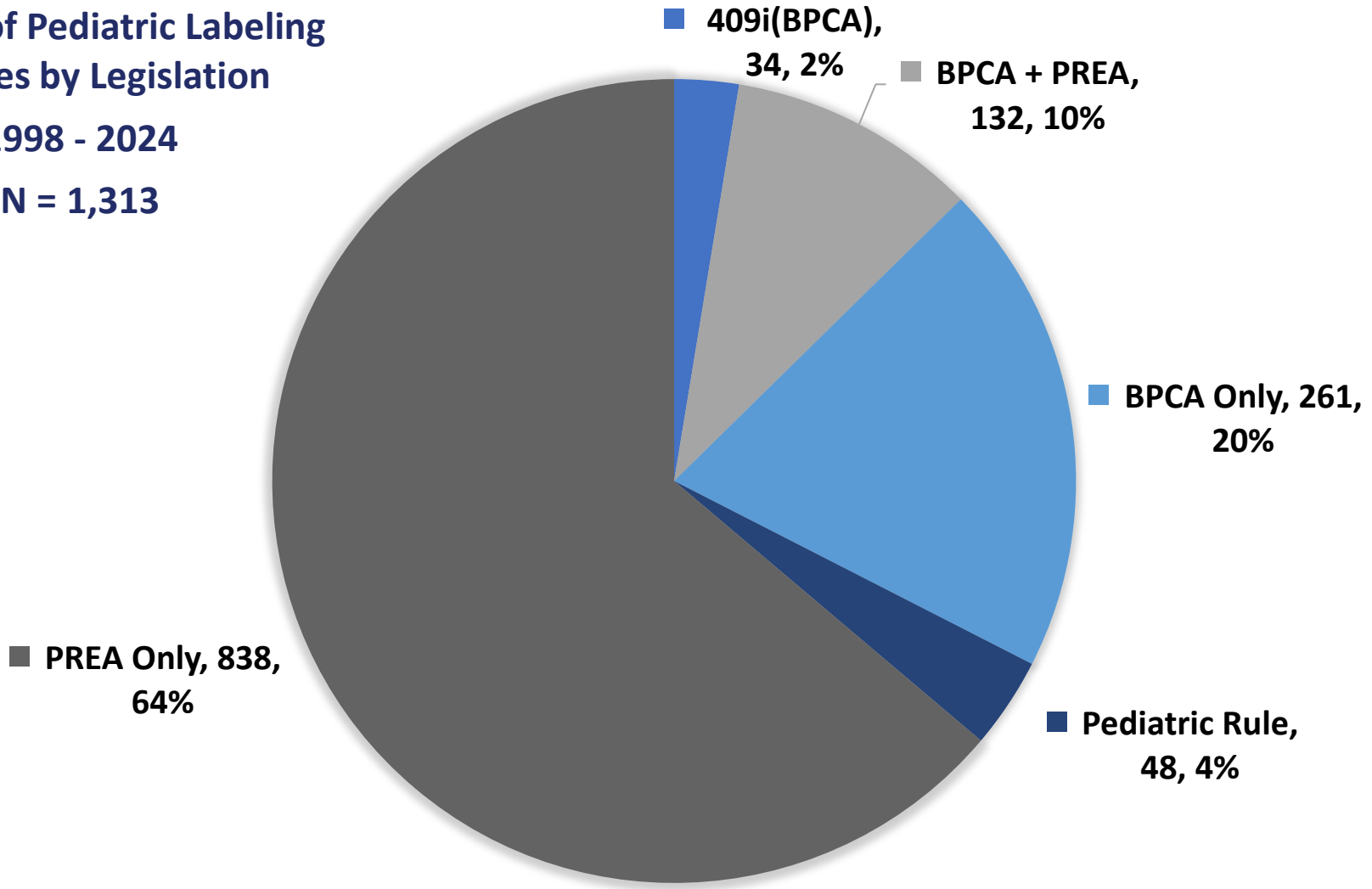
Pediatric Labeling Changes | FDA

Pediatric Labeling Changes

Number of Pediatric Labeling Changes by Legislation

1998 - 2024

N = 1,313



Pediatric Oncology: Early Impact of FDARA

FDARA has increased the development of targeted therapies in pediatric patients since its implementation in August 2020 by increasing the:

- Number of agreed initial pediatric study plans (iPSPs) with plans for pediatric investigations (see table)
- Number of post-marketing requirements (PMRs) for pediatric studies

Planned pediatric studies under the RACE Act that could have been required prior to RACE Act implementation, July 1, 2020, through June 30, 2025 (CDER)*

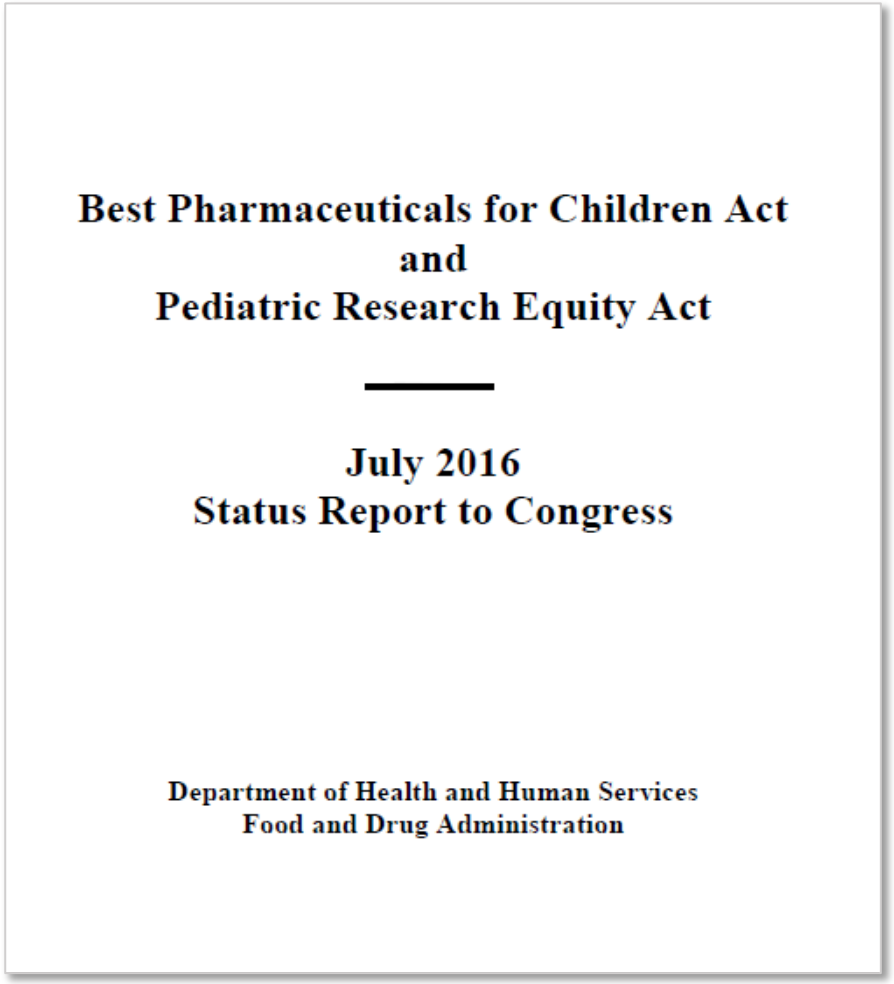
Drug Approval Status	Number of planned pediatric studies under RACE Act	Number of planned pediatric studies that would have received an exemption or waiver pre-RACE Act	Number of planned pediatric studies that could have been required pre-RACE Act
Approved drugs	27	21	6
Drugs in development	46	38	8
Total	73	59	14

*RACE Act: Research to Accelerate Cures and Equity for Children Act; common name for a provision in the FDA Reauthorization Act of 2017 (FDARA); CDER: Center for Drug Evaluation and Research

Opportunities for Improvement

Timely Pediatric Information in Labeling	Optimizing use of Pediatric Extrapolation	Innovative Trial Designs	
Clinical Trial Infrastructure	Clinical Investigator Education	Recruitment & Enrollment	
Developmental Safety	Model-Informed Drug Development	Collaboration among all Interested Parties	
Pediatric Endpoints	Pediatric Patient Voices	Scientific Advances	Postmarket Safety Monitoring
Nonclinical Models of Disease	Product Development for Neonates	Product Development for Rare Pediatric Diseases	
International Alignment	Pediatric Formulations Innovation	Long-Term Safety	
Real-world Data and Evidence	Digital Health Technologies	Financial Incentives	… and more

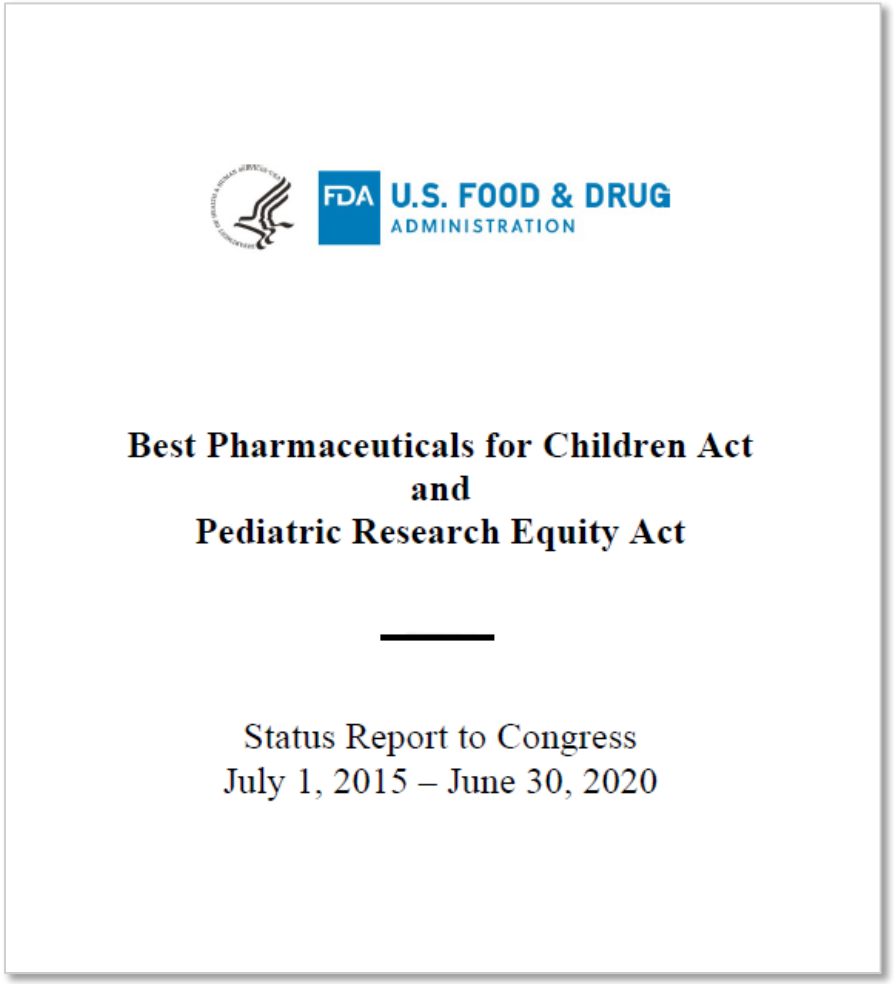
Impact of BPCA and PREA



Best Pharmaceuticals for Children Act
and
Pediatric Research Equity Act

July 2016
Status Report to Congress

Department of Health and Human Services
Food and Drug Administration



FDA U.S. FOOD & DRUG ADMINISTRATION

Best Pharmaceuticals for Children Act
and
Pediatric Research Equity Act

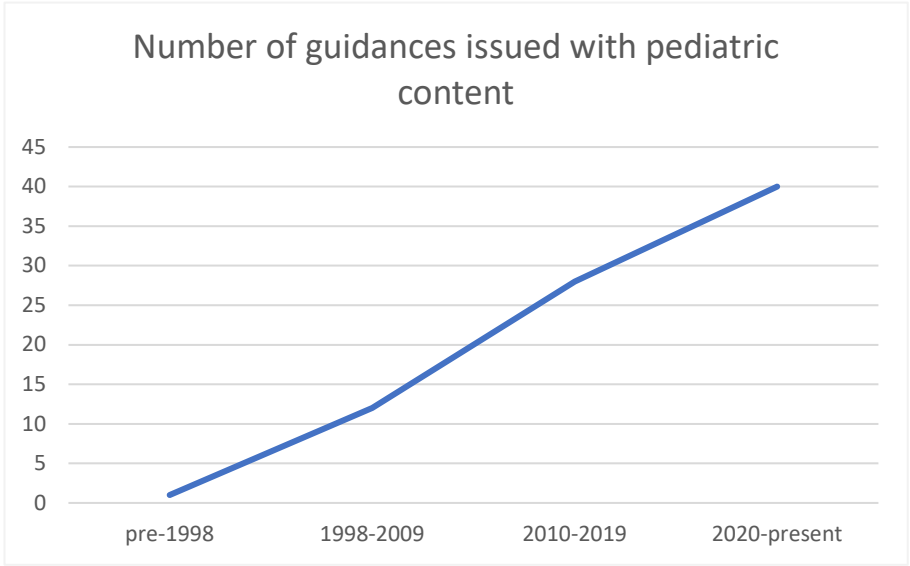
Status Report to Congress
July 1, 2015 – June 30, 2020

2019 Interested Parties Feedback

FDA Guidance Documents

- Means to convey the Agency's interpretation of regulatory issues to interested parties, including regulated industry, FDA staff, and the public
- Guidances address a range of topics including issues that relate to the design, production, labeling, promotion, manufacturing, and testing of regulated products

- 81 FDA guidances discuss pediatric product development (to varying degrees)
- Issuance of pediatric guidances has increased over time (see graph)



www.fda.gov/pediatrics

Search for FDA Guidance Documents | FDA

FDA Guidances Issued for Pediatrics*

- E11A Pediatric Extrapolation (December 2024) (Final)
- Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development (October 2024) (Final)
- Rare Diseases: Considerations for the Development of Drugs and Biological Products (December 2023) (Final)
- Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations (May 2023) (Draft)
- Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act (May 2023) (Draft)
- Ethical Considerations for Clinical Investigations of Medical Products Involving Children (September 2022) (Draft)

*Current reporting period:
July 1, 2020 – June 30, 2025

Search for FDA Guidance Documents | FDA

FDA Guidances Issued for Pediatrics*

- General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products (September 2022) (Draft)
- General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products (July 2022) (Final)
- Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics (March 2022) (Final)
- FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act (May 2021) (Final)
- Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans (July 2020) (Final)
- Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients (July 2020) (Final)

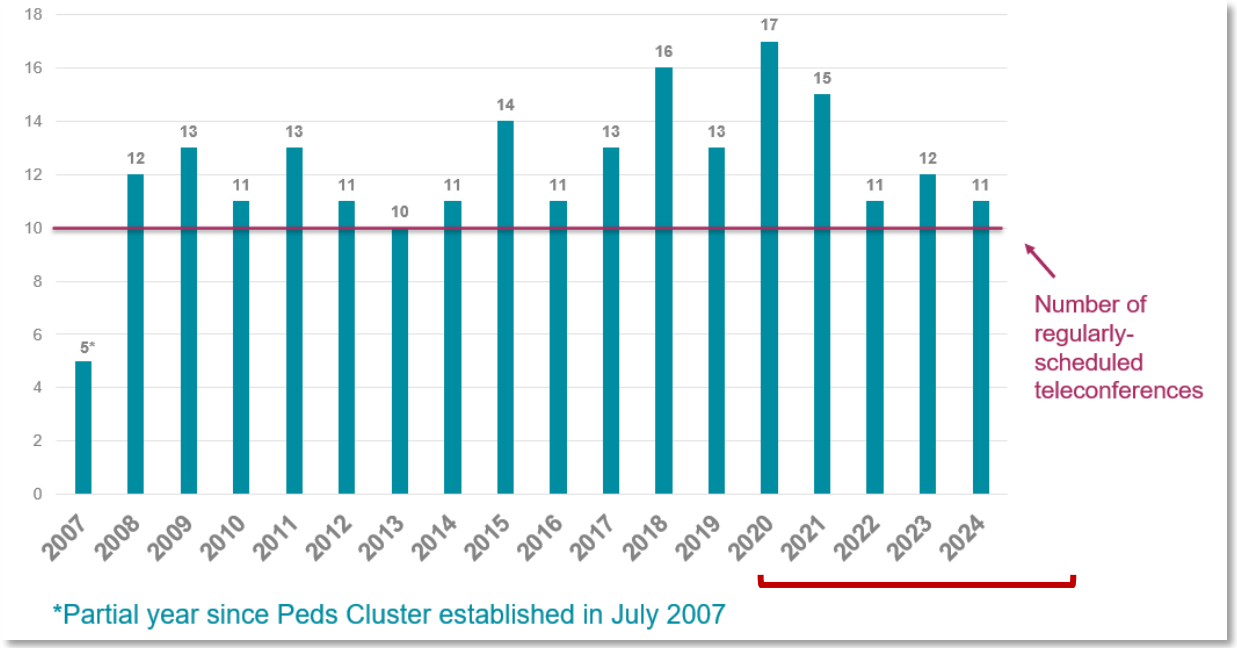
*Current reporting period:
July 1, 2020 – June 30, 2025

Search for FDA Guidance Documents | FDA

International Alignment

Pediatric Cluster Teleconferences

Number of Pediatric Cluster Teleconferences Per Year (2007-2024)
[Additional Teleconferences Held Most Years]

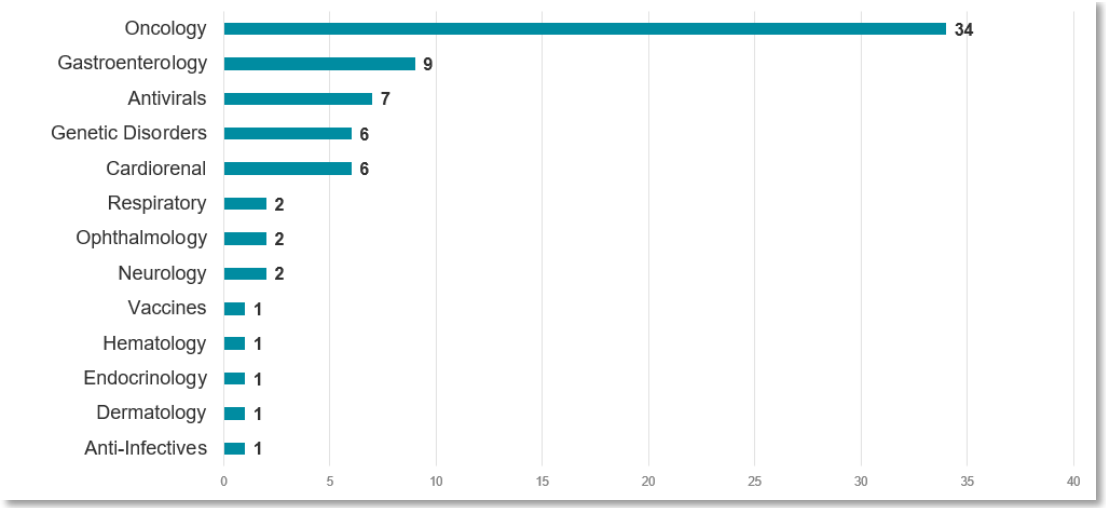


*Partial year since Peds Cluster established in July 2007

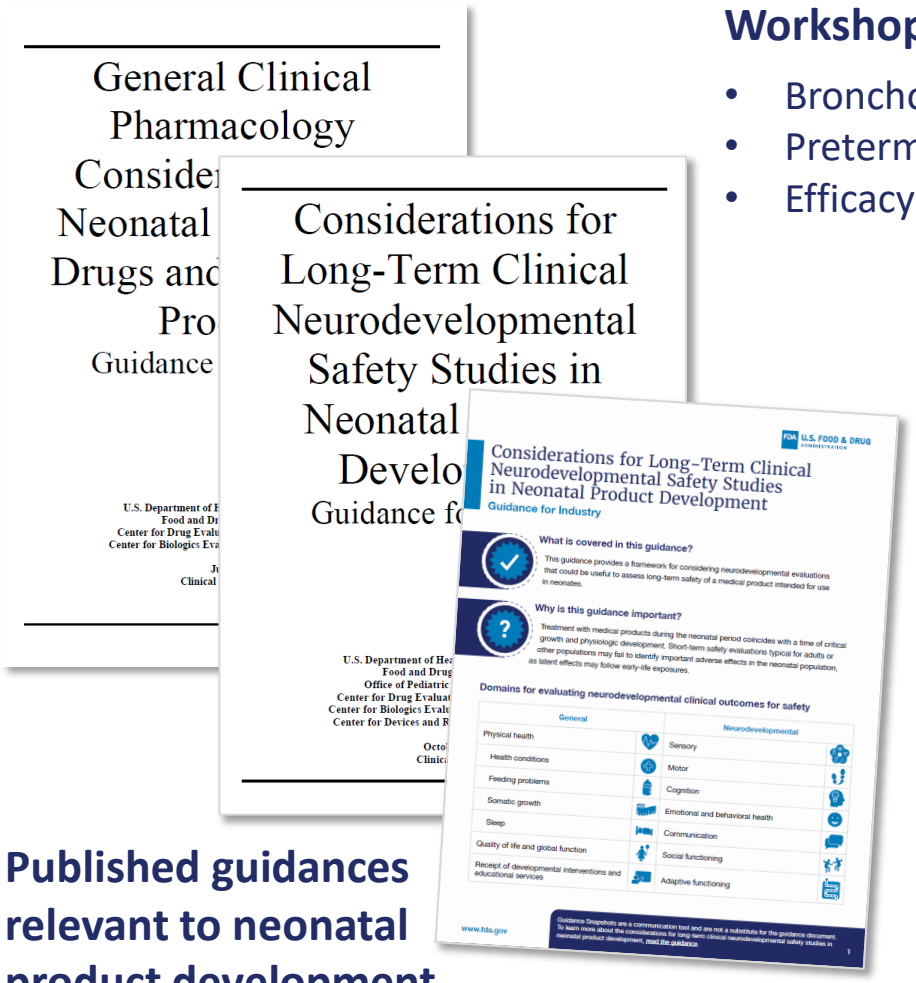
Welcomed Swissmedic to the Pediatric Cluster in 2025!

Common Commentaries

Number of Common Commentaries by Therapeutic Area (2012-2024)



Product Development for Neonates

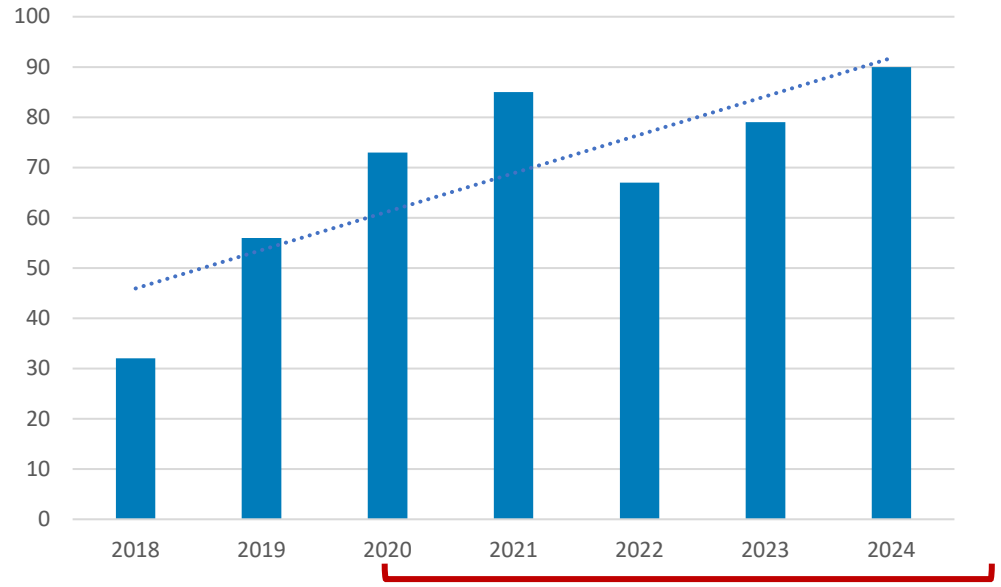


Published guidances relevant to neonatal product development

Workshops relevant to neonatal product development

- Bronchopulmonary dysplasia
- Preterm birth
- Efficacy endpoints for neonatal clinical trials

FDA Office of Pediatric Therapeutics (OPT) Neonatology Program Consultations (2018 to 2024)



Enhanced staffing for OPT Neonatology Program

Collaborated with INC to develop the Neonatal Adverse Event Severity Scale (NAESS)

www.fda.gov/pediatrics

Medical Products for Newborns | FDA

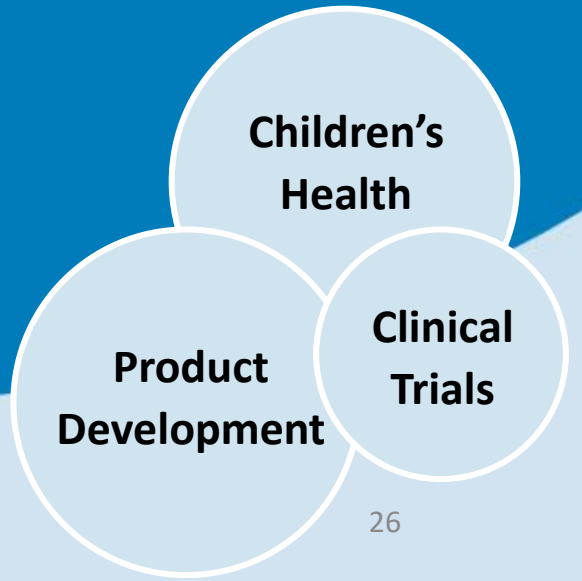
Advancing Pediatric Therapeutics

Advancing the Development of Pediatric Therapeutics (ADEPT) Workshops

2014	2015	2016	2017	2018	2019	2021	2023	2024	2025
ADEPT 1	ADEPT 2	ADEPT 3	ADEPT 4	ADEPT 5	ADEPT 6	ADEPT 7	ADEPT 8	ADEPT 9	ADEPT 10
Pediatric Bone Health	Evaluation of Long-Term Neuro-Development in Pediatrics	Success and Challenges of Performing Long-Term Pediatric Safety Studies	Application of "Big Data" to Pediatric Safety Studies	Advancing Pediatric Pharmaco-vigilance	Pediatric Clinical Trial Endpoints for Rare Diseases with a Focus on Pediatric Patient Perspectives	Complex Clinical Trial Design	Drug Dosing in Pediatric Patients with Renal Impairment	Enhancing Diversity in Therapeutics Development for Pediatric Patients	Coming soon!

Advancing the Development of Pediatric Therapeutics (ADEPT) Workshops | FDA

Interested Parties Meeting 2025



Interested Parties Meeting: Implementation of BPCA and PREA

September 15, 2025

Overview of the Day: Interested Parties Feedback

- Hearing from patients/parents/caregivers and patient/parent/caregiver groups, consumer groups, industry, academia and other interested parties about the **public health impact** that pediatric legislation may have had on them or their communities, including **treatment advances** for children resulting from the legislation, as well as areas of **continued unmet medical need**.

- Understanding the effects of the requirement of pediatric studies under PREA or the incentives under BPCA on drug/biologic development plans, including issues related to the **balance of incentives and requirements** and progress toward **international alignment** on pediatric drug development to the extent practicable.

Federal Register :: Interested Parties Meeting: Implementation of the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act

Overview of the Day: Interested Parties Feedback

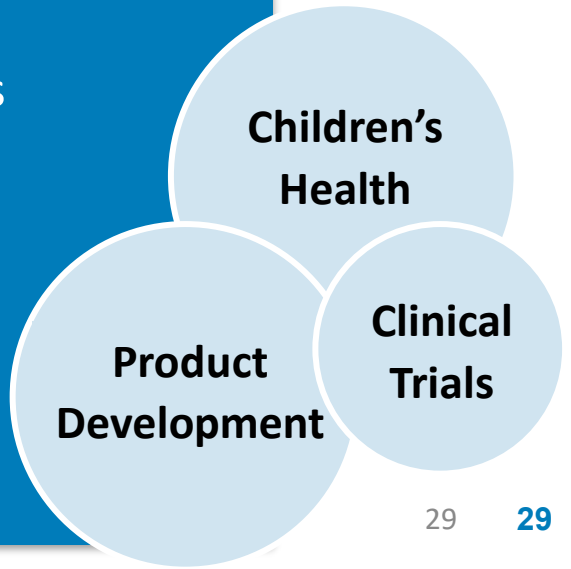
- Understanding if there are any barriers or resource issues preventing undertaking or completing studies under PREA and BPCA, including issues related to **clinical trial infrastructure and enrollment** and ensuring pediatric clinical trial populations reflect the range of children most likely to use and benefit from the therapeutic treatments.

- Understanding successes and challenges with **leveraging scientific advances** in product development, including, but not limited to, use of pediatric extrapolation, adaptive trial designs, biomarkers as surrogates, and real-world data to facilitate more timely evidence-generation for pediatric populations.

Federal Register :: Interested Parties Meeting: Implementation of the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act

Overview of the Day: Agenda

9:00 – 9:20 a.m.	Welcome and Opening Remarks
9:20 – 10:20 a.m.	Session One: Interested Parties Comments
10:20 – 10:40 a.m.	**Break**
10:40 – 11:40 a.m.	Session Two: Interested Parties Comments
11:40 – 12:15 p.m.	Session Three: Interested Parties Comments
12:15 – 1:15 p.m.	**Lunch**
1:15 – 2:10 p.m.	Session Four: Interested Parties Comments
2:10 – 2:50 p.m.	Session Five: Interested Parties Comments
2:50 – 3:15 p.m.	**Break**
3:15 – 4:15 p.m.	Open to Public for Comments
4:15 – 4:30 p.m.	Closing



Thank you for your time and for all you do for children

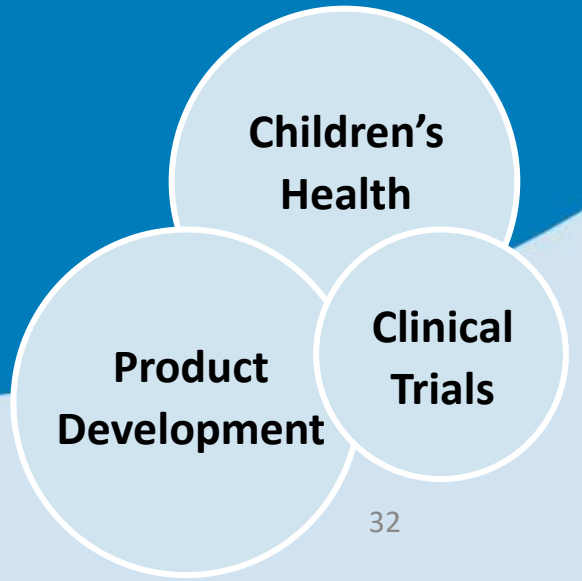
Session One

Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

American Academy of Pediatrics (AAP)

Anjali Deshmukh, MD

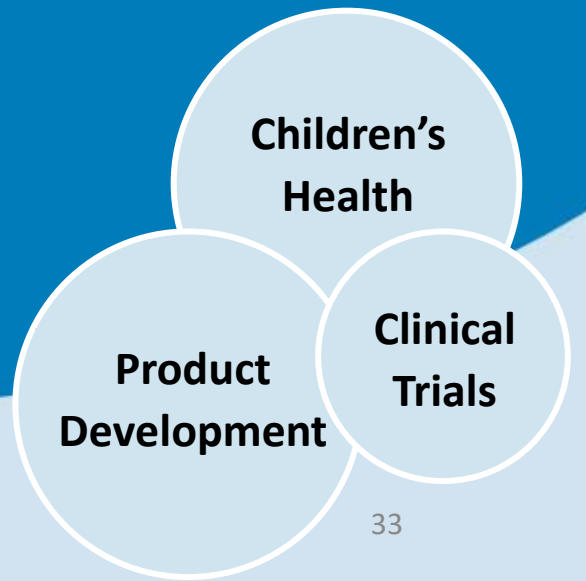


Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

International Children's Advisory Network (iCAN)

Leanne West, MS



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

Patient Centricity and How Pre-Trial Co-Creation is Key to Mitigating Observed Barriers in Clinical Research Aimed Towards Pediatrics.

Leanne West

President, iCAN

What is iCAN?

- A 501(c)3 nonprofit dedicated to empowering every child, everywhere by working to improve pediatric health, medicine, research, and innovation by sharing children's voices
- 46 member organizations working at the local and international level to empower youth voices globally
- A dedicated platform for children and families to give input and feedback into study designs, treatment plans, and educational materials of our industry partners
- Raising the next generation of healthcare professionals through our Young Professionals Network.

www.iCAN.health

The iCAN Model and Impact on Uses of Drugs

At iCAN, we emphasize the need to include kids' voices in the development & testing of drugs making sure that their experiences, preferences, and feedback guide choices for treatment, including off-label practices, in improving safety and guiding care that actually meets the need of pediatric patients!

> **"Having better dosage studies for kids will ensure that a research-backed standard of care is established."**
>
> - Adhiti (KIDS Connecticut, Youth Member)

> **"Our children are unique and not just little adults. So to have adult labeled drugs sized down to an infant's or child's weight is not sufficient for proper help. Our children are our future and they deserve to have their health challenges to be taken seriously as you would any adult condition."**
>
> - **Deb Discenza (Parent Chapter, Co-Chair)**

What do our kids think about off-label drug use?

What would you like to see improved in pediatric drug research?

- Pulling from their expertise as young people, our youth members underscored the importance of including kids in their healthcare experiences and journeys.

- They detailed how they WANT to be more directly involved in the process and how the Child's opinion on how medicine is practiced is paramount for the development of new drugs.

> "I would like for the patient to be listened to more and to be involved more directly in the process rather than thinking of the product first and patient second."
> - iCAN Youth Member

What do our kids think about off-label drug use?

How would you feel if more safe and effective medications were developed for young people?

- Over all the kids answered that they would feel safer in taking drugs if medications were developed specifically for young people.

- Their hopes for improving treatment options for children spanned from making medications more enjoyable, including more options for treatment, and ensuring that clinical trials are more accessible.

> "If drug testing for pediatric patients was actually done on pediatric patients rather than on adults as the effects can be different for different ages…I'd feel better about the situation"
> - iCAN Youth Member

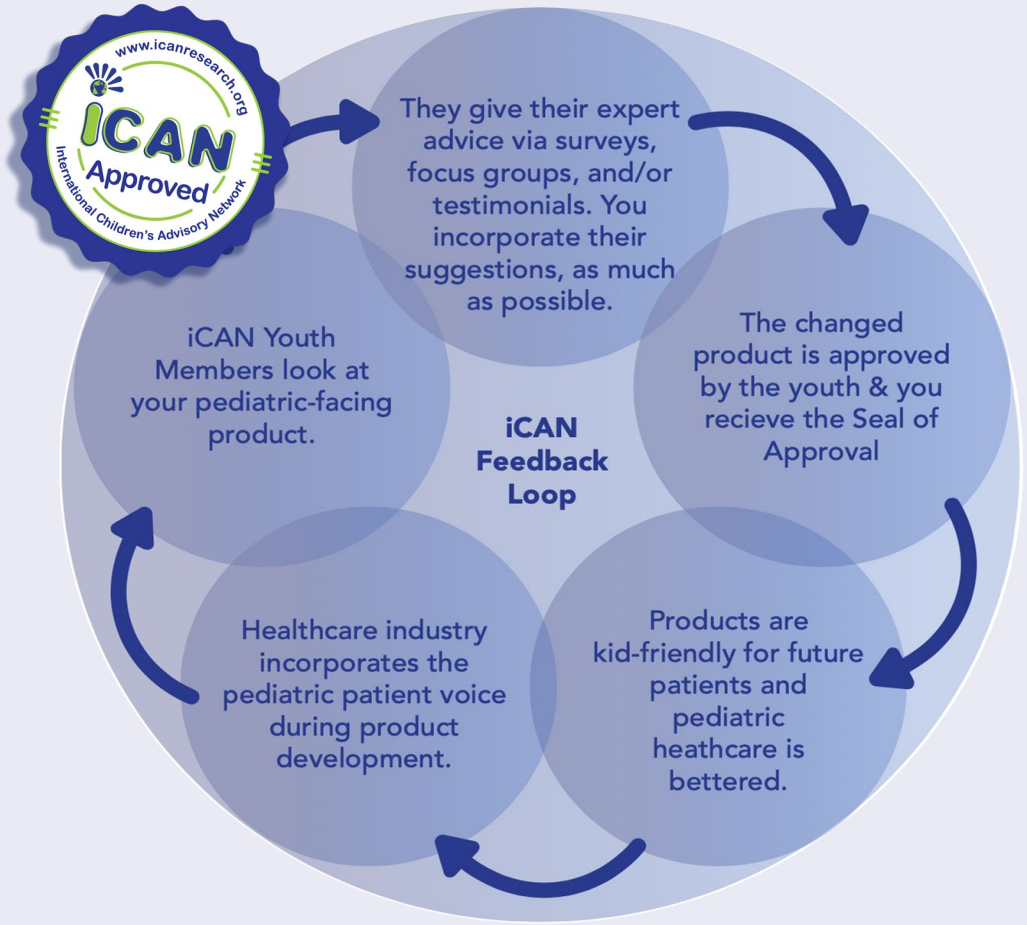
What do our kids think about off-label drug use?

Do you have any hopes or suggestions for improving treatment options for children?

- Youth highlighted the importance of youth involvement in research and clinical trials, their desire that patients are spoken directly to and have more of a voice in healthcare is an overarching theme of the responses.

> "I hope the big pharma companies can see past the fact that kids may be a less profitable demographic than adults and still dedicate resources towards them for better medication and treatment."
> - iCAN Youth Member

Mitigating Barriers Through iCAN Feedback Loop



- **All iCAN activities center around patient and the importance of talking to the patient representatives ahead of time.**
- **iCAN's observational understanding of barriers to pediatric involvement in clinical research reaffirms the importance in working directly with youth to address solutions - particularly in support of pre-clinical trial product co-creation.**
- **Examples of challenges/barriers that impede clinical research in which the iCAN model helps address:**
  - Community distrust for research, accessibility of research, lack of awareness, and general health literacy.

iCAN's Young Professionals Network Public Comment to the FDA on Championing for Engagement of Young Patients in Trial Design Through Incentives to Pharma

"...By partnering with pharmaceutical companies to host direct engagements with pediatric patients and caregivers, iCAN provides a platform for these companies to directly hear from young people and to truly understand the challenges they face..."

iCAN's Young Professionals Network Public Comment to the FDA on Championing for Engagement of Young Patients in Trial Design Through Incentives to Pharma

"...This direct insight allows companies to design clinical trials that are genuinely patient-centric. By fostering open communication and demonstrating a genuine commitment to addressing patient needs, we can significantly improve enrollment and retention rates, ultimately making the research process more efficient and cost-effective..."

iCAN's Young Professionals Network Public Comment to the FDA on Championing for Engagement of Young Patients in Trial Design Through Incentives to Pharma

"...We respectfully recommend that the FDA include a formal requirement or incentive for incorporating pediatric patient groups during feasibility assessments in all pediatric trials. This approach is ultimately necessary for ensuring the successful advancement and delivery of therapies for our most vulnerable patients..."


INTERNATIONAL POSITION PAPER
on youth partnership
IN HEALTHCARE
Montréal July 18 2025
ICAN
George Zaky 18 Ohio
Nicholas Haddad 18 Ohio
Olivia Nach 19 Illinois
Valentina La Marca 20 Ohio
Thuraya Derby 15 UK
Sofia Mathieu 14 Québec
Sofia Kouwabunpat 19 California
Siana Hext 17 California
Elia Hext 17 California
Shelby Fields 14 Kansas
Pedro Español Fernández de Castro 17 España
Orla Linehan 15 UK
Antoine Painchaud 15 Québec
Victoria Cyr 15 Connecticut
Cooper West 21 Ohio
Nele Houben 17 Deutschland
Michael Burgess 17 Illinois
Mary Claire Klein 20 Ohio
Mary Rose Klein 18 Ohio
Maria Chiara Kaeser 19 Italia
Maria Androniki Tolia 19 Ελλάδα
Madeline Hinman 16 California
Madeline Turner 18 Ohio
Meghan Wike 15 Pennsylvania
Lyla Hamilton 16 Illinois
Leo Larvick 17 Illinois
Konstantinos Karathanas 21 Ελλάδα
Kevin Mei 19 Illinois
Karan Muthuraman 18 Illinois
Julia Ramos 19 España
Jasmine Noor 16 UK
Inaaya Shariq 16 Illinois
Huiyun Jiang 19 Illinois
Holden Schroeder 16 California
Heather Hackney 18 Georgia
Gabriella Monacelli 17 Italia
Gabriela Szymańska 15 Polska
Ethan Tailor 17 UK
Emily Woolard 17 Ohio
William Wang 16 Ohio
Hanson Miao 18 Ohio
Capucine Macle 15 France
Cillian Kiernan 16 Ireland
Anvita Ambardekar 17 California
Antonina Franciszka Bryndel 12 Polska
Alex Wu 19 Illinois
Alejandra Wells 17 Nebraska
Haedyn Thompson 14 Michigan
Gabriella Wells 14 Nebraska
Gael Perez Lazcano 15 México
Fiona Kouwabunpat 19 California
Federico Kaeser 23 Italia
Émy Gauthier 16 Québec
Elise Tailor 12 UK
Daniele Sciacqua 21 Italia
Eleri Mcfarlane-Rose 16 UK
Tarun Batchu 16 Ohio
Joseph Haddad 15 Ohio
Luke Klein 22 Ohio
Bartolomeo Sciancalepore 13 Italia
Berkley Blust 16 Illinois
Ashley Ayalen Ocampo Hernández 13 México
Alina Zhao 16 Illinois
Amal Meghani 18 Illinois
Alejandro Huertas Delgado 19 España
Alberto Giandomenico 14 Italia
Ainara Gómez 18 España
Aaisha Seddika Muminah 15 UK

About this Position Paper

This position paper was **co-developed by 76 young people aged 12 to 23 from 11 countries**, during the 2025 iCAN (International Children's Advisory Network) Summit held in Montréal from July 14 to 18.

Through a **co-construction process** with peers and adult allies, youth identified four key priorities to strengthen the development of meaningful partnerships in health with young people. Their voices reflect diverse realities, but a shared goal: to be recognized as active contributors to the health systems.

The following recommendations are a call to action for leaders, professionals, and institutions to build sustainable partnerships with youth on health-related matters.

Accessibility

Accessibility in health partnership for youth means ensuring that all young people — regardless of age, background, literacy level, or support network — can understand, engage with, and benefit from opportunities to be partners in their care and in the healthcare system. This requires access to clear information and a proactive approach to promoting partnership.

- **Use Youth-Friendly Communication Styles & Tools**

  Use clear, positive, and accessible language across various communication tools (social media, portals, videos, printed materials). Focus on personal experience and avoid technical jargon. Ensure that information is easy to find.

- **Actively Explain the Benefits of Engagement**

  Promote partnership through social media campaigns, hospital portals, and peer support. Demonstrate the importance and value of youth involvement in a concrete and appealing way; first for youth and their siblings, then for their parents.

- **Create Support Structures Co-Led by Youth**

  Develop an organization or centralized platform, co-led by young people, that compiles information on opportunities, trustworthy and regularly updated resources. In order to give young people the space and freedom to engage at their own pace; allow trusted adults, such as parents, to be present for support.

Dialogue

The dialogue continuum calls for constant communication reciprocity between young people, patients, and medical professionals. It prioritizes human connection, emotional safety, and transparency over mechanical or repetitive feedback tools in order to guarantee that young people's voices are truly heard and respected.

- **Go Beyond Impersonal and Repetitive Surveys**

  Replace repetitive, impersonal questionnaires with more dynamic and open formats that allow young people to express themselves freely. Use conversations, interviews, or storytelling approaches tailored to each individual.

- **Co-Create Feedback Tools with Youth**

  Engage young people in designing surveys and questions so that they reflect their language, lived experience, and emotional needs — avoiding cold or ambiguous terms, and allowing responses in their own words.

- **Encourage Real Connections and Ongoing Dialogue**

  Ensure professionals actively listen to youth, without discounting, making assumptions or passing judgment. Relationships ought to be intimate rather than business-related. It should promote continuity, trust, and peer support, particularly for young people who receive ongoing or repeated care. Young people should also realize that healthcare personnel are people with their own limitations and difficulties. Realizing this promotes respect for one another and reasonable mutual expectations.

Youth Must Have a Voice in Health Decisions

Young people should be fully involved in the development of policies, social development, services, care and research that impact their health in addition to being listened to when it comes to decision-making in the fields of health, education, and social communities. Real decisions involving hospitals, schools, communities, and the healthcare system at large must be influenced by their opinions.

- **Include Young People in Decision-Making Groups**
  Create youth advisory committees not only in hospitals, but also in schools, public health organizations, research facilities, communities and legislative bodies. Ensure regular meetings, public visibility (e.g., via social media and public spaces), and give them real influence over decisions (e.g., voting rôle).

- **Consider Youth Views in Public Policy Development**
  Engage youth directly in the creation of laws or regulations pertaining to social communities, the educational system, and health. Their viewpoint needs to be methodically collected, taken into account, and presented to decision-makers on an equal basis with any other contextual factor that influences the choices made by those in positions of power.

- **Bring Decision-Makers to Young People**
  Leaders in the fields of health care, education, and social services should meet young people where they are, in youth groups or schools, to help them understand their potential role in those areas. Younger generations can engage with decision-makers, ask questions, provide feedback, and exchange ideas through clubs, podcasts, and open forums.

Education & Training

Young people must have access to an understandable healthcare system and be aware of their own health conditions in order to fully participate. The goal of education and training should be to give young people the skills, information, and self-assurance they need to take charge of their own health, the health of their peers, and ultimately their role as collaborators in the larger healthcare system.

- **Integrate Health Literacy in the Curriculum of Schools**
  Include topics such as shared decision-making, health literacy, and youth rights in health. To enhance learning at all levels, use age-appropriate resources like interactive exercises, infographics, and videos. Educational content should be tailored specifically to young people, but also developed distinctly for their siblings, families, teachers, coaches, and other important individuals in their environment. Providing education and support to these individuals is essential to ensure a shared understanding and meaningful involvement in youth health.

- **Provide Youth Training and Certification Programs**
  To create a sustainable learning environment, youth must be heard and respected by healthcare professionals. Their expertise and contributions need to be acknowledged completely. Whether it concerns themselves, their loved ones' health, or the healthcare system, Official training programs must be created in order to accomplish this. These courses ought to lead to certification, be standardized, and be easily accessible. They need to be co-developed with trained partnership specialists and seasoned youth partners.

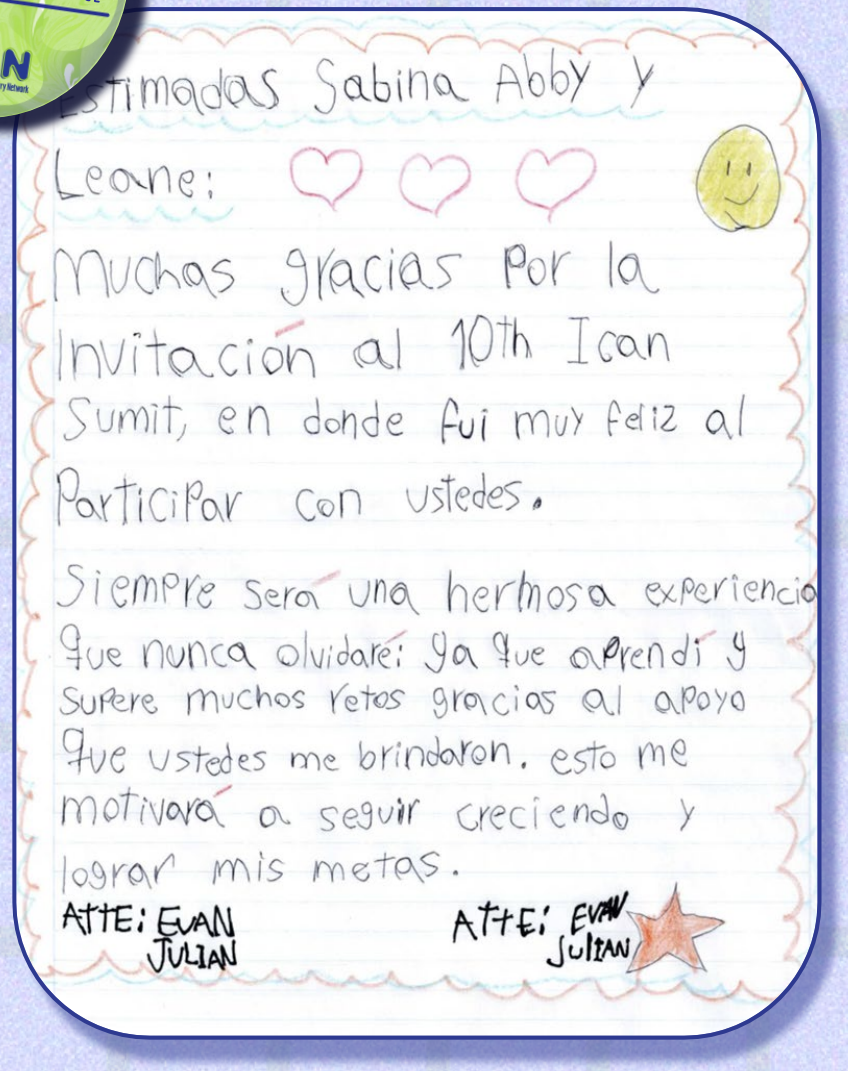
- **Promote Participation that is Empowering and Safe**
  Professionals need to learn how to interact with youth in a safe, inclusive, respectful, and genuine way. Additionally, young people need to learn how to communicate their needs to professionals. Youth can be encouraged to talk freely about health issues through surveys, professional dialogue spaces, or youth-focused organizations, whether they are located online or in schools.

Final Thoughts on Positive Partnership

- Pediatric development can't happen in a silo. It is through partnership of Patient Organizations (iCAN), Regulatory (FDA), and Industry bodies that the youth voice is able to be used in transforming pediatric healthcare.

- Patient partnership should be supported throughout every step of the clinical research process.

- Later in today's call, Meghan Herrington, Anvita Ambardekar, and Inaaya Shariq will speak on their perspectives and experiences with clinical trials and/or unmet medical needs and how those experiences have impacted them.


Estimadas Sabina Abby y Leane:

Muchas gracias por la invitación al 10th Ican Sumit, en donde fui muy feliz al Participar con ustedes.

Siempre será una hermosa experiencia que nunca olvidaré; ya que aprendí y superé muchos retos gracias al apoyo que ustedes me brindaron. esto me motivará a seguir creciendo y lograr mis metas.

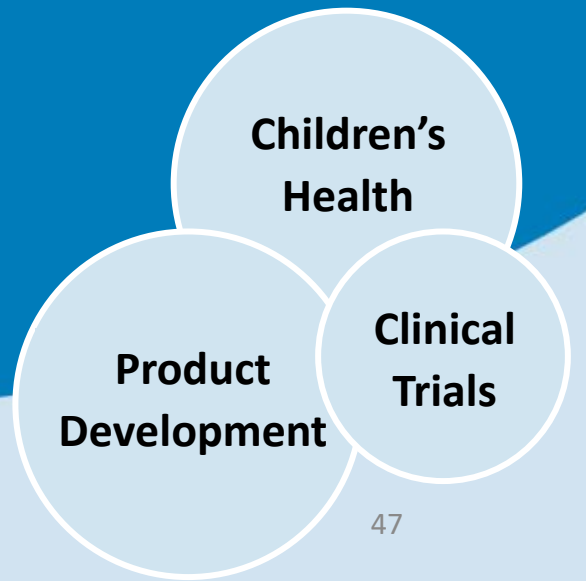
ATTE: EVAN JULIAN

ATTE: EVAN JULIAN

"Patients don't care how much you know until they know how much you care." - Theodore Roosevelt

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Aaron Pawlyk, PhD



Interested Parties Meeting:
Implementation of BPCA and PREA

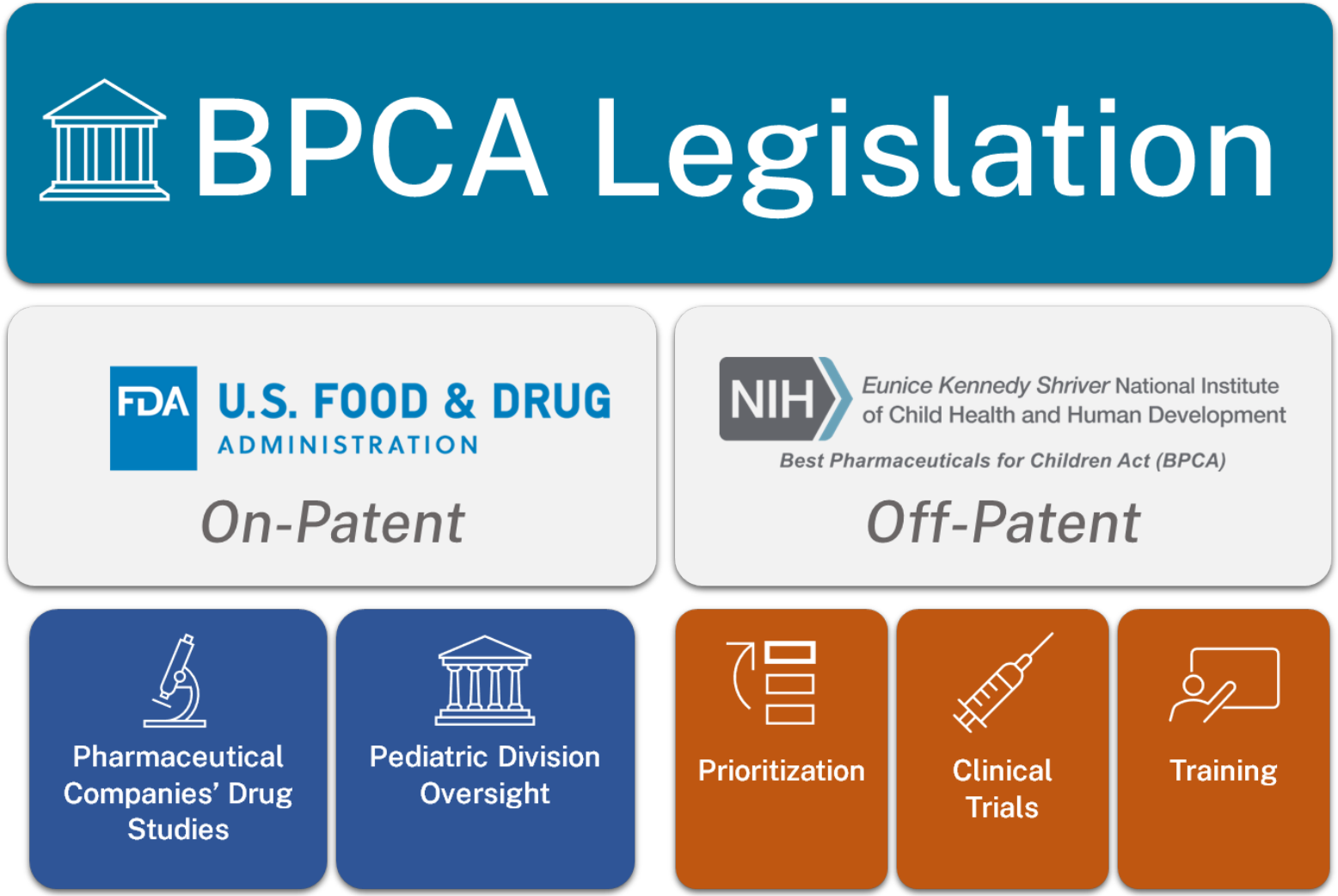
September 15, 2025

Rewriting the pediatric label: Two decades of progress and innovation in the 409i program

Aaron C. Pawlyk, Ph.D.

Chief, Obstetric and Pediatric Pharmacology and Therapeutics Branch
NIH Point of Contact, Pediatric Device Development

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development



NIH portion of legislation renews every 5 years. $25M/yr authorized (not appropriated) since 2002.

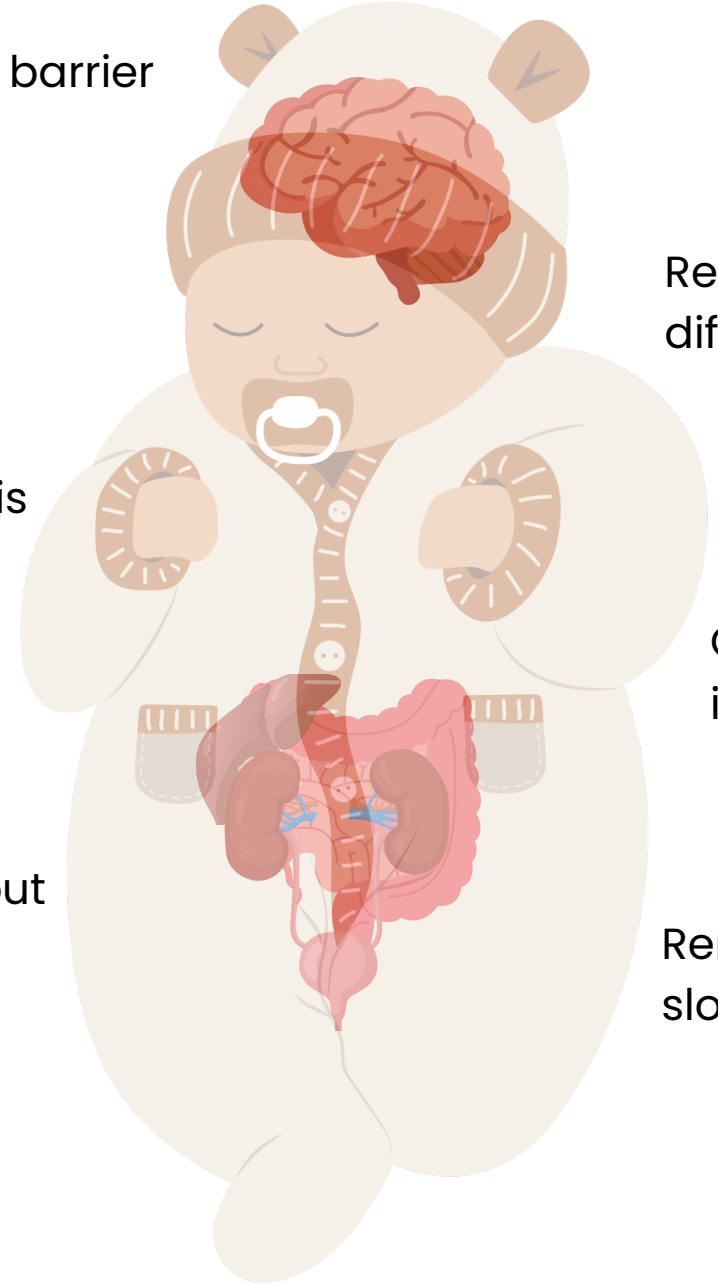
Physiological Differences in Pediatrics

Physiological changes throughout childhood development means that pediatric patients can respond to medications very differently than adult patients do

Blood-brain barrier is immature

Body mass distribution is different

Enzyme activity changes throughout development



Receptors respond differently

Gastric motility is slower

Renal function is slower

mprint

409i program – Goals, approaches, and mechanisms

Prioritization	Prioritization of therapeutic needs Drug development framework
Label changes (Off-patent space)	Label-focused clinical trials infrastructure - Pediatric Trials Network
Pharmacology research	Various NIH grant co-funds MPRINT Hub
Training and career development	T32 and K12 programs in pediatric clinical pharmacology
Improving public health through knowledge	Dissemination & Data Sharing • FDA Docket, DASH • Publications/Methods

Evolution and innovation in BPCA stewardship

Pediatric drug trials

1994 – 1998: Pediatric Pharmacology Research Units (PPRU)

2000: PPRU reorganization

2004 – 2008: PPRU continuation

Launch of BPCA clinical program including 10 legacy BPCA clinical trials

2010: Pediatric Trials Network (PTN) established

2018: PTN v2 awarded

2025: PTN v3 awarded

Pharmacology research

2012 – 2020: Research in Pediatric Developmental Pharmacology (RPDP) Centers

2004-2018: Obstetric Pharmacology Research Units (OPRU)

2020: Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub created

2025: NICHD Council clearance of MPRINT v2

Training and career development

~2007: Collaboration with NIGMS clinical pharmacology T32s

2011-2025: NICHD RFA for pediatric clinical pharmacology T32s

2022: Transition to parent T32 mechanism

2023: Pediatric clinical pharmacology K12 scholar program

2024: Clinical Pharmacology Training Network (CPTN) launched

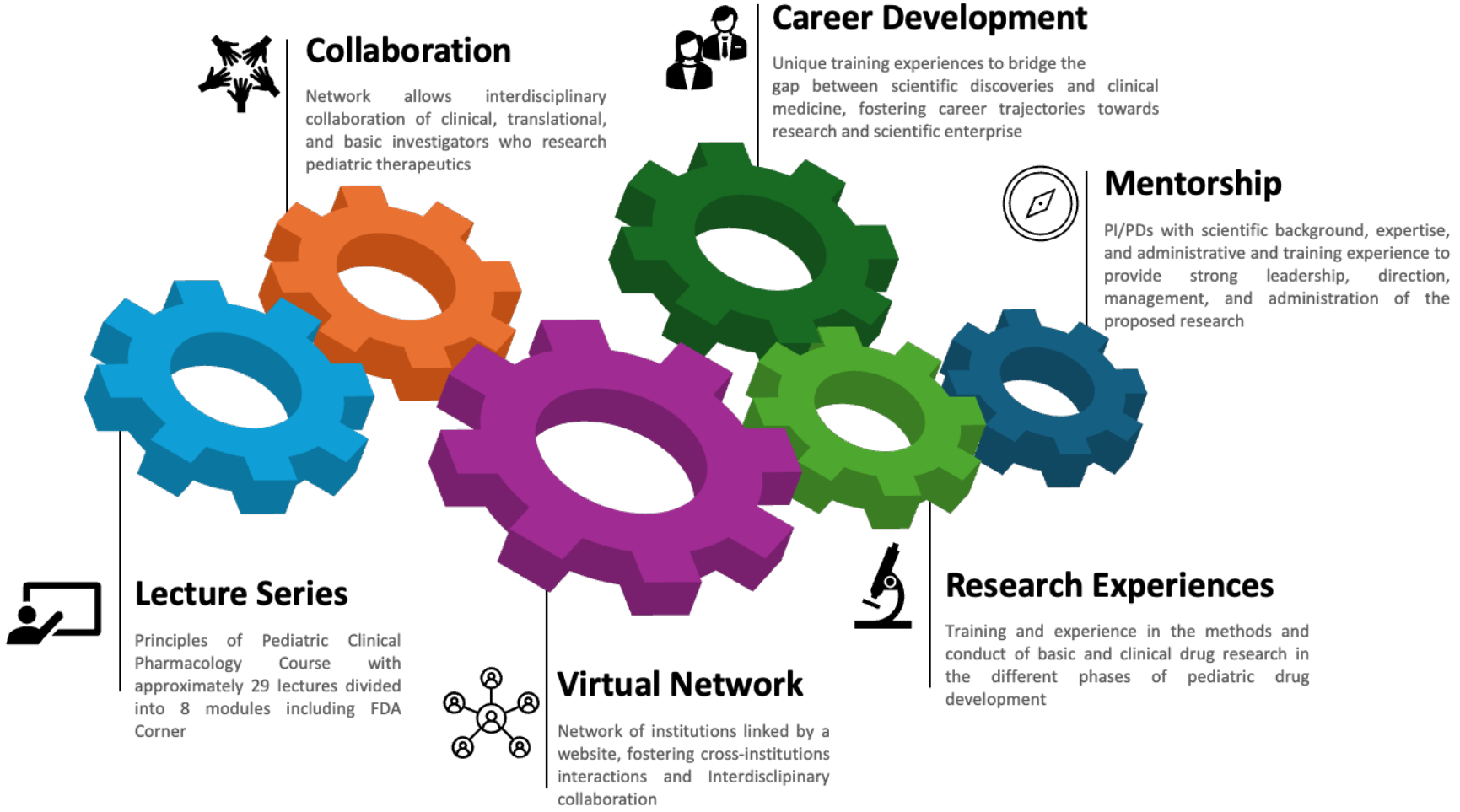
Current T32 trainee sites

- Duke University/University of North Carolina at Chapel Hill
- Children's Mercy Hospitals and Clinics, Kansas City
- Cincinnati Children's Hospital Medical Center*
- University of California, San Diego
- Jefferson/Children's Hospital of Philadelphia
- University of Utah

Current K12 scholar sites

- Cincinnati Children's Hospital Medical Center
- University of North Carolina Chapel Hill,
- Duke University
- University of California, San Diego
- Children's Mercy Kansas City

NICHD Clinical Pharmacology Training Program



Over 100 pediatric clinical pharmacology fellows trained!

mprint is a national resource to improve pediatric and maternal research outcomes by providing support at every step in the research process.

MPRINT.org

Identify gaps in knowledge

Identifying research questions based on community need

Study design that will identify strategic sampling

Establish best practice for study design to maximize research outcomes.

Clear protocols for sample processing and bioanalysis

Provide analytics support

Data, models, and knowledge need to feed back into clinical settings

Extend the reach and impact of research

What is the Pediatric Trials Network?

"Create an infrastructure for investigators to conduct trials that improve pediatric labeling and child health"

- Sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) on behalf of NIH
- Best-in-class science to update off-patent drug labels to ensure safe and effective use of drugs in children only when necessary
- Ultimate goal is improving child health

BPCA clinical program structure

Clinical Coordination Center

Duke Clinical Research Institute

- Pharmacology expertise
- Clinical trial design and implementation
- Clinical site recruitment, management, and monitoring
- IRB approvals
- Drug distribution
- Lab and vendor management

Data Coordination Center

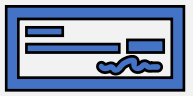
The Emmes Company

- Data management
- Regulatory support
- FDA communications and submissions
- Statistical expertise
- Data quality and Data safety oversight

Logistics Support

Infinity Conferences, LLC

- Communication of research findings
- Website support
- Symposia/Workshop/ Meeting support
- Prioritization Outreach
- Logistics support for training programs



NICHD/NIH

- Oversight
- Policies
- Funding
- Priorities
- Dissemination

$18M total costs annually from trans-NIH funding

NIH 409i label changes – 26 and counting

Ampicillin dosing, safety in neonates	Trimethoprim-sulfamethoxazole dosing	Lithium dosing, safety, efficacy indication in peds bipolar patients	Lorazepam safety in status seizures, EFIC	*Lisinopril dosing in transplant patients	Meropenem dosing, safety in neonates	Doxycycline dosing in peds patients
Acyclovir dosing, safety in neonates with HSV	Caffeine Citrate RWD, exposure response and safety in neonates with apnea	Clindamycin dosing in obesity	*Mercy Tape weight estimation device	*Mercy Baby Tape weight estimation device	*Propylthiouracil Safety signal	*Pralidoxime peds dosing recommendation
Sodium Nitroprusside dosing, safety for BP control	Diazepam dosing and safety in seizures	Clindamycin dosing, safety in infections	Rifampin dosing, safety in infections	Levetiracetam dosing in obesity	Fluconazole dosing and safety in preterm neonates & dosing in ECMO patients	Oxcarbazepine obesity dosing
	Oxycodone breastmilk exposure	Furosemide dosing preterm & term neonates	Metronidazole dosing, safety, effectiveness in peds patients	Topiramate dosing in obesity	Ondansetron breastmilk exposure	

- **4 upcoming and anticipated label changes for 2025/26**
  - **Digoxin (congenital heart failure)**
  - **Metformin (type 2 diabetes)**
  - **Piperacillin-Tazobactam (infectious diseases)**
  - **Nifedipine (breastmilk exposure)**

- **7 additional FDA submissions for label change considerations planned for 2025/26**
  - **Aripiprazole, Risperidone (antipsychotics)**
  - **Sertraline (antidepressant), Clindamycin, Azithromycin (antibiotics)**
  - **Hydromorphone, Ketorolac (anesthetic, analgesic)**

*NOT listed on FDA website but NIH data contributed to label improvements and/or updates

APS | European Society for Paediatric Research | spr Society for Pediatric Research

www.nature.com/pr

REVIEW ARTICLE

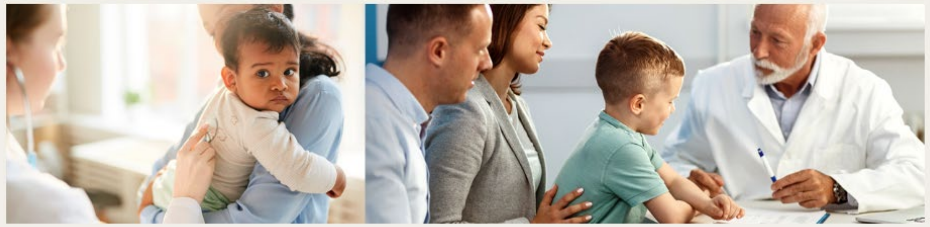
Breaking the silence: challenges and opportunities in pediatric drug development

Kanwaljit Singh[1], Tim Franson[2], Susan McCune[3], Daniel Jorgensen[4], Kenneth Getz[5], Cynthia Bearer[6] and Jonathan M. Davis[7]✉

Check for updates

Strategies to Enhance Pediatric Health Research Funded by NIH

NATIONAL ACADEMIES Sciences Engineering Medicine

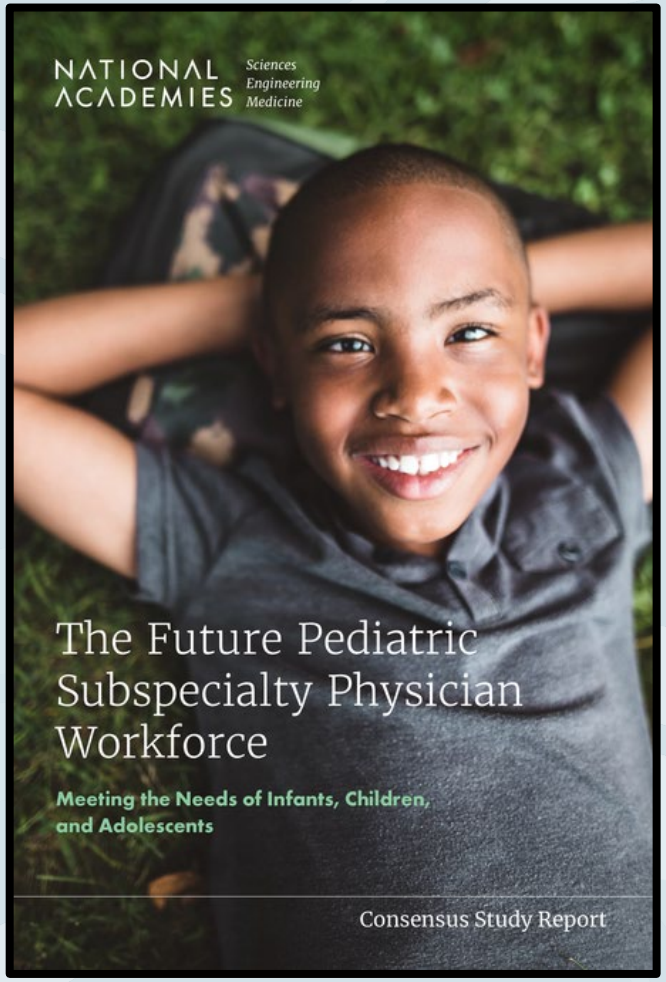


MAHA

MAKE AMERICA HEALTHY AGAIN

SECTION FOUR

The Overmedicalization of Our Kids



JAMA | Original Investigation

Trends in US Children's Mortality, Chronic Conditions, Obesity, Functional Status, and Symptoms

Christopher B. Forrest, MD, PhD; Lauren J. Koenigsberg, BA; Francis Eddy Harvey, BA; Mitchell G. Maltenfort, PhD; Neal Halfon, MD, MPH

BPCA clinical program structure today

Clinical Coordination Center

Duke Clinical Research Institute

- Pharmacology expertise
- Clinical trial design and implementation
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- FDA communications and submissions
- Statistical expertise
- Data quality and Data Safety oversight

Lo[illegible]s S[illegible]ort

Infinity C[illegible]ces, LLC

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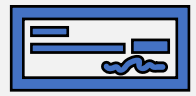


NICHD/NIH

- Oversight
- Policies
- Funding
- Priorities
- Dissemination

Total costs to contracts capped at $11M in 2025

Turning challenges and opportunities…

- Limited resources and need to change ➔ innovative approaches
- New approaches to NICHD networks ➔ opportunities to collaborate
- Momentum in workforce development ➔ prepare for the future
- Pediatric medical device partnership ➔ expand to drug partnership

…into impactful programs for child health!

Potential future trajectories for evolution

- Continue to innovate pediatric clinical trials
- Develop and validate Novel Alternative Methods for pediatrics
- Integrate real-world safety monitoring of pediatric drug usage
- Use AI to accelerate understanding of pediatric pharmacology
- Include long-term, longitudinal safety and efficacy outcomes
- Prepare the pediatric clinical pharmacology workforce for the future
- Linkages to fetal exposure from maternal medication usage
- Verify findings from industry-funded pediatric studies
- Partnerships with pediatric networks and government agencies
- Crowdsource more ideas at forums like this!

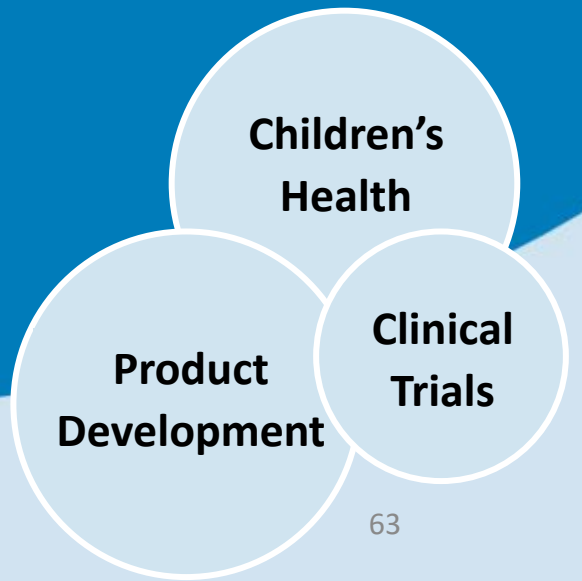
Thank you!

National Organization for Rare Disorders (NORD)

Pamela Gavin, MBA

Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025



Implementation of the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act

National Organization for Rare Disorders

Pamela Gavin, Chief Executive Officer

NORD®
National Organization for Rare Disorders

Alone we are rare. Together we are strong.®

Our Mission

To improve the health and well-being of people with rare diseases by driving advances in care, research, and policy.

NORD®
National Organization for Rare Disorders

Alone we are rare. Together we are strong.®

Pediatric Studies are Critical for Addressing the Needs of the Rare Disease Community

- Before 1983, less than 40 treatments were on the market for rare diseases.
- Today, 882 designations resulted in at least one FDA approval for use in 392 rare diseases.
- 95% of the approximately 10,000 known rare diseases still lack an FDA-approved therapy.
- As many as half of rare disease patients are children.
- Approximately 30 percent of children with rare diseases will not reach their fifth birthday.

See: U.S. Government Accountability. (2021, October 18). *Rare diseases: Although Limited, available evidence suggests medical and other costs can be substantial*. U.S. GAO. https://www.gao.gov/products/gao-22-104235

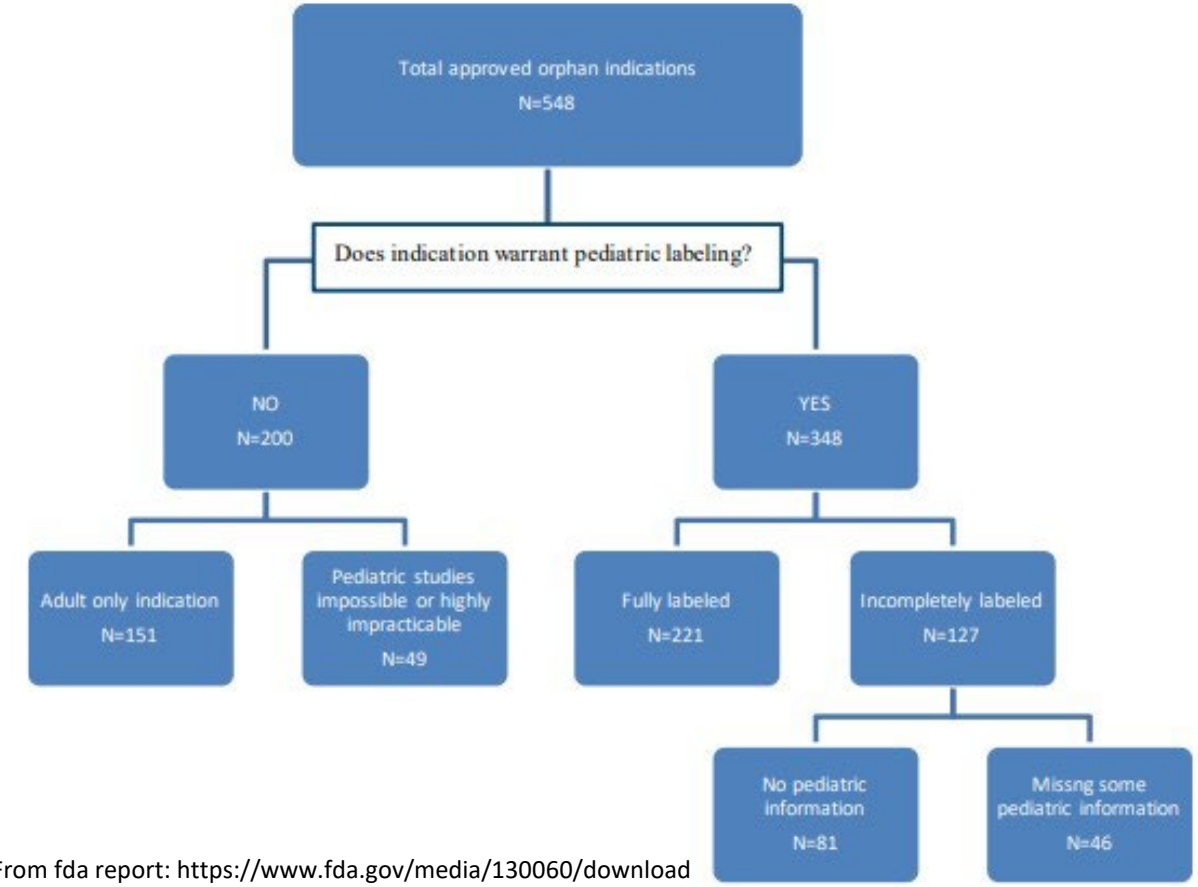
NORD®
National Organization for Rare Disorders

Alone we are rare. Together we are strong.®

PREA and BPCA Advance Treatments for Pediatric Patients

- PREA and BPCA together provide:
  - Incentives
  - Flexibility
  - Accountability
- Notably, orphan indications are exempt from PREA study requirements.
- Written requests may be issued for orphan indications under BPCA.

Figure 1: Orphan Indication Pediatric Labeling Review Process



From fda report: https://www.fda.gov/media/130060/download

NORD® National Organization for Rare Disorders

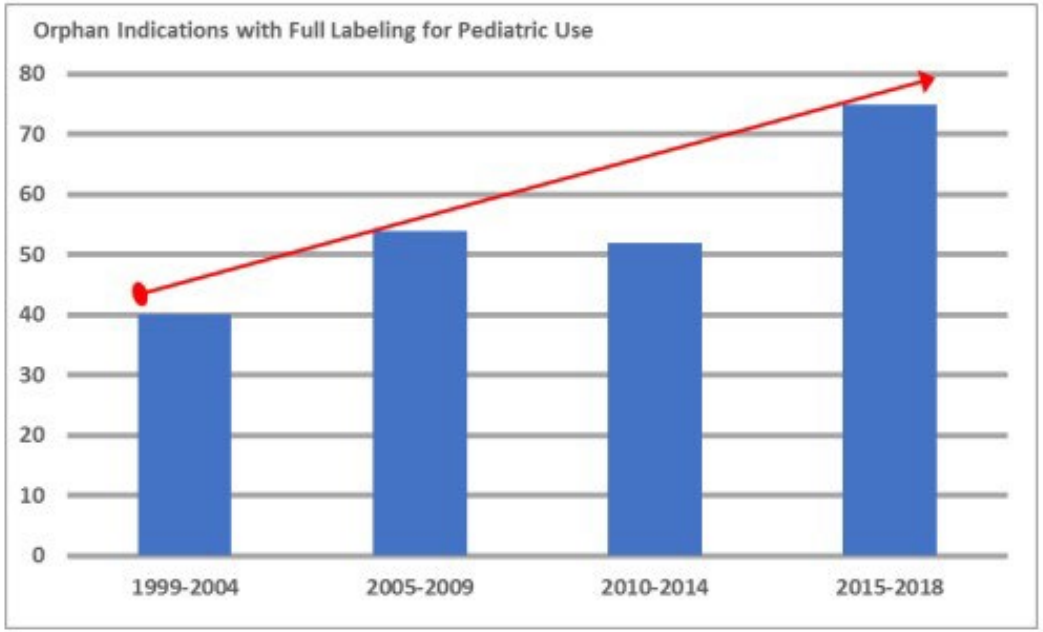
Alone we are rare. Together we are strong.®

Significant Gaps Remain in Rare Pediatric Trials

- BPCA and PREA are designed to improve safety and efficacy in therapies for children.
- However, significant pediatric labeling gaps remain.
  - 40 percent (127 of 348) of orphan indications approved from 1999 to 2018 were incompletely labeled for pediatrics.
  - 81 cases had no pediatric information.
  - 46 missing some pediatric information

See: Department of Health and Human Services, Food and Drug Administration. Pediatric Labeling of Orphan Drugs Report to Congress. Table 5. https://www.fda.gov/media/130060/download, downloaded on November 13, 2019.

Figure 2: Orphan Indications with Appropriate Labeling for Pediatric Use, 1999 to 2018



From fda report: https://www.fda.gov/media/130060/download

PREA, BPCA Refinements Support Rare Pediatric Innovations

- Refinements must balance pediatric labeling with addressing barriers to rare disease research.
- Tools, pilot programs, and additional guidance should be leveraged to further de-risk rare disease product development and reduce the burden associated with rare pediatric studies.
- Legislative refinements, like those included in the Innovation in Pediatric Drugs Act of 2025, should both strengthen enforcement of existing requirements and increase access to incentives.

National Organization for Rare Disorders

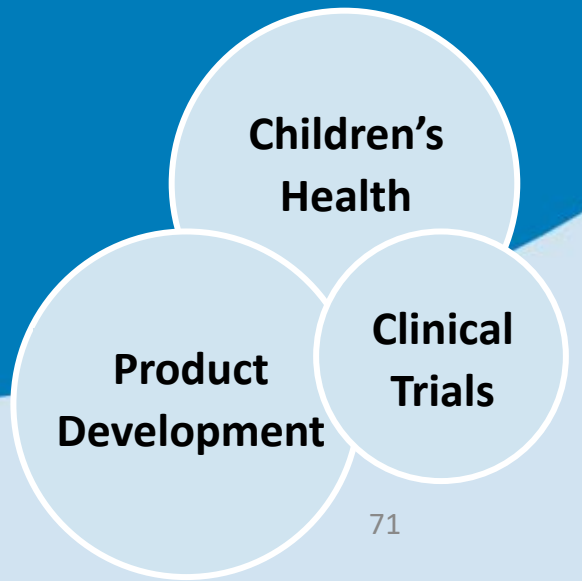
Pamela Gavin, Chief Executive Officer

NORD®
National Organization for Rare Disorders

Alone we are rare. Together we are strong.®

Pediatric Pharmacy Association (PPA)

M. Petrea Cober, PharmD and
Rachel Meyers, PharmD



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

BPCA/PREA Comments

The Pediatric Pharmacy Association

M. Petrea Cober, PharmD, MEd, BCNSP, BCPPS, FASPEN

Rachel Meyers, PharmD, BCPS, BCPPS, FPPA

The Pediatric Pharmacy Association

- Who we are
  - The national organization for pediatric pharmacists
  - 1700+ members
- Our mission
  - The mission of the Pediatric Pharmacy Association is to advance pediatric pharmacy practice, support the health and wellbeing of children, and promote safe and effective medication use in children through **C**ollaboration, **A**dvocacy, **R**esearch, and **E**ducation.

BPCA & PREA: What we love

- Earlier labeling for drugs in pediatrics
  - As practitioners we have better information than case reports
  - We are more confident in using newer drugs in children

BPCA& PREA:
What we’re still missing

The KIDs List

- The pediatric equivalent of the “Beers Criteria”
  - Medications on the KIDs List are POTENTIALLY inappropriate in children
    - Clinical situations may arise where use is appropriate
    - The KIDs List should never be a substitute for clinical judgement

- PPA published the first KIDs List in 2020
  - Updated in 2025


SPECIAL ARTICLE

JPPT | Medication Safety

Key Potentially Inappropriate Drugs in Pediatrics: The KIDs List


SPECIAL ARTICLE

JPPT | 2025 KIDs List

Pediatric Pharmacy Association 2025 KIDs List of Key Potentially Inappropriate Drugs in Pediatrics

Meyers R et al. J Pediatr Pharmacol Ther. 2020;25(3):175-191.
McPherson C et al. J Pediatr Pharmacol Ther. 2025;30(4):422-439.

What the KIDs List Reveals

- The 2025 edition included 39 drugs/drug classes and 10 excipients that are potentially inappropriate in pediatric patients
  - 27 of 39 (69%) have a “low” or “very low” quality of evidence
- Other needs highlighted
  - Lack of clear guidance on ethanol
  - Emerging evidence helps to clarify risks
    - Montelukast, daptomycin

McPherson C et al. J Pediatr Pharmacol Ther. 2025;30(4):422-439.

Old Drugs Need Attention Too

- Most drugs used in day-to-day pediatric practice were approved prior to BPCA and PREA
- Pediatric practitioners use “unapproved” products every day, many of which are standard of care
  - Metronidazole
  - Doxycycline
- Outdated package inserts
  - Chlorothiazide suspension – dose listed is per pound and the volume is listed in mL and teaspoonfuls
  - Liquids with concentrations listed per 5 mL
  - Daptomycin diluent volume based on the age of the child – violates rules for standardized concentrations

Diuril [package insert]. Minneapolis (MN): Paddock Laboratories, Inc.; 2008.
Daptomycin [package insert]. Berkeley Heights (NJ): Hikma Pharmaceuticals USA, Inc.; 2025.

Newer Drugs with Unhelpful Information

- Rivaroxaban 5 mg dose cannot be given with two 2.5 mg tablets, must use liquid
- Combination antibiotics
  - Doses for adults are in total dose
  - Doses for pediatrics are listed for each component and for the total dose
    - Example: Ampicillin/Sulbactam dose for children is 50 mg/kg of the ampicillin component, dose for adults is 1.5 g or 3 g which are 1 and 2 g of ampicillin

Xarelto [package insert]. Titusville (NJ): Janssen Pharmaceuticals, Inc.; 2021.
Unasyn [package insert]. New York (NY): Pfizer Inc.; 2025.

Cost

- Reimbursement for off-label medications remains a problem
  - Especially for expensive infusion medications
  - Treatment is unfortunately dictated by managed care organizations
- Price of newer pediatric friendly dosage forms is often prohibitive

Moving Safety for Children Forward

- Other advocacy items
  - Requiring weight on prescriptions (and height!)
    - Allowing pharmacists to check the dose

JPPT | Pediatric Pharmacy Association Position Paper

Patient Weight Should Be Included on All Medication Prescriptions

Lisa Lubsch, PharmD; Katelin Kimler, PharmD; Nicole Passerrello, PharmD; Mindy Parman, PharmD; Andrea Dunn, PharmD; and Rachel Meyers, PharmD, on behalf of the Advocacy Committee of the Pediatric Pharmacy Association

Lubsch L et al. J Pediatr Pharmacol Ther. 2023;28(4):380-381.

Summary

- What we love
  - Data and labeling for new drugs in pediatrics
- What we recommend
  - Help with old drugs
    - Data on pediatric dosing
    - Updating labeling for safety
      - No more concentrations in teaspoons
  - More practical, user friendly information in labeling
    - Education for parents and caregivers on how to administer medications to children

Thank you for all that you do for children

Break

Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

Interested Parties Meeting for Pediatrics

Provide your feedback on implementation of the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA)

Children's Health

Product Development

Clinical Trials

September 15, 2025

9:00 a.m. to 4:30 p.m. ET

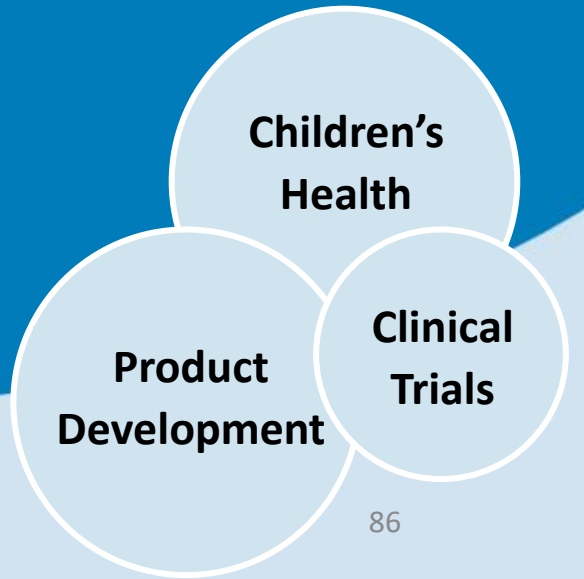
FDA Great Room
White Oak Campus
Silver Spring, MD

Virtual option available

Submit comments to the public docket number FDA-2024-N-5784 until 11:59 p.m. Eastern Time, September 30, 2025

Visit https://www.regulations.gov

Session Two

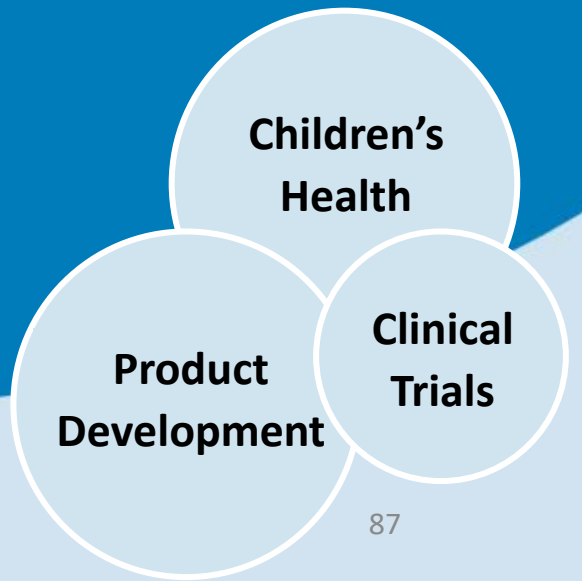


Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

Consumer Healthcare Products Association (CHPA)

Cathy K. Gelotte, PhD



Interested Parties Meeting:
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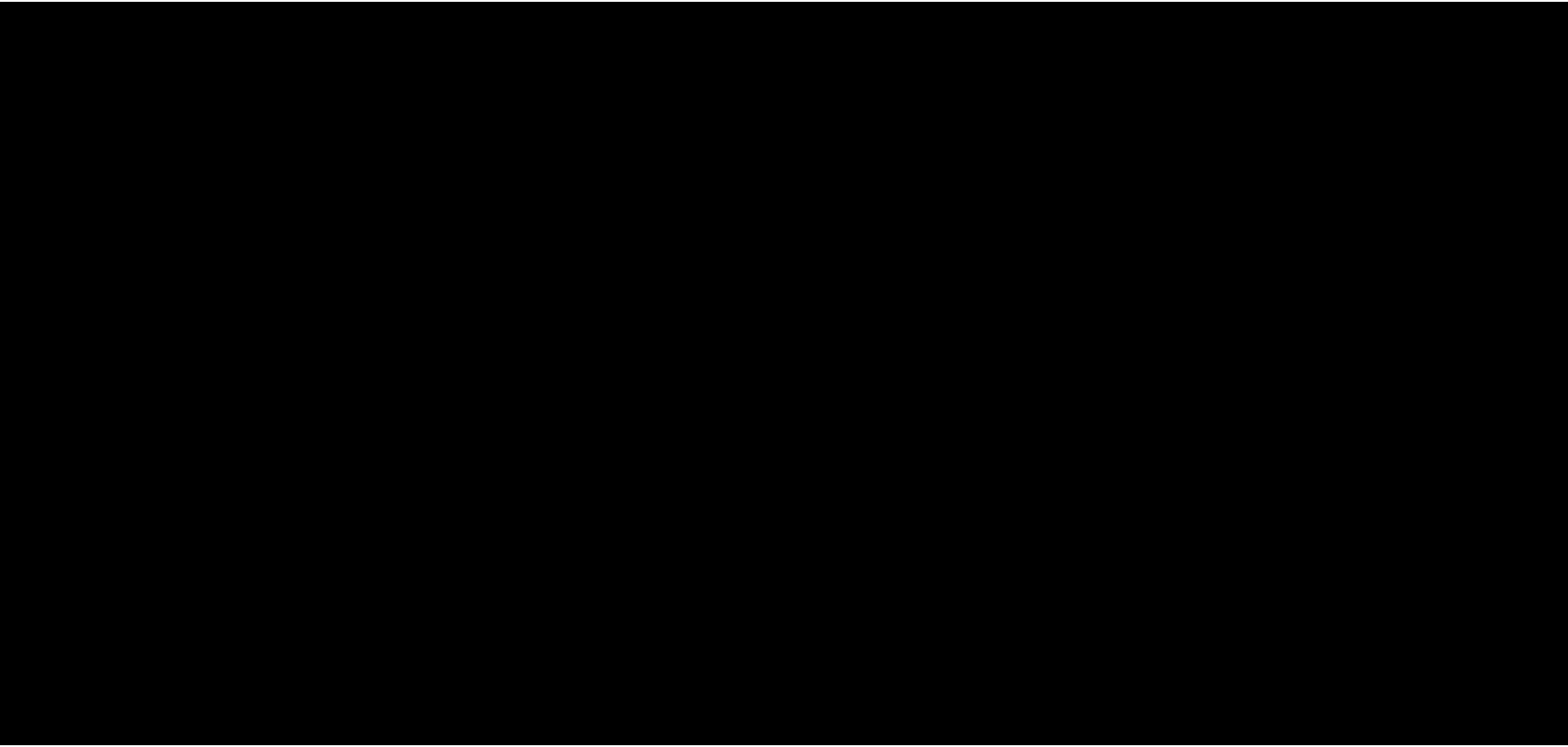
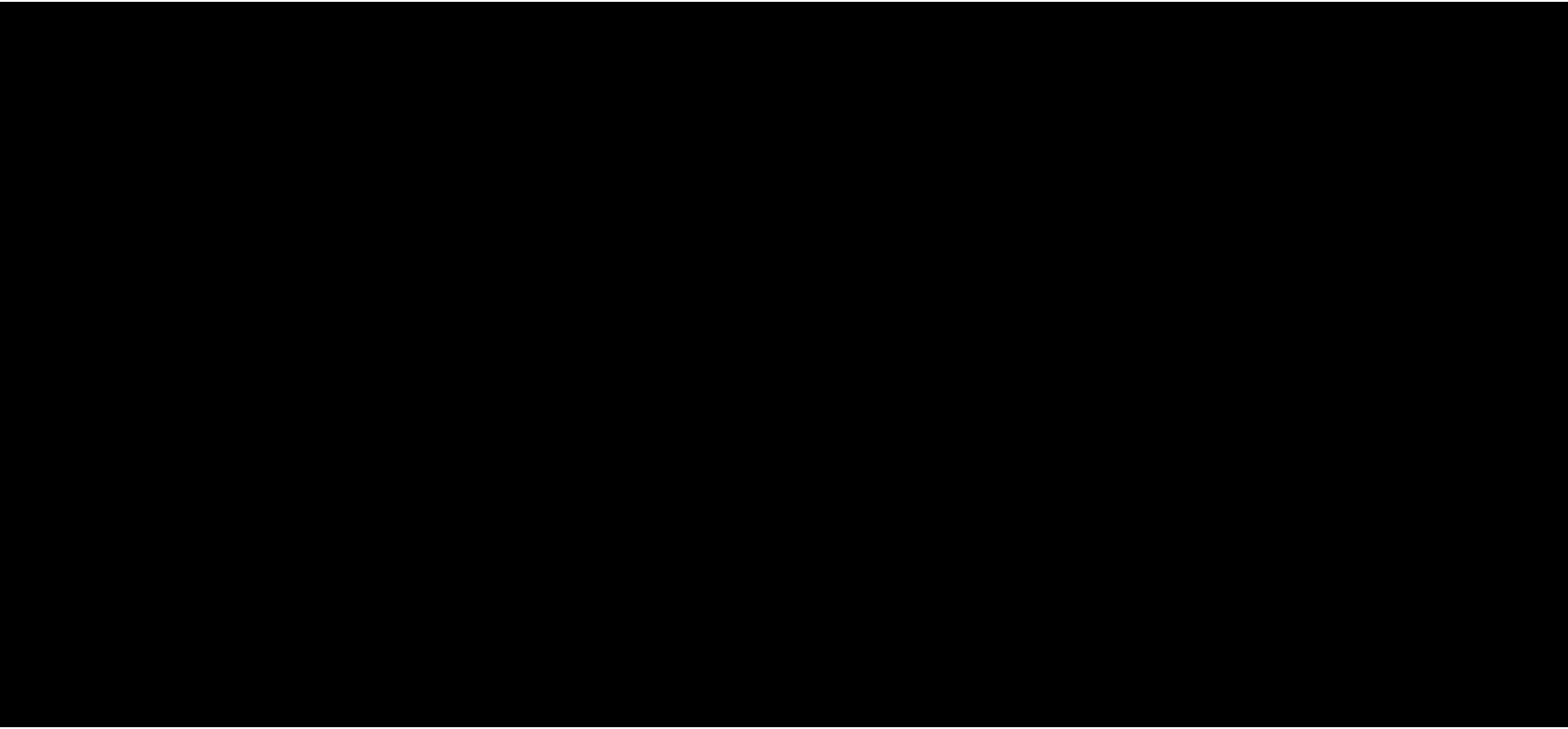


Harvard-MIT Center for Regulatory Science

Florence Bourgeois, MD, MPH

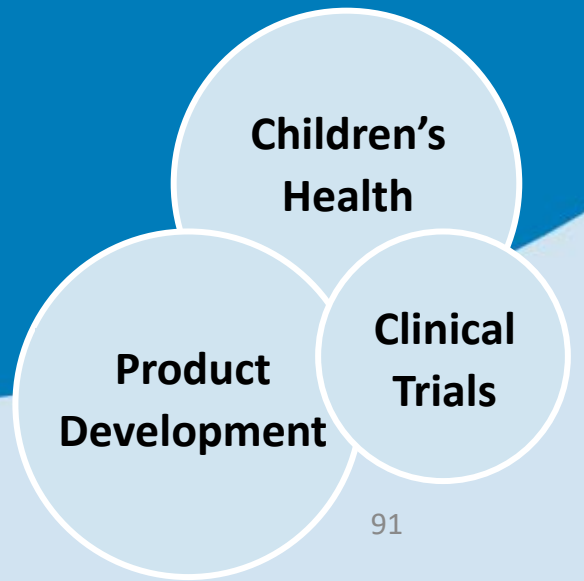
Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025



Multi-Regional Clinical Trials (MRCT) Center of Brigham and Women's Hospital and Harvard

Danny Benjamin, MD, PhD



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

Platform Trials for Children

Danny Benjamin MD PHD
Distinguished Professor of Pediatrics Duke University
Chair, Pediatric Trials Network of NICHD
Collaboration with Multi-Regional Clinical Trials (MRCT) Center of Brigham and Women's Hospital

Definitions and Overview

- Master protocols: answer more than one question at a time
  - Platform trial: multiple treatments or diseases are evaluated within the same protocol
  - Basket trial: one therapy is tested on more than one disease
  - Umbrella trial: multiple therapies are tested for a single disease

- MRCT (Multi-Regional Clinical Trials Center at Brigham and Women's Hospital) assembles broad stakeholders to move forward with global platform trials for regulatory approval initially focused on 3 areas (tuberculosis, oncology, psychiatry)
  - MDR-TB with World Health Organization—this effort has slowed
  - Major Depressive Disorder—seeking to work with third parties, moving forward
  - Oncology—July 2025, industry, patient advocates, leadership team, best practices

- Two slides on experience, and then
- Provide lessons learned
  - For BPCA, and
  - How those lessons can be applied across NIH, and
  - How those lessons can be applied by industry

Summary of Platform Trials That We Have Designed, Completed Enrollment, and Submitted Data to FDA

- **POPs**:
  - Child receiving molecule per standard of care; consent for 1 to 5 drops of blood during standard of care laboratory
  - PTN uses POPS as a funnel: 33,000 biologic samples, >100 validated assays (>200 methods), >50 analyses completed
    - Screening of: Investigators, Sites (300 across PTN trials), Molecules (145), Populations
    - Emerging and difficult populations—neonates (2,700 samples), ECMO (2,000), obesity (6,000), breast feeding (3,000), COVID
- **Cuddle:** Breast Milk Study
  - Mothers receiving medicine per standard of care—sample from mother's blood, breast milk, and infant
- **SCAMP:** Safety and efficacy of antibiotics in premature infants
  - Preterm infants with complicated intra abdominal infection randomized to 5 different molecules, at doses stratified by postmenstrual age. (stricture and resistance)
- **LAPS:** Long-term safety of anti-psychotic medicines
  - (vs 48 weeks in label), >500 children
- **ACTIV-1:** During the pandemic, PTN faculty and staff were asked by NIH to lead a platform study in adults
  - enrolled 1,971 abatacept; infliximab; cenicriviroc; or placebo; international study ACTIV-1

Pediatric Trials Network
Molecules from Platform 2018-2024

POPS: Pediatric Opportunistic PK Study
NCT04278404
CUDDLE: Mother-infant dyads, breast milk
NCT03511118
SCAMP: complicated abdominal infections in infants
NCT01994993
LAPS: Long term anti-psychotic safety study
NCT03522168

ECMO: extra-corporeal membrane oxygenation
NCT01431326
ANA: Anesthetics and Analgesics
NCT03427736
POPS for Children with Obesity
NCT04278404
AED: Anti-epileptic drugs used in obese children
NCT02993861
Anti-Staph Trio: antibiotics to treat S. aureus
NCT01728363
Dosing of Therapeutics in COVID
NCT04278404

Platform Trials Lessons Learned: Stakeholders and Partners

- Infrastructure and Collaboration
  - POPS1 in 2010, extensive pediatric-specific site infrastructure for opportunistic studies
  - Limited compensation, but the prospect of 20 therapeutics or more meant that each site could support a full time
- Key stakeholder input: families, child advocates, professional societies, AAP, NIH, PTN, EMMES, FDA, investigators, and sites
  - Multiple sponsor complicates
- Expertise: this is not a trial design for a widget approach
- Flexibility in bioanalytical methods and how you get the samples (no extra sticks)

- Industry and NIH more broadly:
  - Economics of 2 or 3 molecules vs. 20 or 30 molecules

Platform Trials Lessons Learned: Flexibility

- Flexibility to fill critical knowledge gaps:
  - Opportunistic protocols can be designed to allow for studying variations in PK based on subgroup – i.e. patients on continuous renal replacement therapy, patients with obesity, those with potential drug-drug interactions, etc.
  - Flexibility in sampling schemes depending on the properties of the molecules of interest: the four antiepileptics in AED01 had wide variations in PK properties and the protocol allowed for varying sampling schemes

- Industry application
  - flexibility and compromise around protocol details and sampling schemes, balancing the sites and disease, and the other partners

Platform Trials Lessons Learned: Ability to Pivot

- Molecules in common clinical use:
  - when drugs are rarely prescribed, potential problem in most other designs
  - COVID-19 pandemic, added 15 drugs for COVID and MISC
  - 33 sites; enrolled the first child patient in 6 weeks
  - some worked; and some failed;
  - additional sites cost more on the front end but key to success

- Industry and NIH more broadly
  - Some molecules will be more ‘popular’ than others (Industry);
  - A subset of sites might be crucial for some molecules more so than others
  - Going beyond traditional large centers (NIH)

Platform Trials Lessons Learned: Looking Forward

- BPCA uniquely positioned to innovate in clinical trials; these lessons learned can be applied to not just molecules, but other care questions
- “Reverse engineering” studies:
  - Start with a professional guidance document (e.g., osteomyelitis, traumatic brain injury, or neonatal HIE), usually ~25 recommendations approximately 10-20 with equipoise
  - Select all the recommendations with low or very low quality of evidence
  - First randomize at the site, because children get sick at night & you don’t want to fail
  - Then stack subsequent interventions with different questions at different times
  - E.g., severe traumatic brain injury,
    - what is target intra-cerebral pressure (ICP) monitoring;
    - then randomize at the individual: if ICP exceeds limits, do you use salt or mannitol to reduce ICP;
    - then, if you fail first line therapy, what do you do; primary endpoint 12 months after injury
    - then, how best to improve cognitive outcomes 12-24 months after injury

Long-term goal to answer dozens of questions with each trial

Breast Milk Study 2018-2024

CUDDLE (BMS01)
Ciprofloxacin
Doxycycline
Levofloxacin
Amoxicillin
Duloxetine
Buprenorphine
Bupropion
Hydrocodone
Paroxetine
Levetiracetam

CUDDLE (Expansion)
Amoxicillin
Bupropion
Buprenorphine
Duloxetine
Hydrocodone
Levetiracetam
Paroxetine

BMS02 (Botswana)
Dolutegravir
Emtricitabine
Tenofovir disoproxil fumarate
Lamivudine

BPCA and Platform Trials Lessons Learned: Extrapolation

- It is true that children are not small adults (never extrapolate dosing);
- But it is also true that children are not Martians
- Assess extrapolation of efficacy: full, partial, none
  - "Examples" Intra-abdominal infections; analgesia; premature infant BPD
  - "Typically," dosing & safety; some masking; well-powered trial

- Industry and NIH (more broadly at NICHD or elsewhere) investigators:
  - The details of the challenges you will face are different, and the cost of the trials are different, but much of what you learn in your 1st and 2nd platform trial can be applied to your 3rd, 4th, 5th, and even 10th platform trial

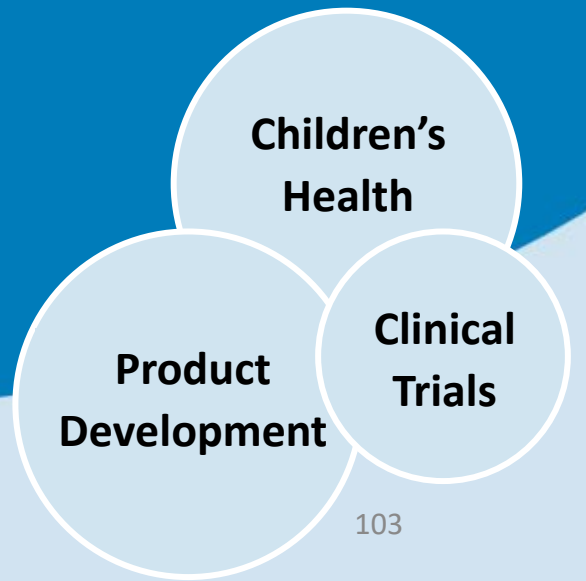
Platform Trials Lessons Learned: Electronic Medical Record

- The current state of the electronic health record and the medication administration record, timing of drug administration is not rigorously recorded.
  - Calculating PK parameter estimates with short half-lives
  - Sites require training on the accurate documentation of timing of drug administration and sample collection. Very variable and not always correlated to children's hospitals or major medical centers.
  - Intensive sampling or documentation needs, and trained research-naïve sites on research processes and maintaining high data quality

- Industry—as many of you know, a pediatric department has 15 or more clinical divisions, and thus, 15 or more potential performance levels

Pediatric Patient Representatives (iCAN)

Anvita, Inaaya, and Meghan

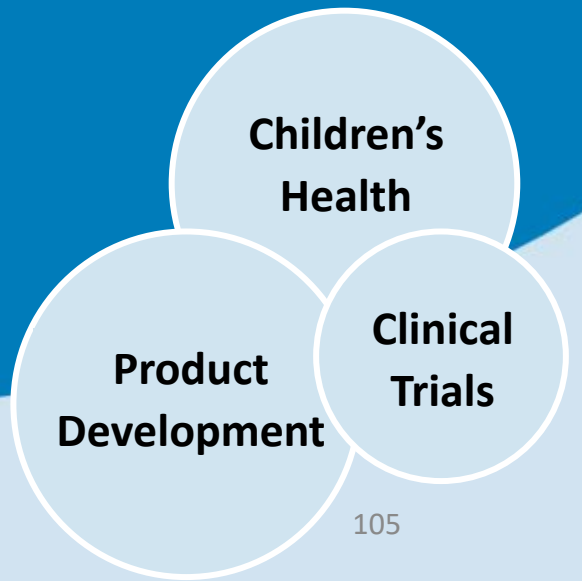


Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

Pediatric Trials Network (PTN)

Rachel G. Greenberg, MD, MB, MHS



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

The Pediatric Trials Network:

Making drugs safer and more effective for children

Rachel Greenberg, MD, MB, MHS

September 15, 2025

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

What is the Pediatric Trials Network?

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

An infrastructure for investigators to conduct trials that improve pediatric labeling and child health

- Sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
- Performs studies to improve dosing, safety information, labeling, and ultimately child health
- Focus on off-patent therapeutics

PTN Public Health Impact

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

>12,500
participants enrolled

33
products submitted to the FDA

301
sites in

45
states and

8
countries outside the U.S.

21
therapeutic areas studied

54
studies (ongoing + complete)

26
label changes

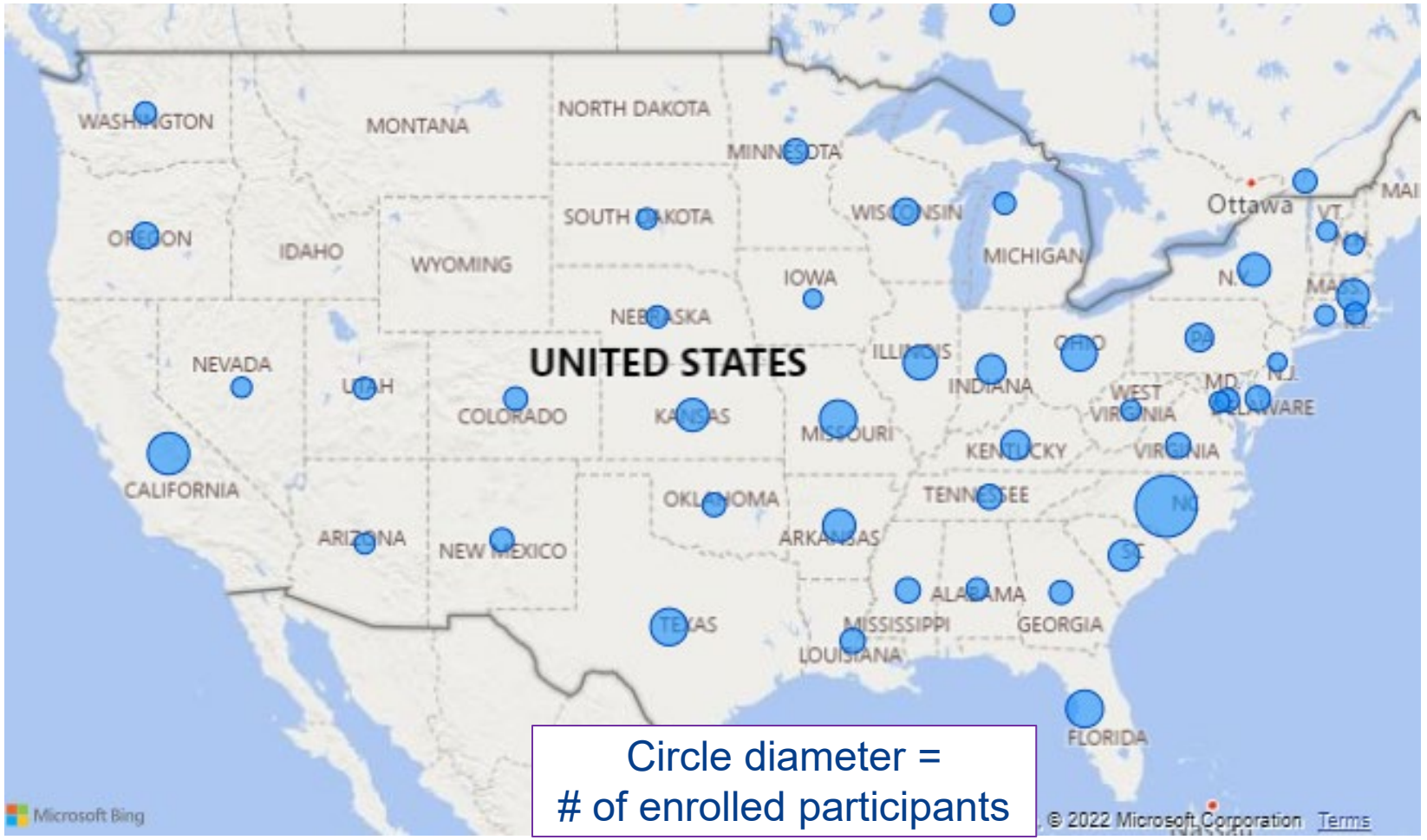
Molecules studied

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

Acyclovir
Alfentanil
Aminocaproic acid
Amiodarone
Amphotericin B deoxycholate
Ampicillin
Anakinra
Aripiprazole
Aspirin
Azithromycin
Baclofen
Bosentan
Bumetanide
Caffeine
Cefdinir
Cefepime
Ceftazidime
Cidofovir
Ciprofloxacin
Citalopram
Clavulanic acid
Clindamycin
Clobazam
Clonidine
Clozapine
Colchicine
Cyclobenzaprine
Dexamethasone
Dexmedetomidine
Dextroamphetamine
Diazepam
Digoxin
Dolutegravir
Dopamine
Doxycycline
Efavirenz
Emtricitabine
Enoxaparin
Epinephrine
Fentanyl
Fluconazole
Fosfomycin
Fosphenytoin
Furosemide
Gabapentin
Granisetron
Guanfacine
Haloperidol
Hydralazine
Hydrocholorothiazide
Hydrocortisone
Hydromorphone
Hydroxychloroquine
Hydroxocobalamin
Hydroxyurea
Inflectra
Ketamine
Ketorolac
Labetalol
Levetiracetam
Levofloxacin
Lidocaine
Lisinopril
Lithium
Lorazepam
Lurasidone
Meropenem
Metoclopramide
Metformin
Methadone
Methylphenidate
Methylprednisolone
Metoclopramide
Metronidazole
Midazolam
Milrinone
Molindone
Morphine
Nalbuphine
Nicardipine
Nifedipine
Norepinephrine
Olanzapine
Ondansetron
Ondansetron
Oseltamivir
Oxcarbazepine + MDH
Oxycodone
Pantoprazole
Pentobarbital
Piperacillin/ Tazobactam
Posaconazole
Pralidoxime
Pravastatin
Propofol
Propylthiouracil
Quetiapine
Ravuconazole
Remdesivir
Ribavirin
Rifampicin
Rifampin
Risperidone
Rocuronium
Rosuvastatin
Ruxolitinib
Sertraline
Sevelemer carbonate
Sildenafil
Simvastatin
Sodium nitroprusside
Spironolactone
Sumatriptan
Tenofovir
Terbutaline
Ticarcillin
Timolol
Tobramycin
Tocilizumab
Topiramate
Tranexamic acid
Trazodone
Trimethoprim-Sulfamethoxazole (Bactrim)
Valganciclovir
Valproic acid
Vasopressin
Venlafaxine
Verapamil
Voriconazole
Warfarin
Ziprasidone
Zolpidem

Sites enrolling participants in PTN studies

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients



Circle diameter =
# of enrolled participants

PTN's response to the challenges of pediatric clinical trials

Challenge	Response / Innovation
Onerous contracting / start-up	Master protocols, opportunistic studies
Limited blood volume	Sensitive assays and minimal sampling methods, available for other researchers
Limited number of available participants	Negotiate trial design with FDA Standard of care and adaptive design trials Pre-IND meetings for all studies Incorporation of real world data/evidence*

CUDDLE Study

Real world evidence in action

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

- PK of ampicillin was determined by enrolling 64 infants in an open label, multi-center, opportunistic PK study
  - Safety was assessed during this study
- Safety was also assessed using Pediatrix Clinical Data Warehouse in >100,000 infants receiving ampicillin
  - Noted that higher exposure was associated with seizures
- Data submitted to FDA → label change

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Electronic Health Records and Pharmacokinetic Modeling to Assess the Relationship between Ampicillin Exposure and Seizure Risk in Neonates

Christoph P. Hornik, MD, MPH[1,2], Daniel K. Benjamin, Jr, MD, MPH, PhD[1,2], P. Brian Smith, MD, MPH, MHS[1,2], Michael J. Pencina, PhD[1], Adriana H. Tremoulet, MD, MAS[3], Edmund V. Capparelli, PharmD[4,5], Jessica E. Ericson, MD[6], Reese H. Clark, MD[7], and Michael Cohen-Wolkowiez, MD, PhD[1,2], on behalf of the Best Pharmaceuticals for Children Act—Pediatric Trials Network*

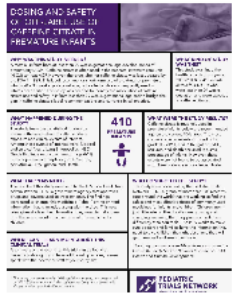
PTN's response to the challenges of pediatric clinical trials (continued)

Challenge	Response / Innovation
Low consent rates	Simplified trial designs Standard of care procedures Participant engagement

Ampicillin Results-At-A-Glance

Completed: June 1, 2022

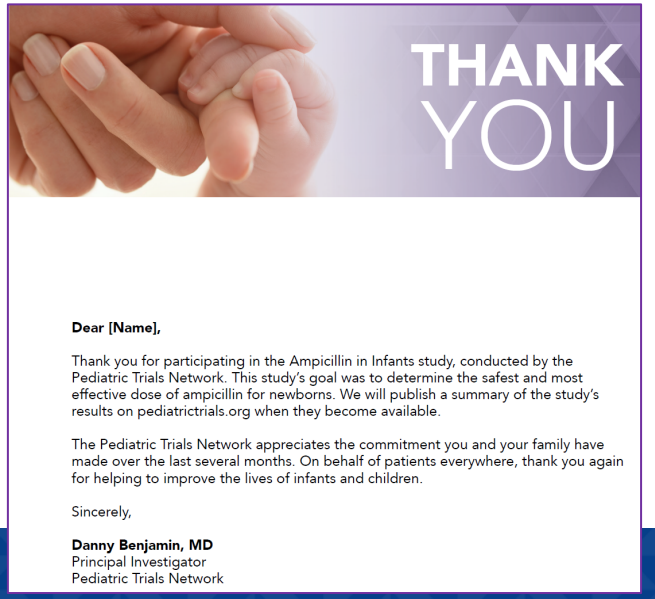
Ampicillin, a medicine used to treat infections, is the most commonly used drug in babies born prematurely who are admitted to the hospital. At the same time, practically no one has ever figured out how the drug is processed in newborns. The goal of the "Ampicillin in Infants Study" was to find...



Caffeine Citrate Results-At-A-Glance

Completed: January 1, 2022

Almost all infants born at less than 29 weeks gestational age develop apnea of prematurity (AOP). Caffeine citrate is often used in the neonatal intensive care unit (NICU) to treat AOP. However, the drug label for caffeine citrate was last updated by the FDA in 1999. This label recommends...



Beyond clinical trials: Training the next generation

- >300 trainees supported by PTN, across the training spectrum
  - Undergraduate students
  - Medical and PhD students
  - Post-graduate medical and pharmacology trainees (residents, fellows, post-docs)
  - Early career faculty
- Trainees embedded into leadership and administration of the Network

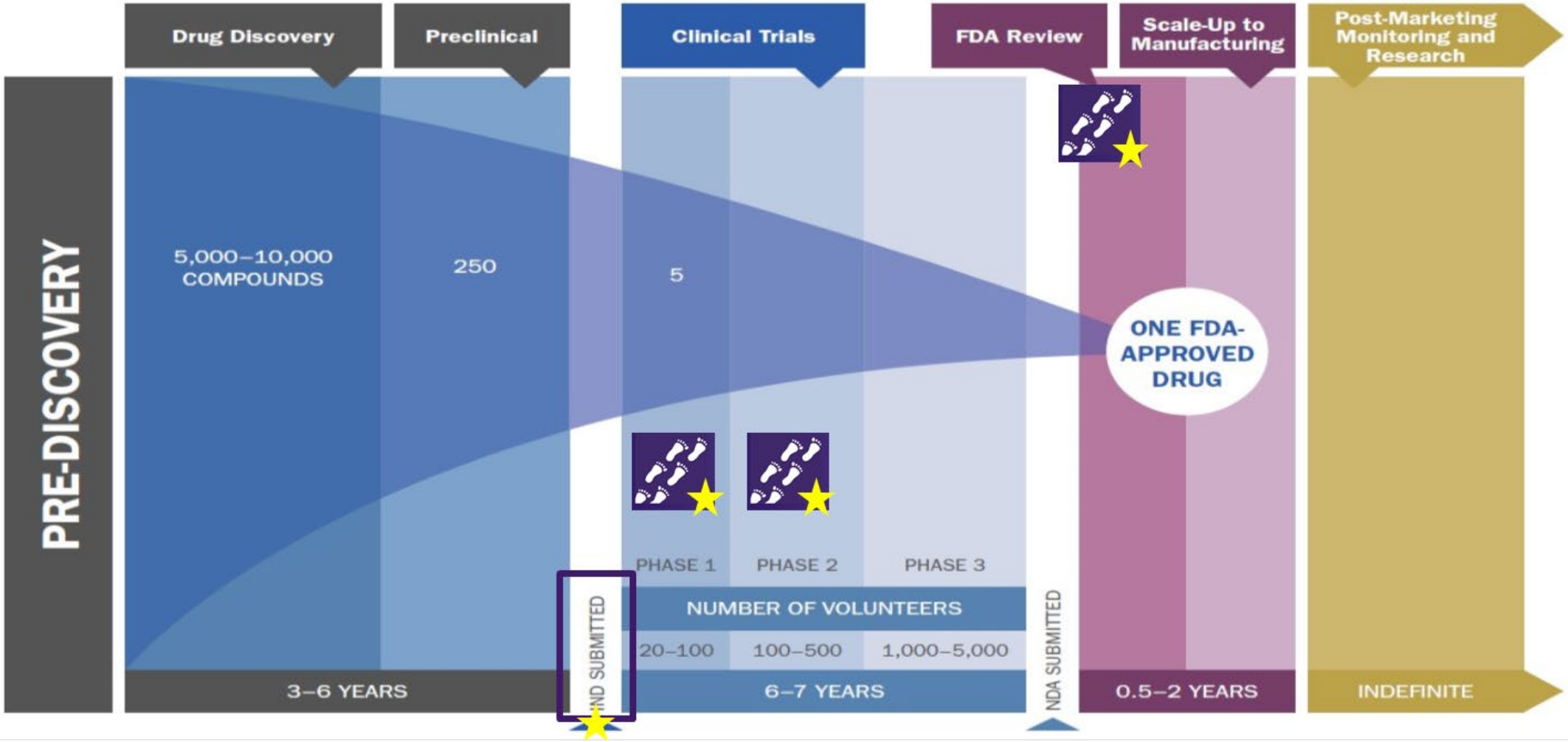
STAR

Beyond clinical trials: Training the next generation

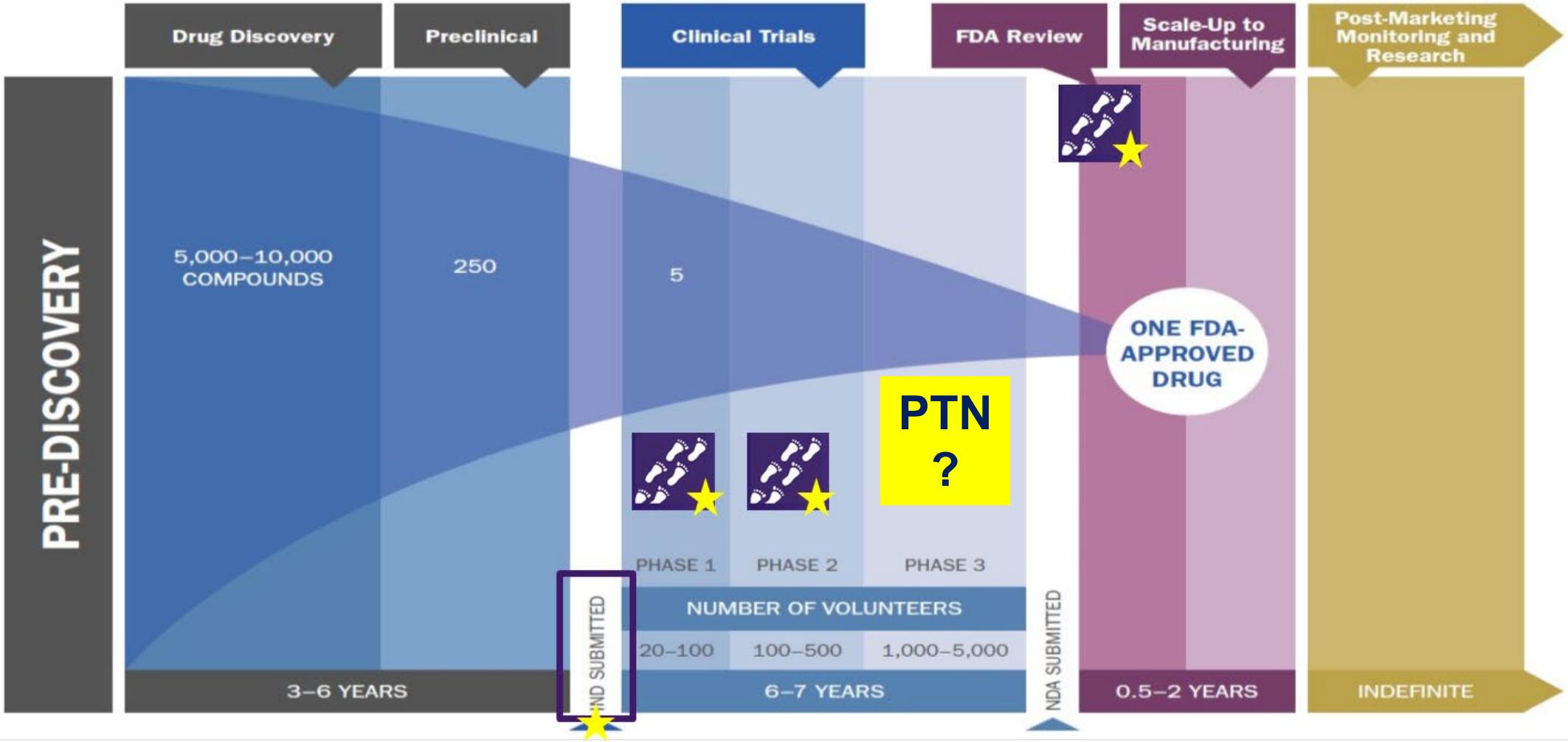
- Investigators can lead studies via several pathways
  - Submit proposals and serve as protocol chair
  - Each protocol typically has one or more junior investigators on the protocol development team and the team that publishes the study
  - Leading enrollers in studies serve not only on writing teams, but also join subsequent protocol development teams

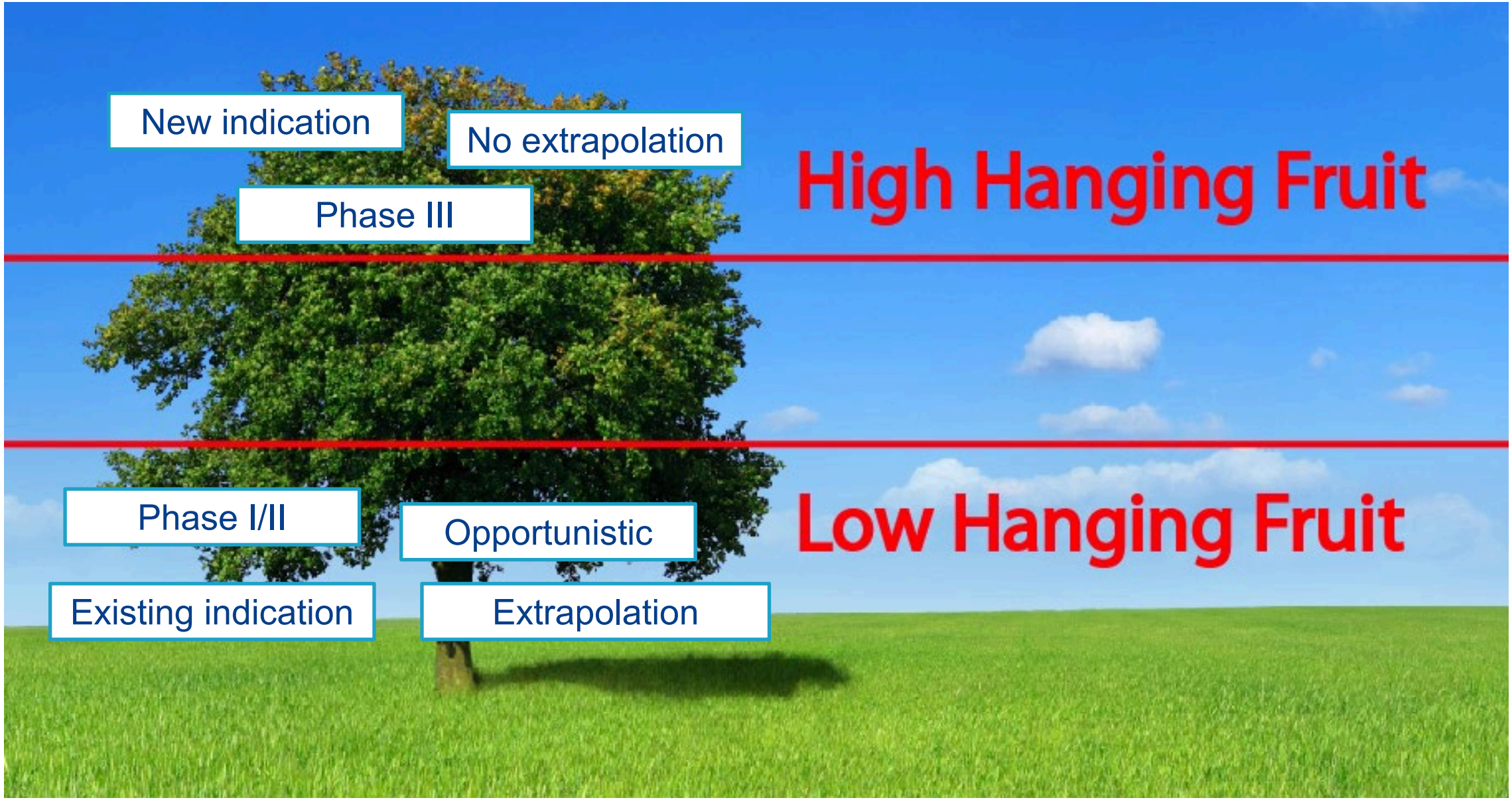
- Expansion in this iteration of PTN
  - Steering Committee members will each have a role in training by mentoring, providing projects for training

PTN's traditional focus



The potential for future




New indication
No extrapolation
Phase III
High Hanging Fruit
Phase I/II
Opportunistic
Existing indication
Extrapolation
Low Hanging Fruit

Next Steps: Existing and Planned Collaborations

Duke Clinical Research Institute

Institutional Partners

- The University of Utah
- Vanderbilt University
- Indiana University
- The University of North Carolina at Chapel Hill
- UC San Diego
- PennState
- Children's Mercy Hospitals & Clinics Kansas City
- Children's Hospital of Philadelphia Research Institute
- TCU
- SickKids

Program Partners

- IDeA States Pediatric Network ECHO A program supported by the NIH
- The American Academy of Pediatrics
- pediatrix Medical Group
- conect 4children — Collaborative Network for European Clinical Trials for Children
- iCAN — International Children's Advisory Network
- MICYRN — better health for mothers and children
- imi innovative medicines initiative
- CARRA — Childhood Arthritis and Rheumatology Research Alliance
- mprint
- NorthEast BioLab
- Emmes
- OpAns — optimized analytical solutions
- FRONTAGE
- INCLUDE — INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE
- pcori — Patient-Centered Outcomes Research Institute
- Laborie — For Dignity. For Life.

Thank you

rachel.greenberg@duke.edu

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

Session Three

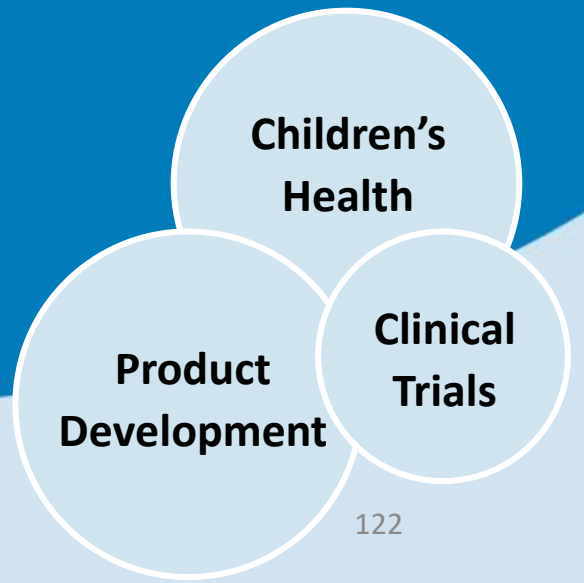
Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

AbbVie

David Horton, PhD and

Anne Martin Robinson, Pharm D



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

Pediatric Development Recommendations

AbbVie Inc.

Implementation of BPCA and PREA Interested Parties Meeting

AbbVie shares FDA's goal to improve medical product research in children

AbbVie's mission is to discover and deliver innovative medicines and solutions that address complex health issues and enhance people's lives

- Our approximately 50,000 employees strive to make a remarkable impact that lasts, driven by our compassion for people, commitment to innovation and inclusion, service to the community and uncompromising integrity
- Today our products help more than 60 million people living in more than 175 countries, and we are making significant advancements with a robust pipeline of potential new medicines as we look to find the treatments of tomorrow

AbbVie recognizes the importance of the **timely** provision of data that enables prescribers to make informed treatment choices for children who may benefit from our products

Collaboration between Sponsors and FDA can facilitate timely development of safer and more effective treatments for pediatric patients

Agile, transparent, and predictable global pediatric regulatory standards and processes

Accelerate execution of and incentivize harmonized global development programs

Provide Post Marketing Requirement (PMR) language earlier during drug and biologic application reviews to allow opportunity for alignment before finalization

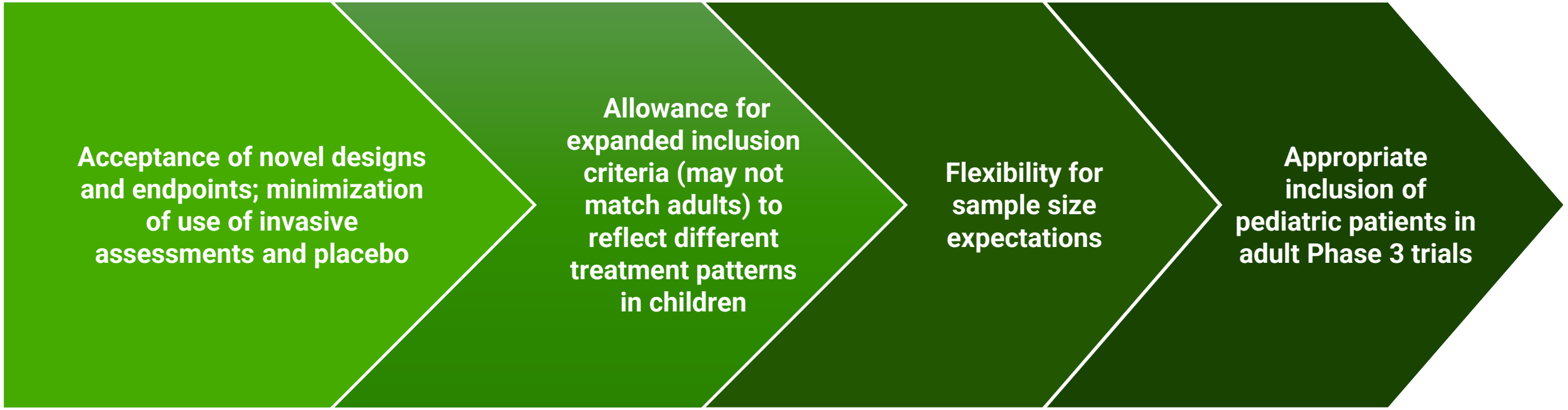
More flexible and collaborative process to revise PMR language and Pediatric Study Plans based on emerging information or study executional challenges

Continuous, transparent, agile process for Sponsor/parallel-Agency dialogue to accelerate global pediatric development planning and modifications

Focused Pediatric Written Requests that reflect feasible study completion scope and timelines to support efficient pediatric development activities and reinforce incentives for pediatric research

A collaborative approach should consider the unique aspects of pediatric study execution

Enhance enrollability, leading to timely completion of studies in representative populations



Opportunities for continuous dialogue and Agency willingness to adapt study design expectations in light of emerging information

Consistent application of extrapolation to rapidly advance approvals

FDA endorses the International Council for Harmonisation (ICH) E11A “Pediatric extrapolation” framework to support pediatric drug development, which strives to reduce the need for pediatric subjects to participate in clinical trials

Recent examples of full implementation is the FDA’s expanded use of extrapolation for juvenile idiopathic arthritis and juvenile psoriatic arthritis indications

Recommendation
Expanded and consistent application of ICH E11A across indications to reduce the delay between adult and pediatric approvals
Use of novel data sources, including Real World Evidence, to support extrapolation
Time-bound and collaborative approaches to re-evaluate previously agreed pediatric plans if new data support extrapolation

Summary

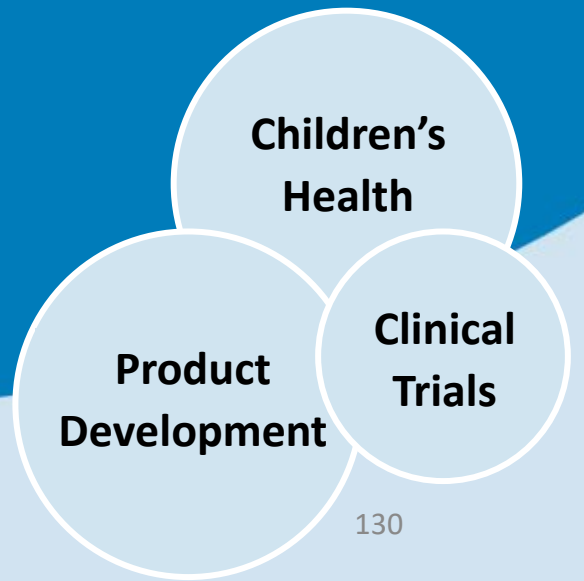
AbbVie shares the FDA's goal to provide robust and timely evidence to support the appropriate use of medications in children

Pediatric clinical development provides opportunities for partnership and flexibility between Sponsors, FDA, and other global regulatory agencies to achieve this goal

AbbVie is willing to continue to share our experience with pediatric clinical development with FDA to achieve this important goal

Otsuka Pharmaceutical Development & Commercialization

Michaela Schultz, PhD and
Aditi Shah, MBS



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

Discussion Topics

Impact of Decreasing the scope of Written Requests Issued under BPCA	Michaela Schultz
Use of “Other” trials to support BPCA	Aditi Shah

Impact of Decreasing the scope of Written Requests Issued under BPCA

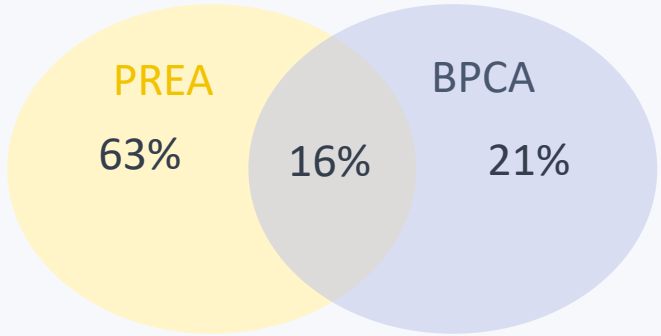
Michaela Schultz, PhD

Director, Global Regulatory Affairs

Otsuka Pharmaceutical Development & Commercialization

Otsuka

PREA & BPCA Draft Guidance proposal of "Additional Studies"



*Per draft guidance, 2002-2019

May 2023 Draft Guidance:

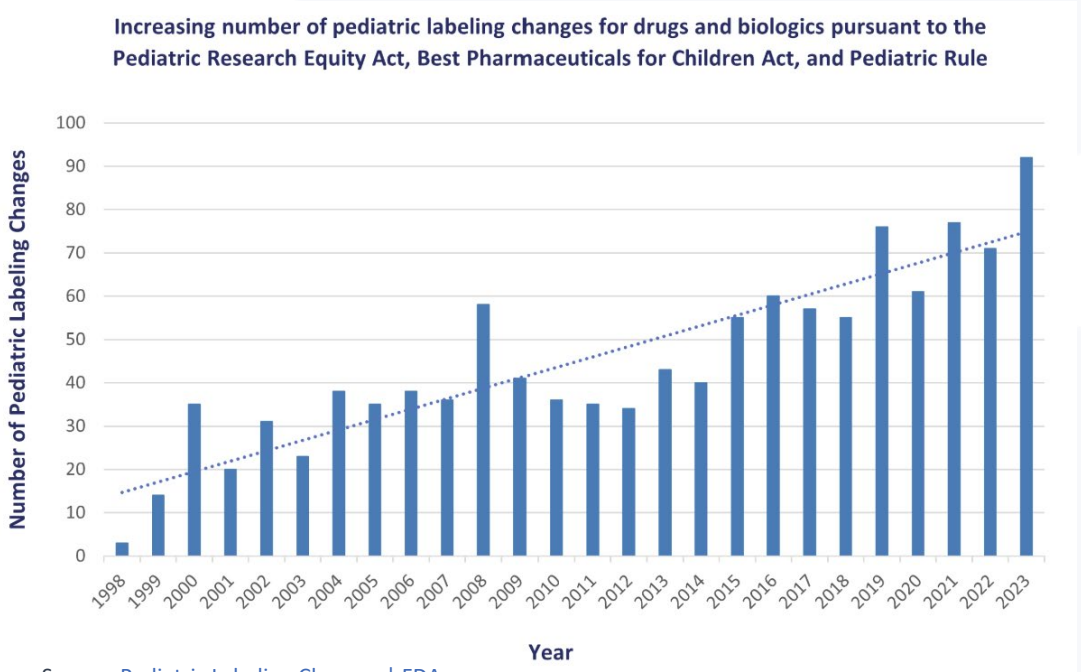
- "*PREA requirements have resulted in an increase in pediatric labeling, even without the added incentive of the BPCA*"

- Moving forth, Agency anticipates BPCA eligibility to only extend to "*additional pediatric studies*"; and clarified that: "*FDA does not expect to issue Written Requests solely for studies or planned studies that are required under PREA.*"
- This is a significant change to the Agency's long held interpretation of the law.

Intend to address:

- Is pediatric labeling increasing over time and if so, is this driven by the implementation of PREA, BPCA, or both?
- What is the potential impact of disrupting the balance between PREA and BPCA by decreasing the scope of BPCA eligibility?

Source: Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act, Draft guidance May 2023



Source: Pediatric Labeling Changes | FDA

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Pediatric Labeling Trends over Time

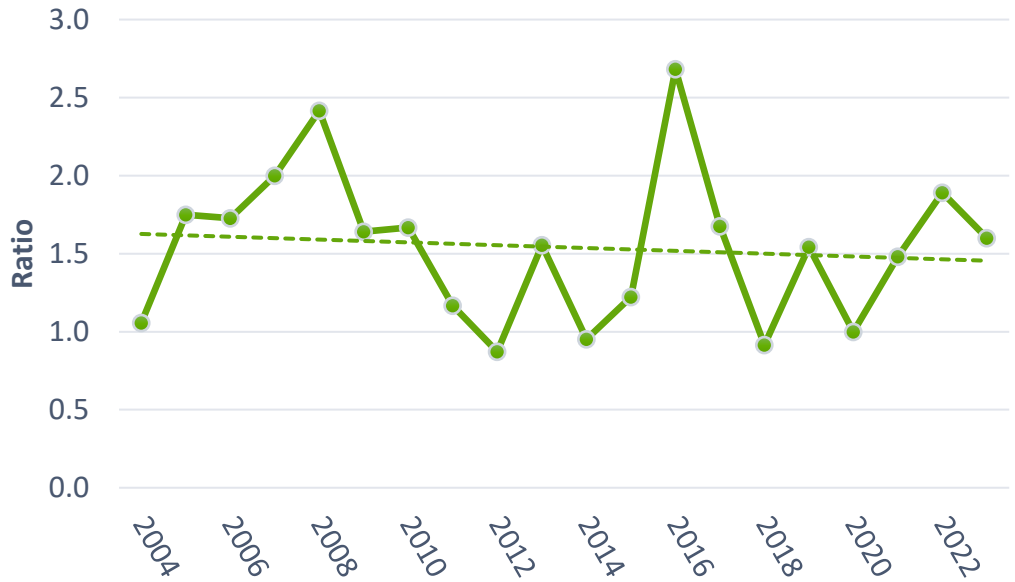


Figure 1: Pediatric labeling relative to New Drug Approvals (proxy for industry growth) is **steady to slightly decreasing**

Limitations: Drug labeling is delayed relative to clinical trial conduct.*;*
New drug approvals (new chemical entities) are used as a proxy to estimate the rate of drug development. This does not reflect new indications and thus the ratio itself cannot be interpreted, only trends over time.

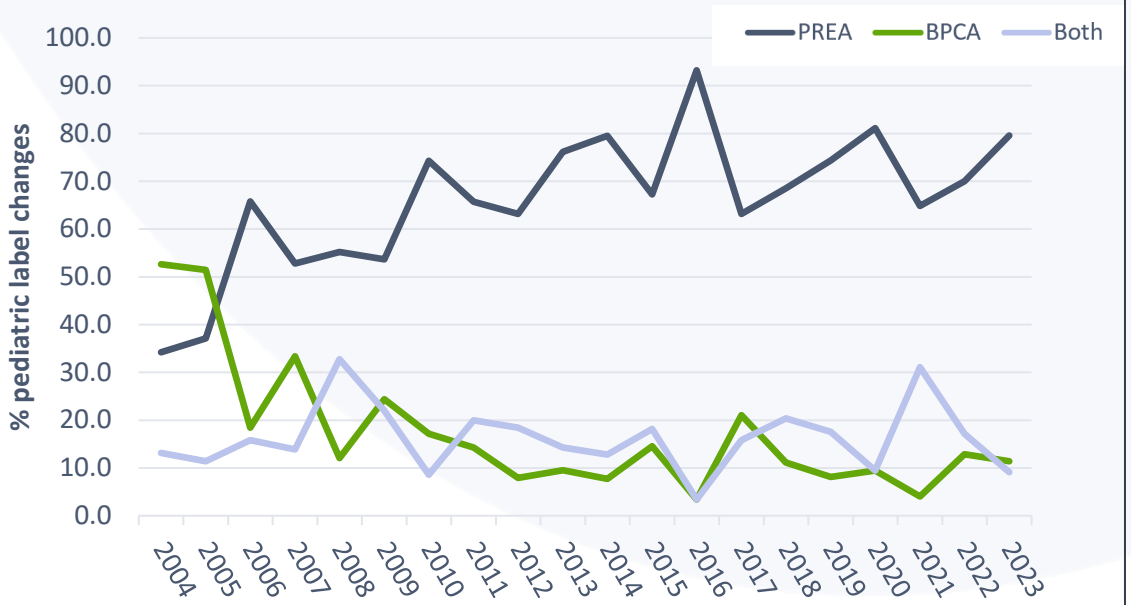


Figure 2: Drug labeling supported by **BPCA has decreased** from 2004 to 2023

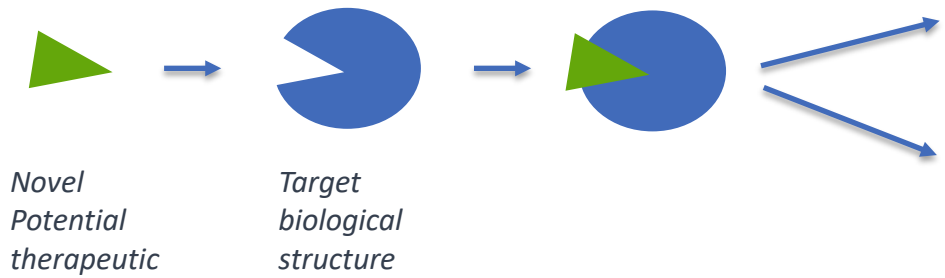
Limitations: Drug labeling is delayed relative to clinical trial conduct.

Current incentives are imbalanced and pediatric labeling does not appear to be increasing. Given this trend, we would like to next discuss the importance of balanced incentives to promote innovation.

Sources: Pediatric Labeling Changes Spreadsheet (XLSX - 311 KB)
Mullard et al 2025 "2024 FDA approvals" Figure 1

Industry perspective: Impact of decreasing the scope of BPCA

Industry sponsors consider requirements under PREA and incentives under BPCA to assess and balance risk of innovation when determining a target indication.



Disease A (high probability of success) – *lead indication*

Disease B (low probability of success) - *secondary indication*

Probability of technical & regulatory success trends with

- *available data to inform likelihood of success*
- *heterogeneity of population*
- *total number of studies and patients appropriate to demonstrate meaningful effect.*

Reducing scope of Written Requests issued under BPCA to exclude trials required under PREA favors:

- **Prioritization of rare pediatric diseases over common pediatric diseases.**
  - Rare diseases will retain eligibility for PWR with pediatric trials due to exemption from PREA.
- **Decreased innovation in secondary indications.**
  - Secondary indications are often higher risk indications.
  - In search for “additional studies”, the agency is increasingly issuing written requests for pediatric studies in exploratory indications in the absence of proof-of-concept that the drug will work in a given disease.
  - To avoid this issue altogether, **sponsors are less likely to propose exploratory studies in new indications due to risk that the agency may request that pediatric trials** be added to the product PWR. This tethers the success and opportunity of the lead indication to exploratory investigations.

Otsuka

In conclusion, we ask the Agency to:

- Reconsider the eligibility for studies under BPCA in the absence of ‘additional trials’ beyond those required under PREA.
- Consider the data to support the reasonable conduct of additional study requests for novel indications in a Pediatric Written Requests under BPCA

Use of “Other” trials to support BPCA

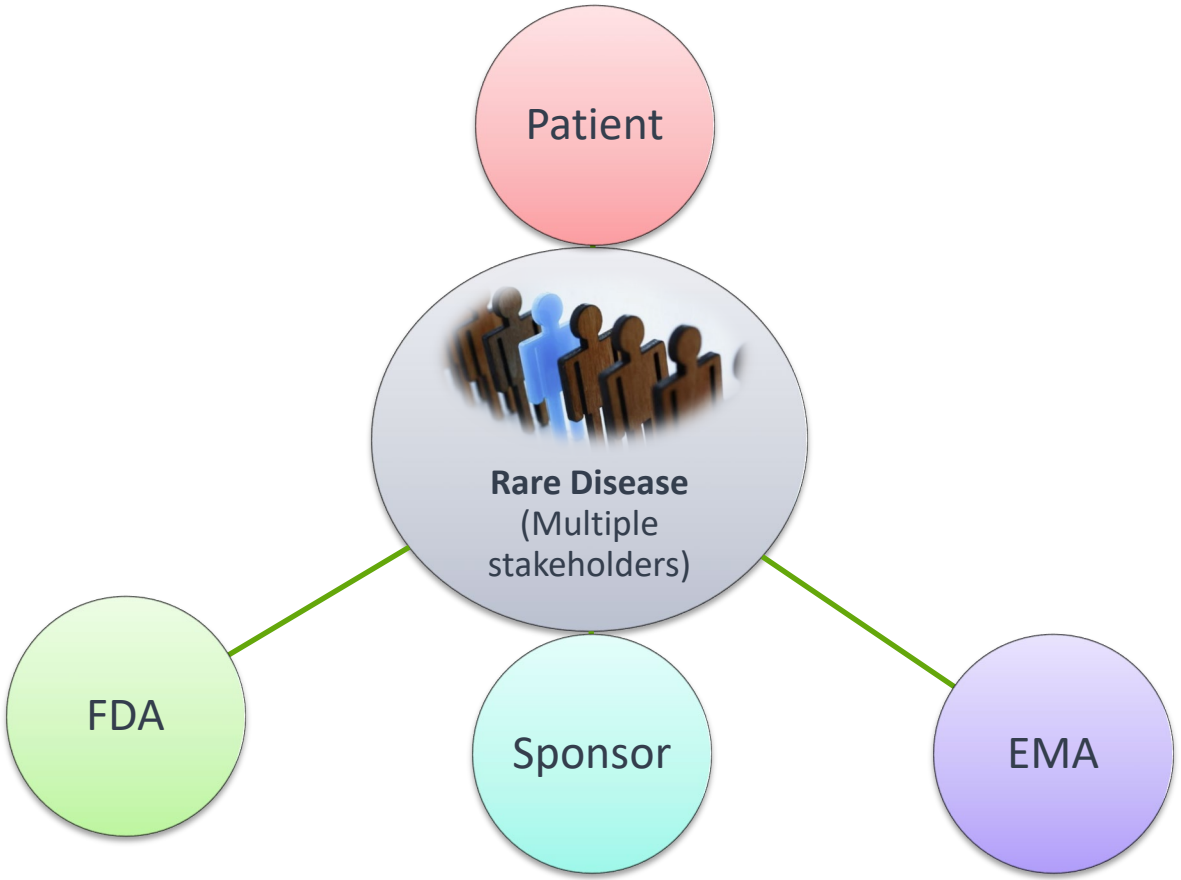
Aditi Shah

Associate Director, Global Regulatory Affairs

Otsuka Pharmaceutical Development & Commercialization

Otsuka

Use of Global Pediatric Trials to Satisfy BPCA



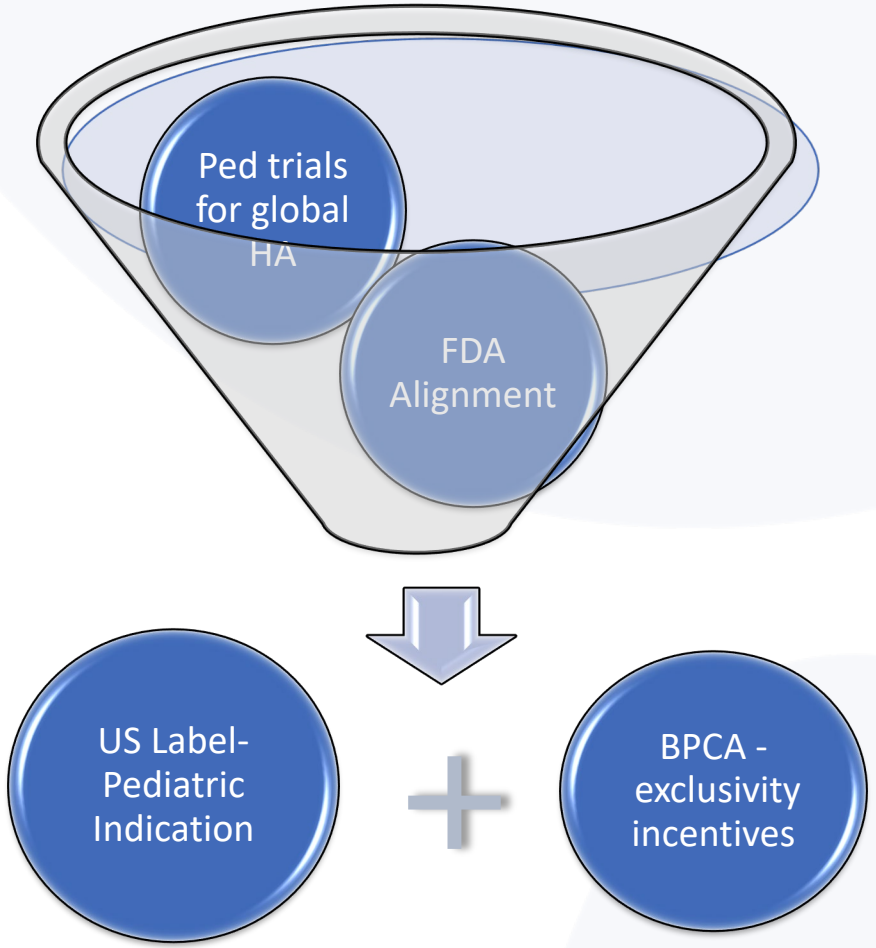
- **Challenge:** To address global regulatory requirements, sponsors need to conduct multiple or complex trials in rare disease pediatric populations
- **Background:**
  - Serious unmet need for effective treatments in many pediatric rare diseases
  - Sponsors must accommodate multiple stakeholder considerations when designing and conducting clinical trials; often a "fit for all" is neither possible nor practical from sponsor perspective but also poses burden to patients
  - Challenge to conduct multiple or complex trials in rare diseases leads to slow trials due to recruitment challenges thereby impeding pediatric patient access to treatments

Conclusion

In rare diseases, sponsors undertake clinical studies to fulfill global pediatric regulatory requirements. In some regions (i.e., EU), sponsor innovation risks are partially offset by associated incentives.

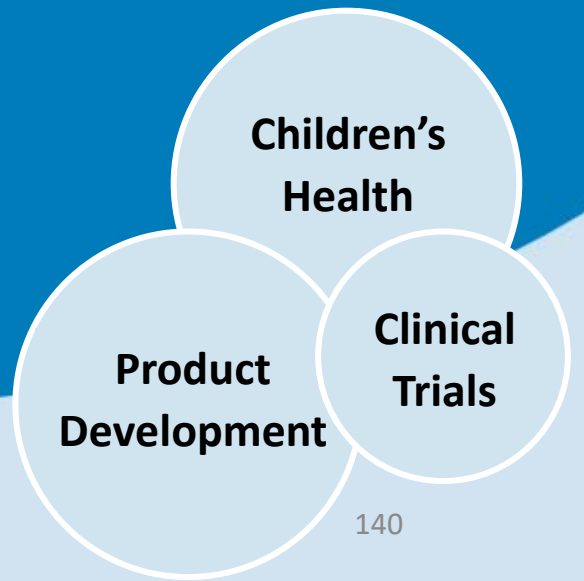
In US, if alignment with the FDA on pediatric written request (issued under BPCA) cannot be reached within scientific reason, sponsors are not adequately incentivized to the conduct of pediatric trials in rare diseases.

Opportunity: Leverage existing initiatives like pediatric cluster to advance scientific engagement across Health authorities, thereby creating harmonized pediatric clinical programs which benefits all stakeholders, specially helping patients access important treatment sooner.



Pharmaceutical Research and Manufacturers of America (PhRMA)

Eeshan Khandekar, MSc



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

Lunch

Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

FDA

Interested Parties Meeting for Pediatrics

Provide your feedback on implementation of the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA)

Children's Health

Product Development

Clinical Trials

September 15, 2025

9:00 a.m. to 4:30 p.m. ET

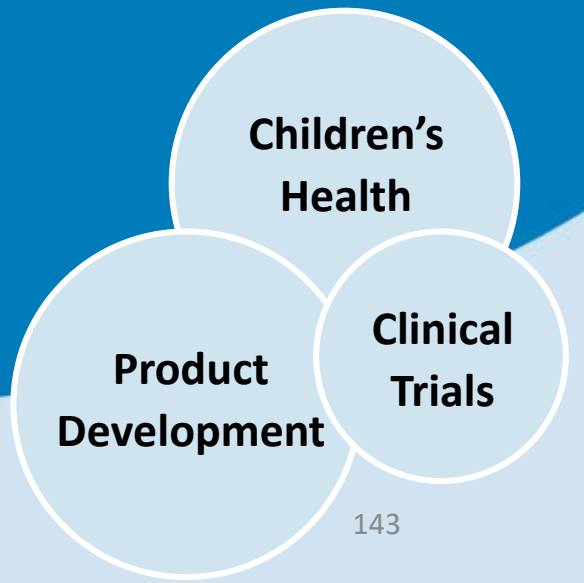
FDA Great Room
White Oak Campus
Silver Spring, MD

Virtual option available

Submit comments to the public docket number FDA-2024-N-5784 until 11:59 p.m. Eastern Time, September 30, 2025

Visit https://www.regulations.gov

Session Four



Interested Parties Meeting:
Implementation of BPCA and PREA

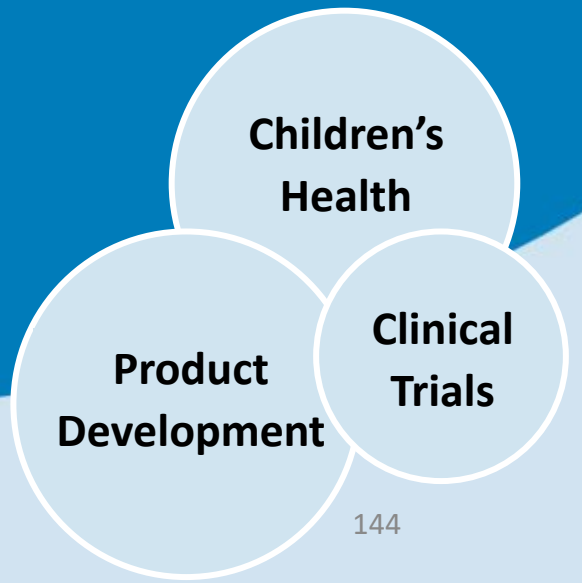
September 15, 2025

Hope for HIE

Betsy Pilon

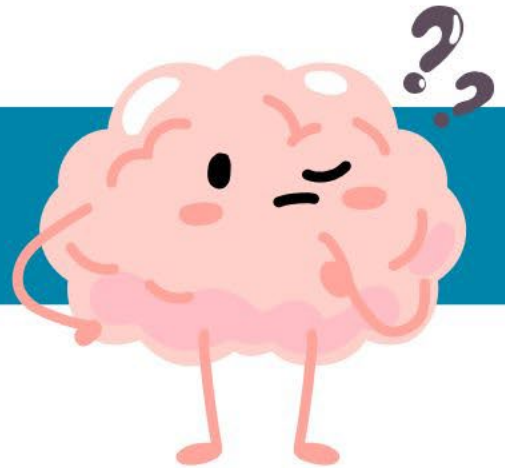
Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025



Addressing the unmet needs in pediatric drug development:
A Neonatal & Neurological Perspective

Betsy Pilon
Executive Director, Hope for HIE



WHAT IS HIE - HYPOXIC ISCHEMIC ENCEPHALOPATHY

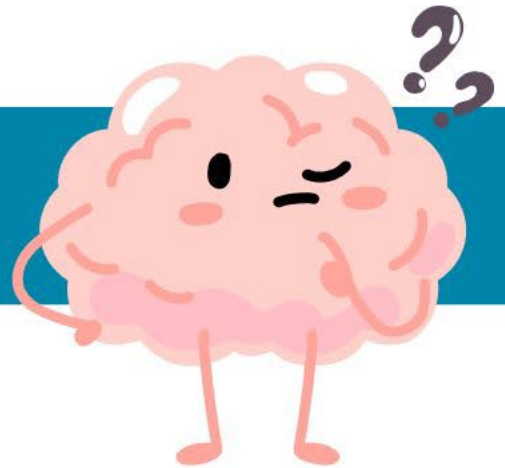
Hypoxic
(lack of oxygen)

Ischemic
(restricted blood flow)

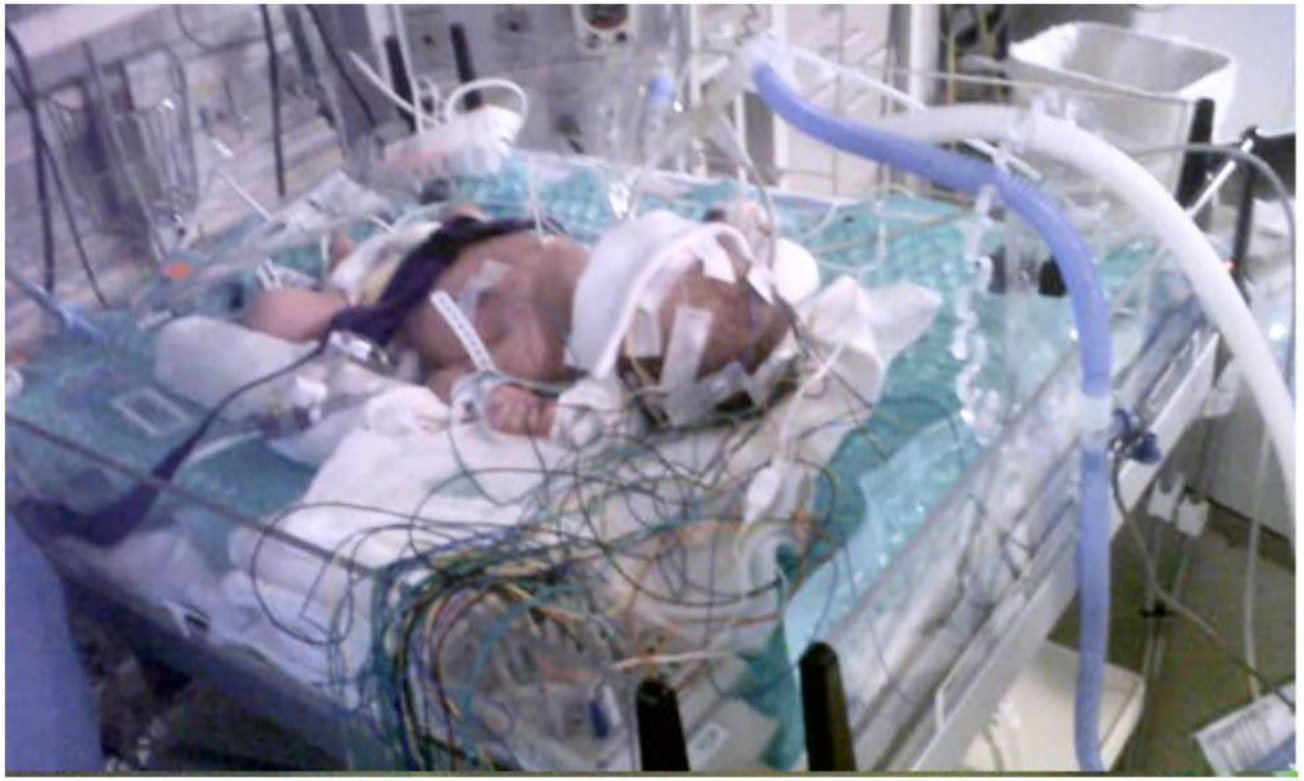
Encephalopathy
(affecting the brain)

- ***Second leading cause*** of infant mortality and morbidity, globally.
- Primarily ***full term infants.***
- Significant uncertainty in outcomes, even wtih advanced prognostic tools.
- Lack of investment in follow-up care and research (although that is changing).
- Heterogenous causation, structural (genetic overlap is around <5%), perception of "difficult to make an impact" and a lot of shoulder shrugs.
- ***Where is the incentive for therapeutics to advance???***

Aslam et al, Neonatal Encephalopathy: Need for Recognition of Multiple Etiologies for Optimal Management, Frontiers in Pediatrics, April 2019



WHAT DOES HIE LOOK LIKE IN THE NICU?



- Laying on a cold blanket (therapeutic hypothermia is the ***one approved intervention*** – *time and resource dependent)*
- *EEG - Top cause of neonatal seizures*
- *Doped up on ASMs and pain control*
- *Respiratory support*
- *Any system can be impacted: cardiovascular, renal, vision, etc.*
- *Often too unstable to hold during cooling*
- *Families often separated due to level of care needed (III & IV)*

THE NICU IS JUST THE BEGINNING: LONG TERM IMPACTS OF HIE

- ***HIE is a catalyst diagnosis***, causing a variety of subsequent diagnoses across a range of severity - from mildly affected through loss of life.

CEREBRAL PALSY

Cerebral Palsy is the most common motor disability in children. Although HIE only accounts for 10-15% of all cases.

CP can affect any muscle in the body, potentially affecting movement, speech, and muscle tone. Depending on the study, CP affects roughly 40% of all children with HIE, across varying degrees.

Timeline of Diagnosis: Cerebral palsy is typically diagnosed within the first two years, with more mild CP diagnosed up until age 10.

EPILEPSY

Epilepsy is a grouping of various seizure disorders. Epilepsy affects upwards of 50-60% of all HIE cases, across all HIE "levels". HIE is a leading cause of neonatal seizures and several rare epilepsies.

There are several different types of seizures, and medical and surgical options to control them. Neonatal seizures are common with HIE, and may or may not turn into epilepsy.

Timeline of Diagnosis: Epilepsy can appear at anytime, but tends to either persist from neonatal seizures, or pop up during key developmental spurts around ages 4, 6, 8 and in puberty.

SECONDARY MICROCEPHALY

Many children with HIE get diagnosed with secondary microcephaly. This is not the same as congenital microcephaly and simply means "smaller head", due to the damage that restricts brain growth.

It has no bearing on cognition like primary, congenital microcephaly.

Timeline of Diagnosis: Secondary microcephaly is typically diagnosed within the first year, as brain growth is heavily tracked and measured post-injury.

LEARNING & ATTENTION ISSUES

Learning disabilities and differences, executive functioning, processing and attention issues such as ADHD, dyslexia, dysgraphia, dyscalculia, and others are common in children with HIE., with greater incidence than the general population.

Many children who do not have physical impacts end up with learning and attention issues. There are many strategies and accommodations to help students learn how their brains work best.

Timeline of Diagnosis: Learning and attention issues can show up early between the ages of 3-5, but most are diagnosed between the ages of 5-8.

AUTISM

Autism has been noted to be more prevalent in children with HIE. It is difficult to tell if there are autistic-like traits/symptoms that lead to a diagnosis, or truly an autism diagnosis.

Timeline of Diagnosis: Depending on the severity, autism with HIE can be diagnosed between 18 months and 5 years old, with some diagnoses coming later into the early teen years..

BEHAVIORAL CHALLENGES

Brain injuries are known to exacerbate enhanced behavioral responses. Sometimes this is related to frontal lobe damage, sometimes it is due to sensory processing difficulties.

Timeline of Diagnosis: It is hard to tease out what may be typical behavior early on. Many behavioral and sensory issues due to HIE are diagnosed between the ages of 2-5, and sometimes again between 7-10, due to frontal lobe development.

HEARING ISSUES

Sensorineural hearing loss, progressive hearing loss, auditory processing differences and disabilities, and other hearing-related issues are common with HIE.

Some children may benefit from hearing aids, cochlear implants, or auditory amplification devices in school.

Timeline of Diagnosis: Some babies will not pass their initial hearing test in the NICU and hospital. Others will be diagnosed within the first two years, usually through ordered hearing tests.

VISION ISSUES

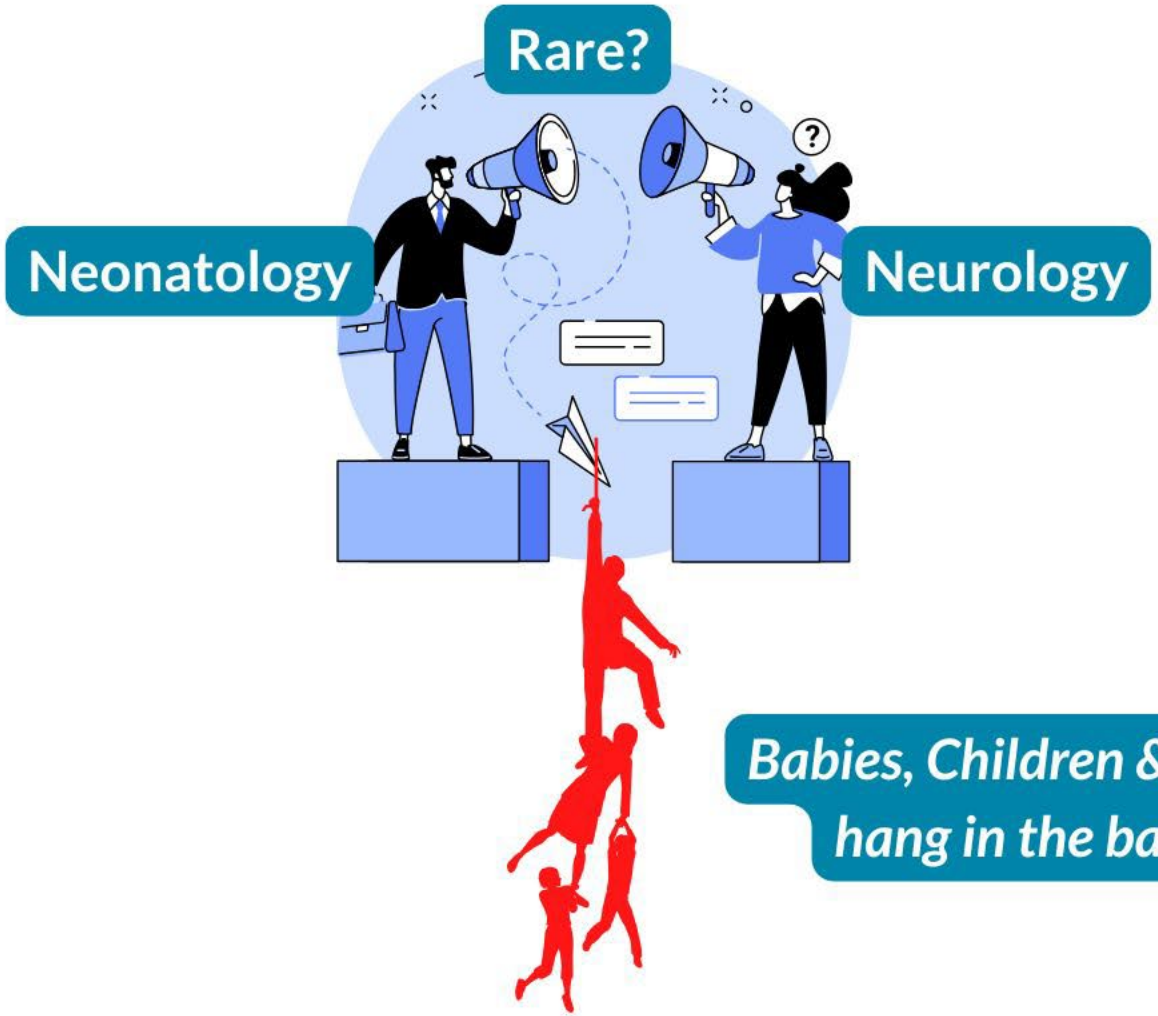
HIE can cause certain vision challenges such as delayed visual maturation, cortical vision impairment, various types of strabismus are all very common.

Early identification of vision issues can help develop more functional vision, ideally with a multidisciplanary team of pediatric ophthalmology, optometry, and low vision specialists in schools.

Timeline of Diagnosis: Early vision assessments within the first few months and upwards of two years typically identify the majority of vision issues.

NEONATAL DRUG DEVELOPMENT - WHO'S ON FIRST?

- Pediatric incentives don't reach neonates
- Agency fragmentation within and across (FDA, NIH – NICHD, NINDS) exists
- Regulatory, research and clinical culture change is overdue



NEONATAL DRUG DEVELOPMENT - BIAS IMPACTING ADVANCEMENT

Research & Therapeutic Advancement

Paternalism in Medicine, Regulatory, etc. & Especially in Neonates

- Culture of protecting babies *from* research.
- Bias exists across all areas – *clinical, research, regulatory*
- *HIE funding is deprioritized in the context of neonatology*
- *"Structural is hard!"*
- ***Listen to the lived experiences!*** *Endpoints that matter, stop lumping death and disability into one outcome.*

HIE NEONATAL CLINICAL TRIALS

Lots of variables working against researchers & families

- Time-sensitive (cooling initiated within 6 hours)
- Resource variability
- Mother/baby health and separation
- Overwhelming consent insisted by IRBs
- Quick health literacy lessons to consent
- Mistrust of medical system
- Era of medical misinformation
- Trauma
- Bias/Gatekeeping/Misperceptions of Families
- Systemic inequity

WE MUST ACCEPT
FINITE DISAPPOINTMENT,
BUT NEVER LOSE
Infinite Hope

- MARTIN LUTHER KING, JR.

NEONATAL GAP AREAS TO CONSIDER

Silos, Bias & Impact to Enrollment

- Center the community you're studying & avoid tokenization for funding
- Early multidisciplinary stakeholder involvement - think outside neonatology - early in the trial design process
- Site training on communcation is ***essential*** to enrollment success. Decrease bias of protecting families and "fragile babies" ***from*** research.

Measures

- Develop measures that matter - composite vs. lumping death & disability, across multiple impact areas outside of CP: neurodevelopmental cognition, epilepsy, vision, sleep, feeding/swallowing
- Help patient-family stakeholders understand biomarkers
- Impact of new measures on parent well-being (anxiety, etc): HINE
- Need better than the Bayley: not great for cognitive prediction in school age & beyond
- Ensuring biomarkers are within the usual care: MRI, EEG, serum or within sphere of acceptability for families in follow-up care.

Longitudinal Engagement & Support

- Proactive communication planning should be formalized, using best practices, patient-family engagement with considerations to build health literacy, and include longitudinal support resources for enrolled families to decrease attrition.
- Industry/pharma can't use years of long-term data, but this is why supporting a registry is critically important to understand how the truly LTOs relate to biomarkers measured early.

HIE NEONATAL CLINICAL TRIALS

Lots of exciting work with researchers & families

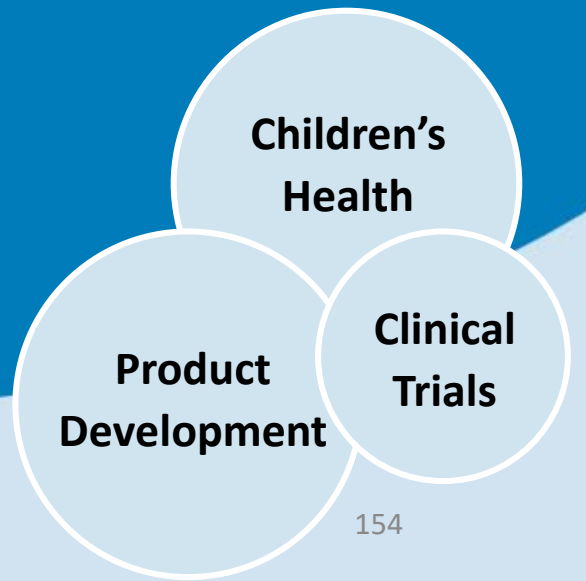
- 30+ years of research with HIE
- Cooling: head cooling vs. whole body
  - Longer, quicker, colder, gestation modifiers
  - COOL PRIME, HEAL (powerful secondary analyses)
- Gates Foundation preclinical pipeline harmonization:
  - Various small and large animal models, human organoid model
  - Equity for LMIC
- Novel and repurposed medication possibilities:
  - Stem cells
  - Peptides
  - Biologic
  - Melatonin

HOPE IS THAT THING INSIDE US THAT INSISTS, DESPITE ALL THE EVIDENCE TO THE CONTRARY, THAT SOMETHING BETTER AWAITS US IF WE HAVE THE COURAGE TO REACH FOR IT AND TO WORK FOR IT AND TO FIGHT FOR IT.

BARACK OBAMA

International Neonatal Consortium (INC)

Kanwaljit Singh, MD, MPH, MBA



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

CRITICAL PATH INSTITUTE 20 YEARS OF IMPACT

Neonates as Therapeutic Orphans*

How the International Neonatal Consortium is Responding

Kanwaljit Singh, MD, MPH, MBA
Executive Director, International Neonatal Consortium
Critical Path Institute

**Neonates remain therapeutic orphans. More than 90% of NICU drugs are off-label, and no new drugs have been approved for major neonatal diseases in 30+ years*

Why Neonates are Therapeutic Orphans

What This Means

- Very few drugs are developed or labeled specifically for neonates.
- **>90% of NICU drugs are off-label, no new therapies in 30+ years** *(Major neonatal diseases [e.g., BPD, NEC, brain injury, sepsis] have seen no new approved therapies).*

Challenging Biology

- Rapidly evolving physiology → PK/PD change week to week.
- Immature organs & unique conditions with no adult analogues.

High Risk, Low Reward

- Risk/benefit calculus skews toward *high-risk perception*.
- Fragile patients, ethical constraints, and small numbers make trials difficult.

The Off-Label Cycle

- Off-label use fills the gap → *creates the impression that existing practice is sufficient*
- Industry sees little incentive to conduct neonatal trials.
- Cycle continues: no new studies → persistent off-label reliance.

Result: Therapeutic Abandonment

- Neonates remain systematically excluded from drug development.
- The most vulnerable patients are left behind by the modern therapeutic ecosystem.

👉 **Take-Home Message:** Neonates are therapeutic orphans because they face **no dedicated drug pipeline, nearly universal off-label exposure, and decades of neglect** in innovation.

Why PREA/BPCA Haven't Fully Addressed Neonates

BPCA and PREA have been transformative for pediatric drug development overall — but their impact has not extended to neonates

- **Unique Physiology:** Neonates are **not just "tiny children"** — physiology changes dramatically week to week (organ immaturity, enzyme expression, receptor development). Adult/pediatric dosing or endpoints **cannot be simply scaled down**.
- **Disease Mismatch:** Many neonatal conditions (e.g., BPD, HIE, NEC, RDS) have **no adult analogues**. PREA commitments tied to adult indications **don't translate** to neonatal-specific diseases. Neonates don't get PREA commitments in the same way — so the very mechanism that drives pediatric studies doesn't apply here.
- **Lack of Biomarkers & Endpoints:** Few **validated biomarkers** or regulatory-accepted endpoints for efficacy or safety. Makes trial design risky, underpowered, and prone to **high failure rates**.
- **Regulatory Gap:** While effective for older pediatrics, PREA/BPCA offer limited applicability in neonates. Result: no requirement, limited investment, and stalled drug development in neonates.
- **The Path Forward:** To integrate neonates into drug development, we need not just incentives, but **new tools**:
  - **Innovative trial design methods** to improve feasibility of conducting trials.
  - **Validated Biomarkers** to enable efficient trial design.
  - **Regulatory-grade data platforms** to reduce uncertainty.

👉 **Take-Home Message:** Without tailored approaches beyond PREA/BPCA, neonates will continue to remain **systematically excluded** from drug development.

C-Path's International Neonatal Consortium

Why Collaboration is Essential

- Neonatal drug development challenges are too complex for any single company or institution.
- Unique physiology, small numbers, ethical constraints, and lack of biomarkers require shared solutions.
- Progress demands a neutral, pre-competitive space, where stakeholders pool expertise and data.
- **Critical Path Institute's International Neonatal Consortium (INC) serves as that home.**

👉 **Take-Home Message:** INC exists because no one can solve neonatal drug development alone — it takes a global village working together in a neutral, science-driven partnership.

Back To The Basics

The INC White Paper (Ward et al. Pediatr Res 2017*)

- Published as an INC consensus white paper on neonatal drug development.
- Brought together FDA, EMA, PMDA, Health Canada, industry, academia, and patient advocates.
- Delivered the first global framework for how to design and conduct neonatal clinical trials.

What It Achieved

- **Addressed the fundamentals**: ethics, dosing, PK/PD modeling, safety, endpoints, trial design.
- Directly informed FDA and EMA neonatal guidance.
- Became a reference point for sponsors, ensuring neonatal studies were feasible *and* regulator-acceptable.

Why It Matters

- Showed that pre-competitive collaboration works — consensus science can shape regulation.
- Provided the regulatory foundation on which today's advanced tools (RW-DAP, NAESS, biomarkers, digital twins) are being built.

👉 **Take-Home Message:** The Ward et al. (2017) INC white paper proved that **starting with the basics — consensus and feasibility — can deliver regulatory impact.** Today, INC is applying that same model to the next generation of neonatal tools.

** Ward RM, Benjamin DK, Barrett JS, et al. Pediatr Res. 2017;81:692–711*

NAESS: Setting the Standard for Neonatal Safety

The Problem

- No standardized AE severity grading for neonates — adult/pediatric scales failed to capture neonatal physiology.
- Result: inconsistent safety reporting, difficulty comparing across trials, and regulatory uncertainty.

The Solution (NAESS)

- **First neonatal-specific AE severity scale (35 adverse events).**
- Developed collaboratively by INC, FDA, EMA, industry, clinicians, and families.
- Provides clear, harmonized grading criteria for neonatal trials.

Impact

- Regulatory recognition (FDA, EMA) as a key neonatal drug development tool.
- Standardizes neonatal safety reporting, enabling comparability across studies and sites.
- Reduces regulatory uncertainty in trial review, supporting more efficient approvals

NAESS 2.0 – The Next Phase

- Expand scope: beyond the original 35 AEs to cover additional organ systems.
- Digitize: standalone app for real-time AE scoring and automated reporting.
- Patient-centered: integrate parental perspectives to ensure alignment with family priorities.
- Regulatory-grade: designed for adoption in upcoming neonatal and pediatric trials.

👉 **Take-Home Message:** NAESS solved a **critical gap in neonatal safety assessment**, and **NAESS 2.0 will expand and modernize the tool**, ensuring it remains the global standard for neonatal trial safety.

INC Real-World Data & Analytics Platform (RW-DAP)

What It Is

- Global neonatal EHR dataset: ~380,000 NICU patients across 30 hospitals.
- Longitudinal, high-resolution clinical data: demographics, diagnoses, labs, medications, respiratory support, and outcomes.
- Hosted on C-Path's secure platform, leveraging RDCA-DAP infrastructure for analytics and regulatory alignment.

Why It Matters

- First-of-its-kind neonatal RWD resource, enabling standardized, harmonized data across multiple health systems.
- Provides granular NICU and post-NICU outcomes (e.g., BPD trajectories, neurodevelopment, rehospitalizations).
- Addresses data gaps regulators and industry face in planning and evaluating neonatal trials.

Impact for Regulators & Industry

- External control arms for rare and ethically constrained neonatal trials.
- Predictive models and trial simulators to optimize study design, sample size, and endpoints.
- Regulatory-grade reference tools (e.g., lab values, severity scales, disease progression models).
- Faster, more efficient drug development by reducing uncertainty and improving evidence quality.

👉 **Take-Home Message:** RW-DAP transforms neonatal real-world evidence into **regulatory-grade drug development tools**, bridging critical evidence gaps and accelerating therapies for the most vulnerable patients.

INC's Neonatal Lab Values Initiative

CRITICAL PATH INSTITUTE 20 YEARS

Problem

- No standardized neonatal lab reference ranges → inconsistent trial design and safety assessment
- Current variability across sites makes cross-study comparisons and regulatory review difficult.

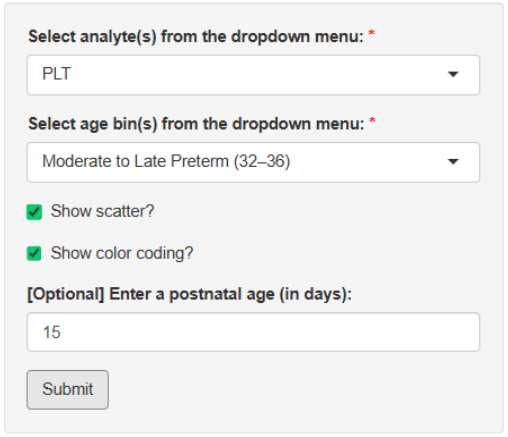
Solution

- Harmonizes key **hematology, chemistry, liver function, and metabolic labs** across gestational and postnatal ages.
- Applies a standardized, data-driven framework to generate reference curves aligned with regulatory expectations.

Impact

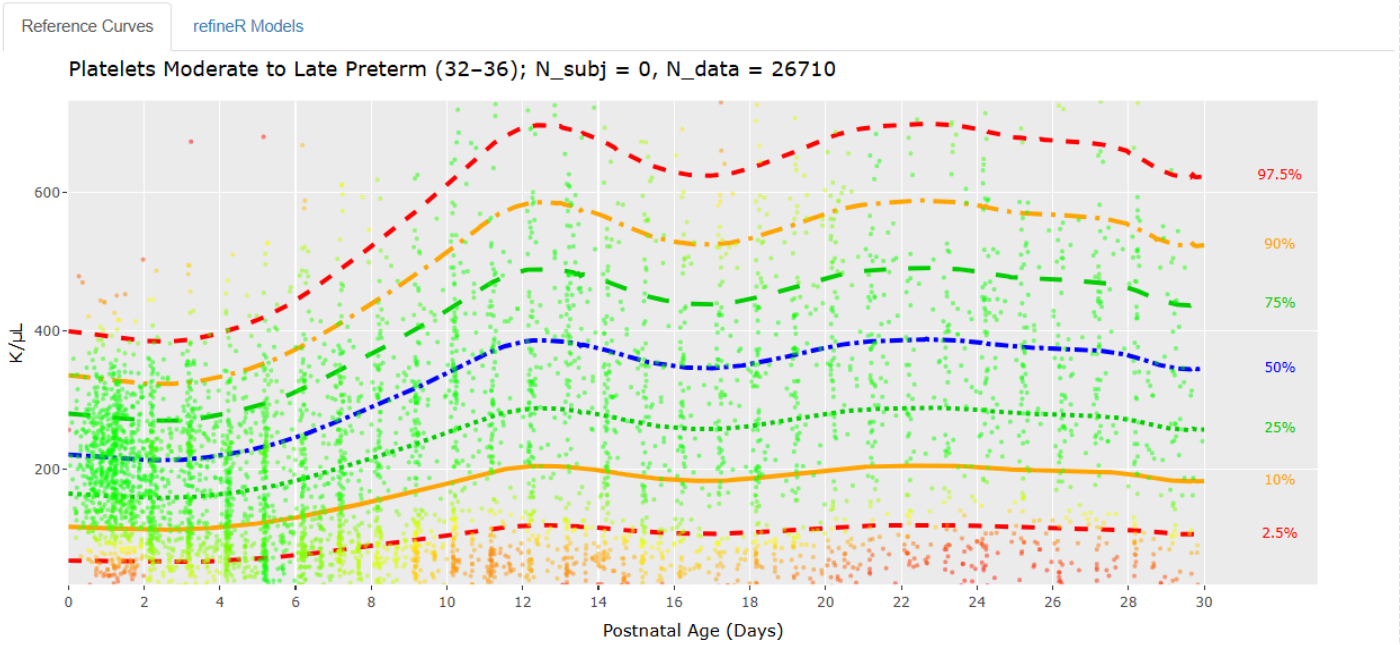
- Provides percentile-based curves that reflect developmental physiology, accessible through an interactive GUI tool.
- Supports trial design, safety monitoring, and cross-study comparability, improving confidence in neonatal data.

INC Lab Values GUI



Scope and Roadmap

- **Version 1 (EOY 2025):** Harmonized reference ranges for 14 key labs *(WBC, Hemoglobin, Hematocrit, Platelets, Sodium, Potassium, Chloride, Bicarbonate, BUN, Creatinine, AST, ALT, ALP, Total Bilirubin).*
- **Version 2 (in development):** "Bring your own data," patient-specific benchmarking, expanded analytes.
- **Reference curves stratified** by both **gestational and postnatal age** — not available in existing standards.
- Developed using the **REFINE-R framework** (Blum et al., 2023) for robust, reproducible curves.



INC's Neonatal Brain Injury Collaborative (NBIC)*

**A Partnership of INC and Hope for HIE*

CRITICAL PATH INSTITUTE 20 YEARS

Problem

- Neonatal brain injuries (e.g., hypoxic-ischemic encephalopathy, white matter injury, IVH) are leading causes of death and lifelong disability.
- Beyond therapeutic hypothermia, no approved therapies exist, and drug development is stalled by lack of validated biomarkers, enrichment strategies, and endpoints.

Solution

- **INC and Hope for HIE** co-lead a global pre-competitive collaborative with FDA, industry, academia, and advocacy partners.
- Focus on advancing regulatory-grade biomarkers (MRI, EEG, fluid biomarkers, clinical measures) and enabling innovative trial designs.

Impact

- Creates the first structured pathway to qualify biomarkers for prognosis, enrichment, and exploratory endpoints in neonatal brain injury.
- Builds a shared regulatory science foundation to make HIE trials feasible, reduce uncertainty, and accelerate development of much-needed therapies.

👉 **Take-Home Message:** Together with Hope for HIE, INC is driving the collaborative science needed to bring new therapies to babies with brain injury.

Biomarkers: Difference Between "Known" and "Validated"

Known biomarkers in NBI

- Examples: **MRI injury patterns, EEG background activity, blood/CSF biomarkers**.
- Observed in research and clinical practice.
- Associations with outcomes are published, but data are variable and not standardized.
- Useful for hypothesis generation, but not sufficient for regulatory decision-making.

Validated biomarkers

- Undergo rigorous, regulatory-grade evaluation across datasets and populations.
- Shown to be reliable, reproducible, and clinically meaningful.
- Can be used in trial enrichment, endpoints, and regulatory review.

👉 **Why it matters:** HIE drug development cannot advance without moving biomarkers like MRI and EEG from *"known"* to *"validated."*

INC's Proposed Work on Digital Twins & External Controls

Problem

- Neonatal trials are often **underpowered, delayed, or ethically constrained**.
- Small, heterogeneous populations and lack of validated endpoints make traditional RCTs difficult to execute.

Solution

- **External Control Arms (ECAs):** Use INC's RW-DAP (~380,000 NICU patients) to provide high-quality comparator data when randomization is not feasible.
- **Digital Twins:** Develop predictive "virtual comparators" that mirror individual neonatal trajectories using clinical, biomarker, and imaging data.
- **Trial Simulators:** Test trial designs *before* enrollment to refine feasibility, optimize endpoints, and inform enrichment strategies.

Impact

- **Adjunct to RCTs** — strengthens, rather than replaces placebo-controlled trials ***(the gold standard)***
- Provides **regulators and sponsors** with complementary evidence where traditional data are limited.
- **De-risks neonatal drug development** by reducing trial failure risk, making studies more efficient and feasible.
- **Initial applications: BPD, HIE, neonatal sepsis/rare disorders** — areas with high unmet need and limited trial feasibility.

Why This Matters for Neonatal Drug Development?

- Digital twins and ECAs are **not substitutes** for RCTs.
- They provide regulator-ready, complementary evidence in contexts where:
- RCTs are *ethically infeasible* (e.g., life-threatening neonatal diseases).
- Populations are *too small or heterogeneous* for conventional design.
- Additional context is needed to interpret single-arm or underpowered trials.

👉 **Goal:** Enable stakeholders to make better-informed regulatory decisions by integrating advanced tools with the gold standard of RCTs.

Circling Back: Why INC Exists

Neonates remain therapeutic orphans → >90% off-label use, no new drugs in 30+ years

- **Pediatric frameworks haven't fully addressed neonates →** unique physiology, no adult analogues, limited incentives
- **Barriers require new tools** → e.g., lab values, NAESS, RW-DAP, biomarkers, digital twins, ECAs.
- **No single group can solve this** → it takes regulators, industry, academia, advocacy, and government working together.
- **INC exists to fill this gap** → a pre-competitive home for collaborative science.

👉 Take-Home Closing Thought

INC provides the global table where everyone can work together to finally bring **safe, effective therapies to neonates.**

👉 Message to All Who Care about Neonatal Drug Development:

Please collaborate with us. Together we can deliver the tools, data, and frameworks needed to finally bring safe, effective therapies to neonates.

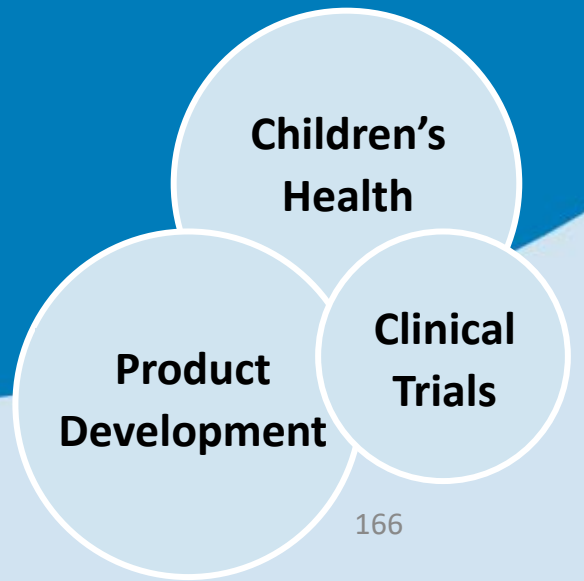
For more information, please contact us: incinfo@c-path.org

Visit our website: https://c-path.org/program/international-neonatal-consortium-inc/

Contact me directly: ksingh@c-path.org, Cell: (617) 953-1480

Neonatal Research Network (NRN)

Augusto Schmidt, MD, PhD



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

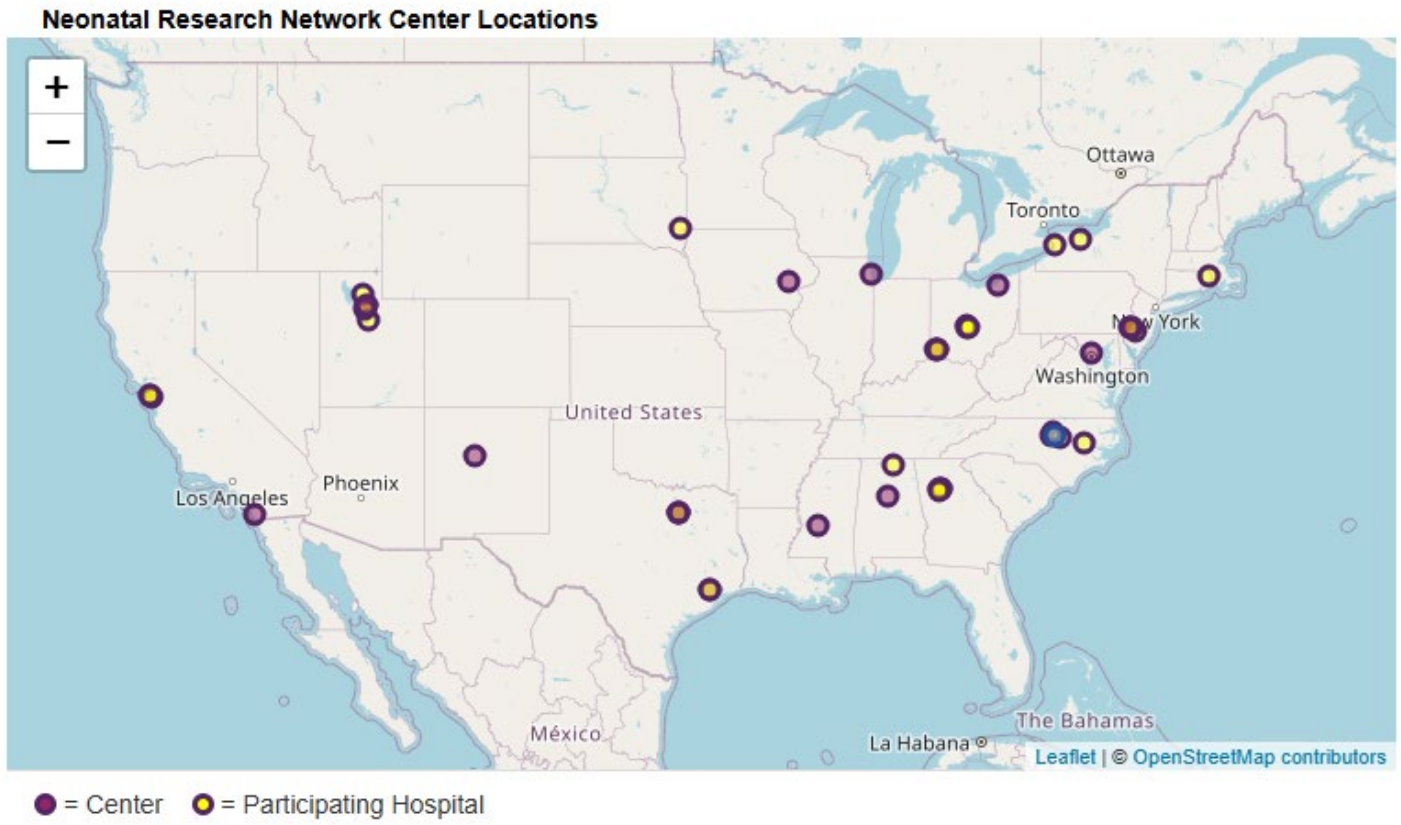
Implementation of BPCA & PREA: Neonatal Research Network (NRN) Perspective

Augusto F. Schmidt, MD, PhD

Project Scientist, NICHD Neonatal Research Network

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

The NICHD Neonatal Research Network



- Started in 1986: 15 clinical centers and a data coordinating center
- Large multisite randomized controlled trials in preterm and term newborns
- Respiratory management in the delivery room, inhaled nitric oxide for persistent pulmonary hypertension of the newborn, therapeutic hypothermia

BPCA & PREA Impact on Newborns

- BPCA + PREA → major pediatric labeling gains
- Nwborns remain the least studied group
- Most labeling changes do not include newborns
  - 1999-2023: 1164 pediatric labeling changes: 88 included information on newborns, 69 resulted from studies in newborns, 65 resulted in an indication for newborns
- Incentives often fail to generate trials in newborns

Stark et al., Medication used in the Neonatal Intensive care Unit and Changes from 2010to 2018. J Pediatr. 2022; 240:66-71
US FDA. Medica Products for Newborns. https://www.fda.gov/science-research/pediatrics/medical-products-newborns

Why Newborns Are Different?

- Newborns are a distinct population
- Unique diseases not shared between preterm / term infants and older children
- Physiologic immaturity (respiratory, digestive, immune, metabolic)
- Cannot reliably extrapolate from older children
- Many therapies bypass newborns under BPCA/PREA

ICH E11A: Pediatric Extrapolation. *ICH Guideline* (2022)
Institute of Medicine. Safe and Effective Medicines for Children: Pediatric
U.S. FDA. *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products; Guidance for Industry. 2022.*

Diseases with Unmet Needs: Preterm Newborns

- Bronchopulmonary dysplasia
  - Most common complication of prematurity, no approved therapies
- Necrotizing enterocolitis
  - Uncommon but potentially devastating, no proven prevention/treatment
  - Barriers to studying probiotics in newborns is impeding progress in a promising prevention
- Intraventricular hemorrhage and brain injury
- Retinopathy of prematurity
  - Bevacizumab (anti-VEGF) is currently the standard of care
  - Off-label, limited neonatal PK/safety data

Diseases with Unmet Needs: Term Newborns

- Hypoxic ischemic encephalopathy
  - Therapeutic hypothermia remains the only proven therapy
  - Limitations: newborns with severe HIE benefit the least, unclear benefit in mild hypoxic ischemic encephalopathy, lack of effectiveness and possibility of harm in late preterm infants
  - Adjunct treatments so far unsuccessful in clinical trials
- Neonatal Opioid Withdrawal Syndrome
  - Care is variable, most treatments off-label, limited neonatal PK/safety data
  - Consent complicated by maternal and social context
  - Buprenorphine promising treatment but current formulations include ethanol; an alcohol-free formulation has been developed but requirement for individual consent is prohibitive

Consequences of Neonatal Gaps

- Routine NICU drugs remain off-label
  - Among the 50 most used drugs on 40% are labeled for infants
- Heterogeneity of care
- Sickest and most vulnerable children lack evidence-based therapies
- Long-term public health burden and chronic diseases:
  - Neurodevelopmental disabilities
  - Chronic lung disease
  - Increased cardiovascular risk in adulthood
  - Metabolic syndrome / diabetes

Barriers for diseases affecting term and preterm newborns

- Extrapolation impossible for preterm or term newborn-only diseases
- Small populations → slow enrollment
- Acute unpredictable events: timing of birth, onset of NEC, IVH → hard to capture in trials
- Long term outcomes (18-24 months corrected age) → resource -intensive

Barriers in practice

- Consent challenges: acute illness, maternal illness and stress
- Antenatal consent needed for delivery room interventions →very resource-intensive
- Formulation issues: lack of neonatal-friendly preparations (liquids, dosing)
- Limited validated neonatal endpoints

NRN Successes & Capacity

- Multi-site infrastructure for rapid start-up and more efficient recruitment
- Increased available population for recruitment and likelihood of successful trial completion
- Experience with time-sensitive consent models
- New system allows external investigators to propose studies
- Rigorous standardized neurodevelopmental follow-up
- Innovative trials designs: Bayesian, target trial emulation

Leveraging Advances for Newborns

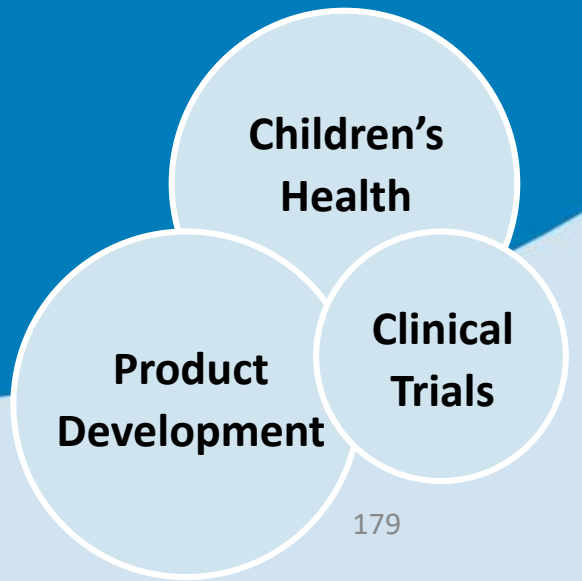
- External control groups & RWE from NICU registries
- Model-informed drug development and neonatal PK modeling
- Adaptive/Bayesian designs conserve enrollment
- Potential resource for sampling and biobanking
- Biomarkers and imaging across multiple preterm diseases

Zisowsky et al. Drug Development for Pediatric Populations: Regulatory Aspects. Pharmaceutics. 2010 2(4):364-388.
Lewis et al. Challenges and opportunities for improving access to approved neonatal drugs and devices. J Perinatol. 2022 42(6):825-828

Thank you!

Preemie World

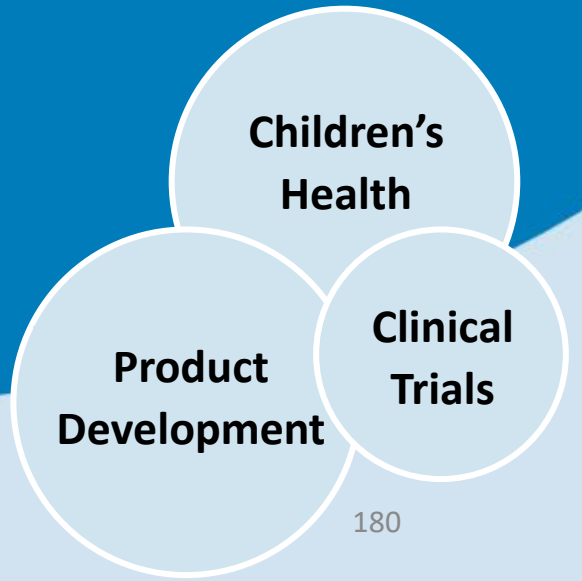
Deborah Discenza, MA



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

Session Five



Interested Parties Meeting:
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Children's Oncology Group (COG)

Elizabeth Fox, MD

Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

Children's Oncology Group (COG) and Pediatric Early Phase Clinical Trials Network (PEPCTN)

Perspectives on Best Pharmaceutical Act for Children and Pediatric Research Equity Act

Elizabeth Fox, MD
COG Developmental Therapeutics Committee Chair and PEPCTN Chair
September 15, 2025

A program funded by the National Cancer Institute of the National Institutes of Health

Best Pharmaceuticals for Children Act has improved safety of drugs for children

Exclusivity Determinations for 46 Oncology and Oncology Supportive Care Drugs (excludes antibiotics & pain medication)					
< 2000	2000-2005	2006-2010	2011-2015	2016-2020	2021-2025
N= 4	N= 12	N= 3	N= 8	N= 6	N=13
Sunitinib	Anagrilide	Docetaxel	Bendamustine	Atezolizumab	Afatinib
Tbo-filgrastim	Busulfan	**Imatinib**	Bortezomib	Cabazitaxel	Axitinib
Tocilizumab	Carboplatin	Oxaliplatin	Capecitabine	**Dasatinib**	**Blinatumomab**
Trabectedin	Clofarabine		Erlotinib	Ipilimumab	**Bosutinib**
	Fludarabine		Everolimus	Nab-paclitaxel	**Brentuximab vendotin**
	Gemcitabine		Ixabepilone	**Nilotinib**	**Cobimetinib**
	Irinotecan		Palonosetron		**Dabrafenib**
	Ondansetron		Temsirolimus		Eribulin
	Pomalidomide				Ibrutinib
	Temozolomide				Lenvantinib
	Topotecan				**Lutetium dotatate**
	Vinorelbine				Nivolumab
					Trametinib

March 2025 Pediatric Exclusivity Granted
https://www.fda.gov/drugs/development-resources/pediatric-exclusivity-granted

A program funded by the National Cancer Institute of the National Institutes of Health

Research to Accelerate Cure and Equity (RACE) for Children: FDA Reauthorization Act Title V 504

- Requires evaluation in children of new targeted drugs and biologicals being evaluated cancers in adults if the molecular target is relevant to pediatric cancer.
- Promotes earlier evaluation of targeted therapy in children with cancer.
- Increased number of trials planned for children with cancer.
- Perpetuates dependence of pediatric drug development on development programs in adults.

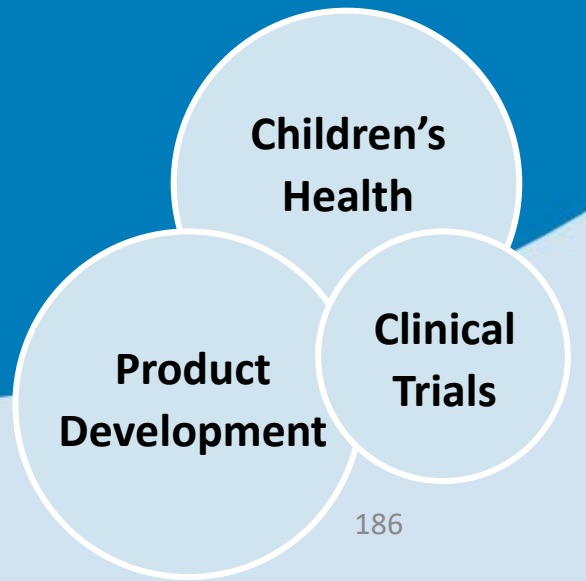
Oncology Perspectives

- Initiatives have had a positive impact on number of drugs with safety data and number of planned studies.
- Potential to decrease time from first-in-human to first-in-child trials, however, not aligned with timelines for negotiating Pediatric Study Plan or Pediatric Investigational Plan.
- Increase in the number of planned but not activated or completed trials for children.
- Incentives, conditions for deferrals, and new economic models of drug development are needed to fill the gap in clinical drug development plan for practice changing trials in children.
- Forums with the FDA are productive and critical for children- Thank you!

A program funded by the National Cancer Institute of the National Institutes of Health

National Cancer Institute (NCI)

Malcolm Smith, MD, PhD



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

BPCA and PREA Interested Parties Meeting – A Perspective from the National Cancer Institute

Malcolm A. Smith, MD, PhD
Cancer Therapy Evaluation Program
National Cancer Institute

September 2025

NCI Support for Clinical Trials for Children with Cancer

NCI supports Children's Oncology Group for developing and conducting definitive, practice-changing clinical trials

NCI has supported consortia for "first-in-children" studies for more than 30 years [e.g., Pediatric Early Phase Clinical Trials Network (PEP-CTN)]

Goal: to reduce barriers for testing new agents and treatments in children to expedite the highest priority agents moving into clinical trials to improve outcome for children with cancer

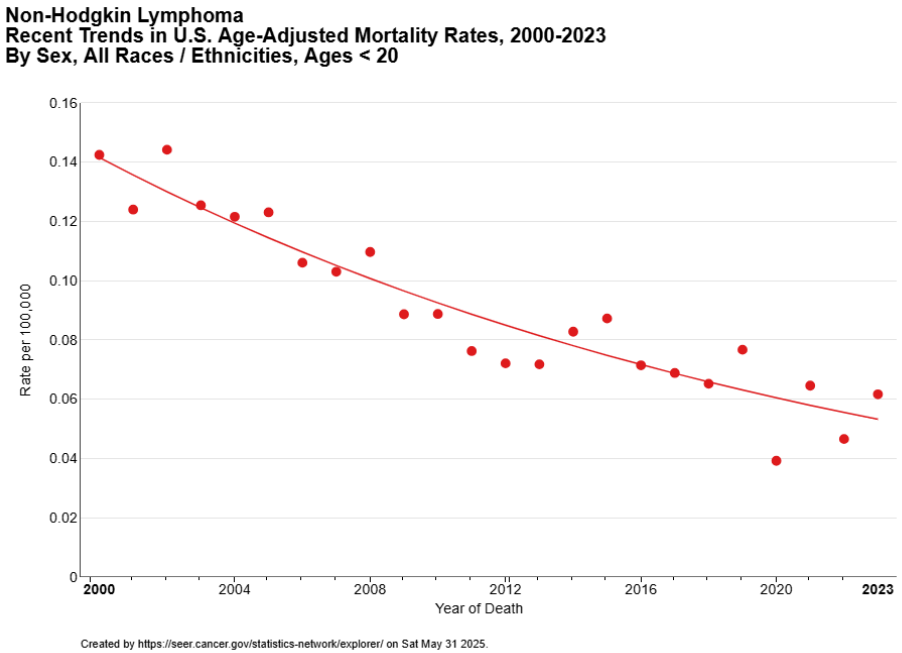
Measuring Success

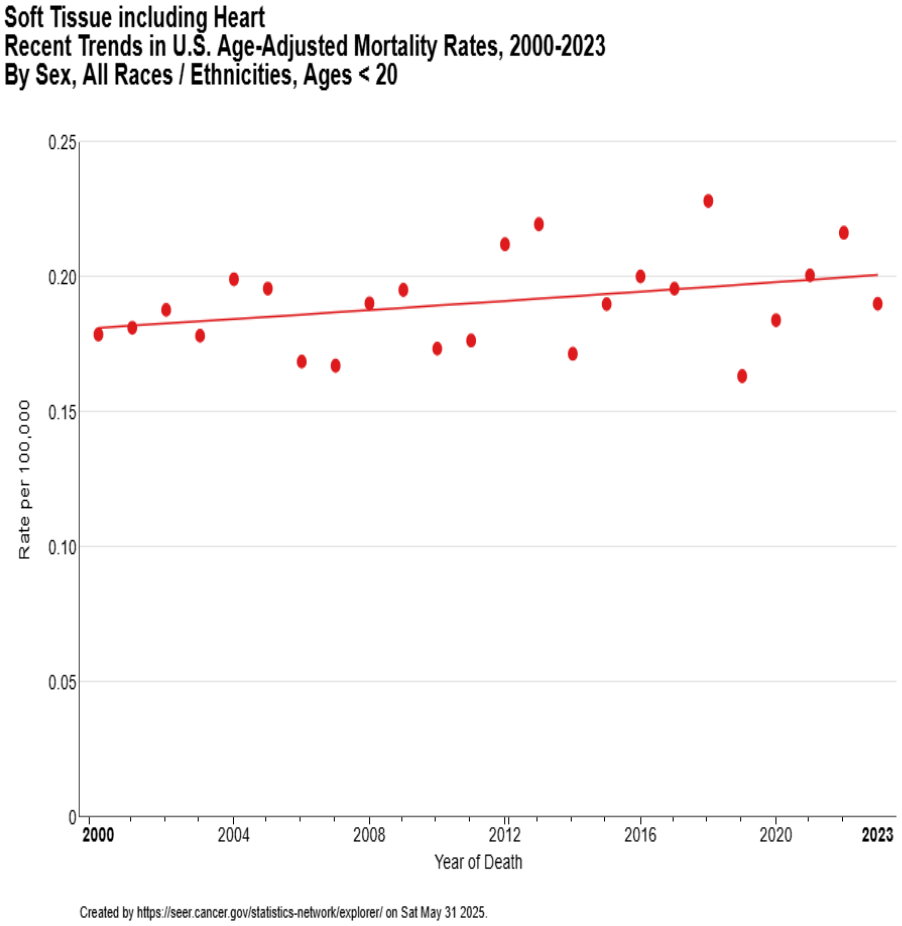
Short-term measures may be informative, but may also mislead

Increasing the number of children who survive their cancer diagnosis, thereby reducing cancer mortality for children

For those cancers with effective therapy, reducing late effects becomes a primary metric for success

Mortality rates for non-Hodgkin lymphoma and soft tissue cancers



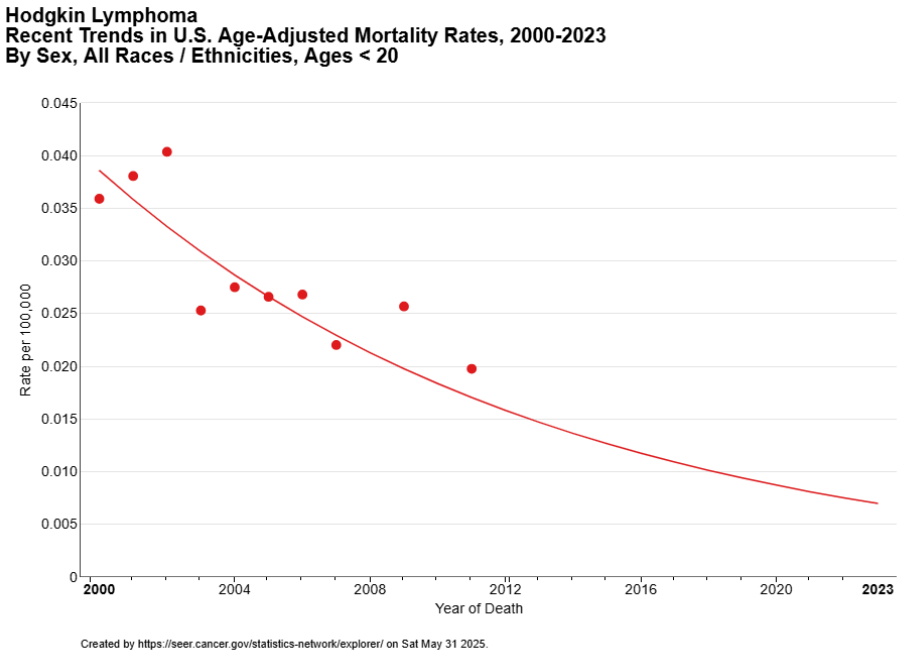


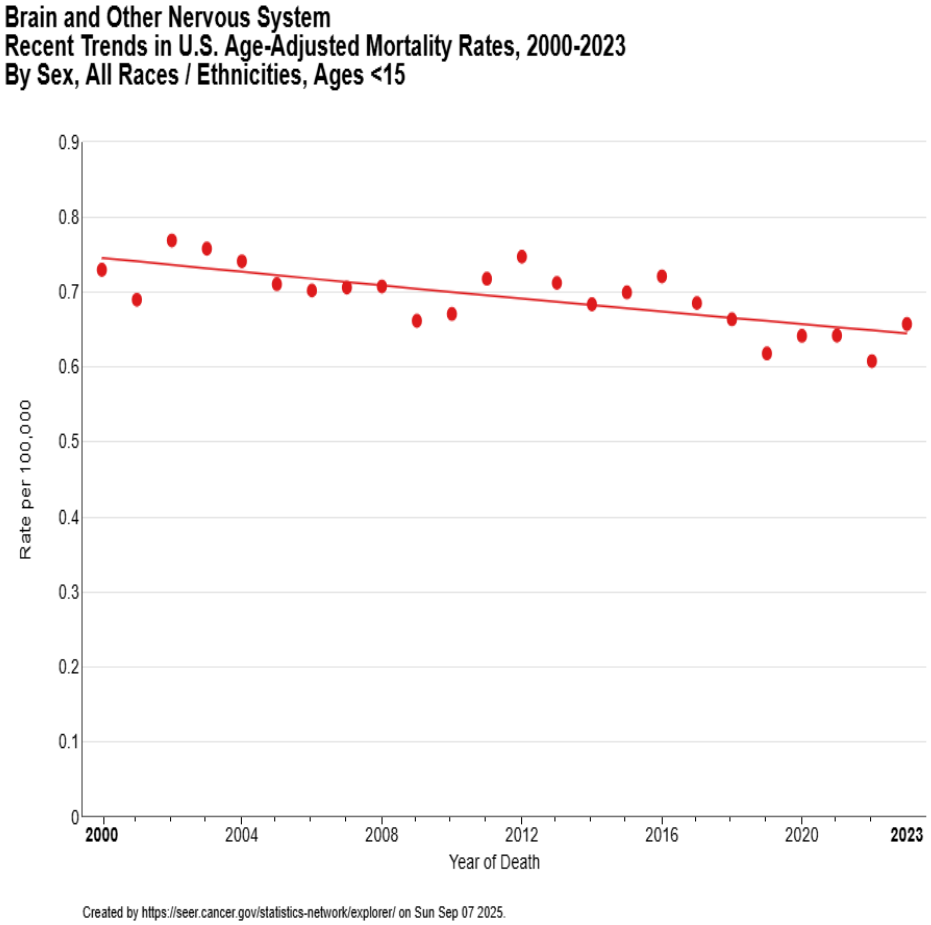
Non-Hodgkin Lymphoma

SEER*Explorer

Soft Tissue Cancer

Mortality rates for Hodgkin lymphoma and CNS tumors



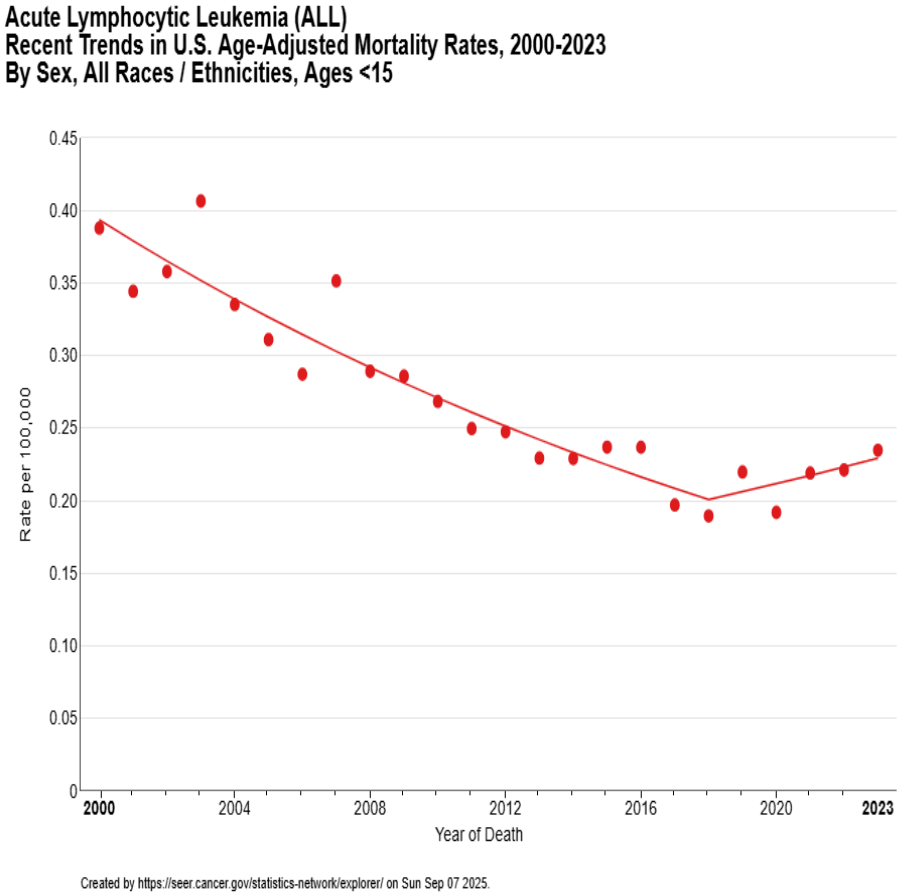


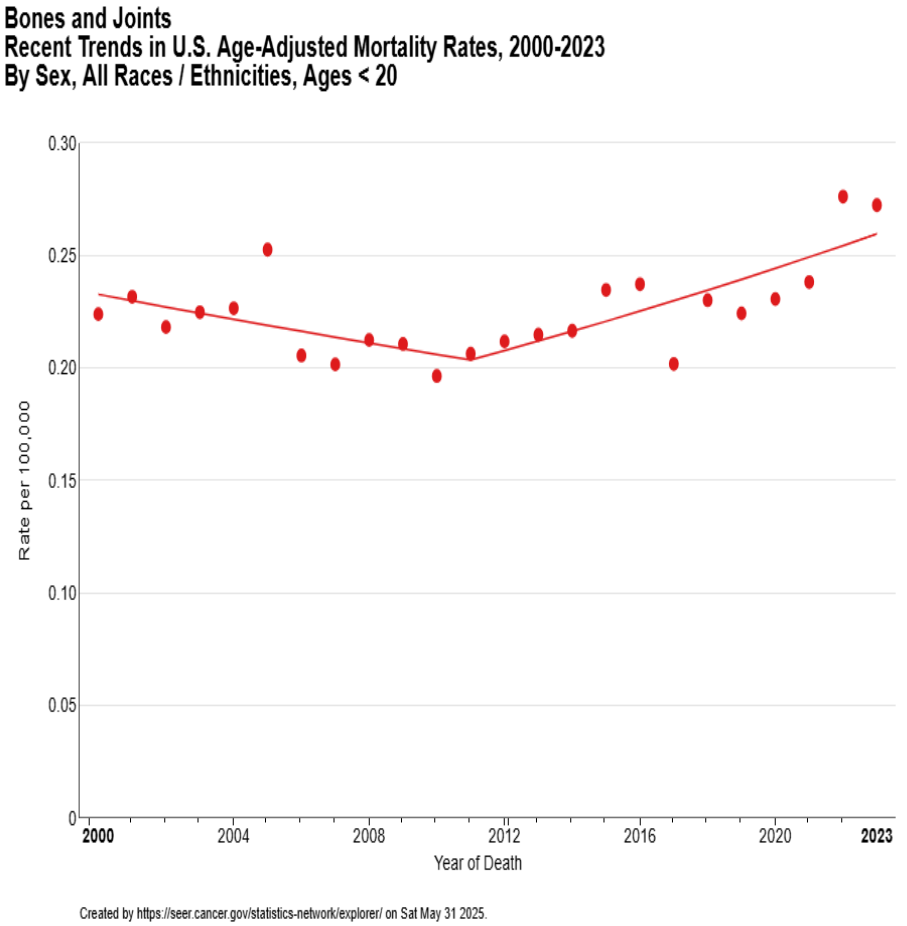
Hodgkin Lymphoma

SEER*Explorer

CNS Tumors

Mortality rates for acute lymphoblastic leukemia and bone cancers





Acute Lymphoblastic Leukemia

SEER*Explorer

Bone Cancers

Active New Agents for Childhood Cancers

ALL, NHL, & Hodgkin Lymphoma

- Anti-PD1 MABs
- CD30 antibody-drug conjugate
- CD20 targeting agents
- CD19 bispecific T cell engagers and CAR T cells
- ALK inhibitors for anaplastic large cell lymphoma

Soft Tissue Cancers

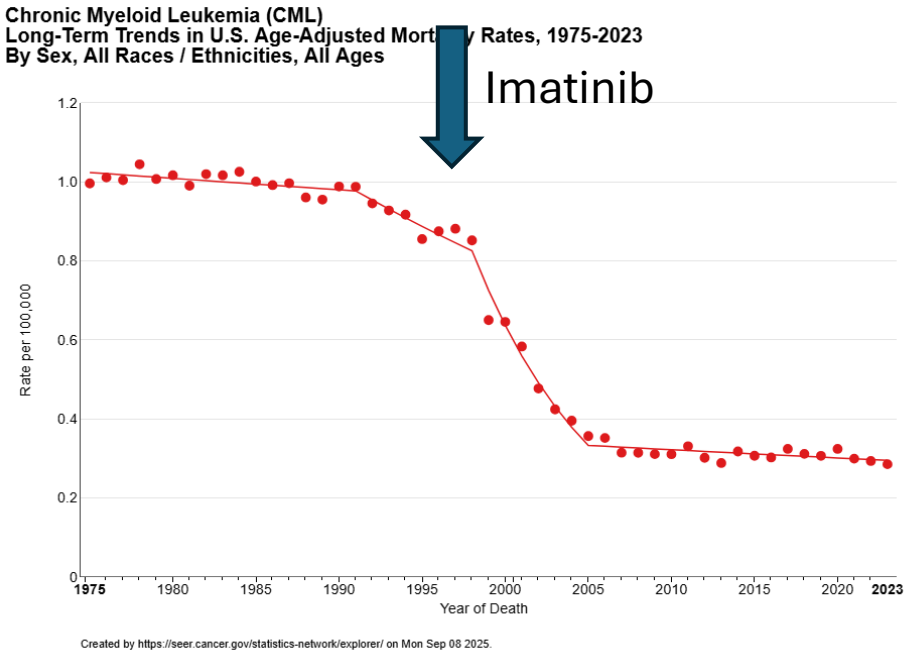
- Topo-I inhibitors

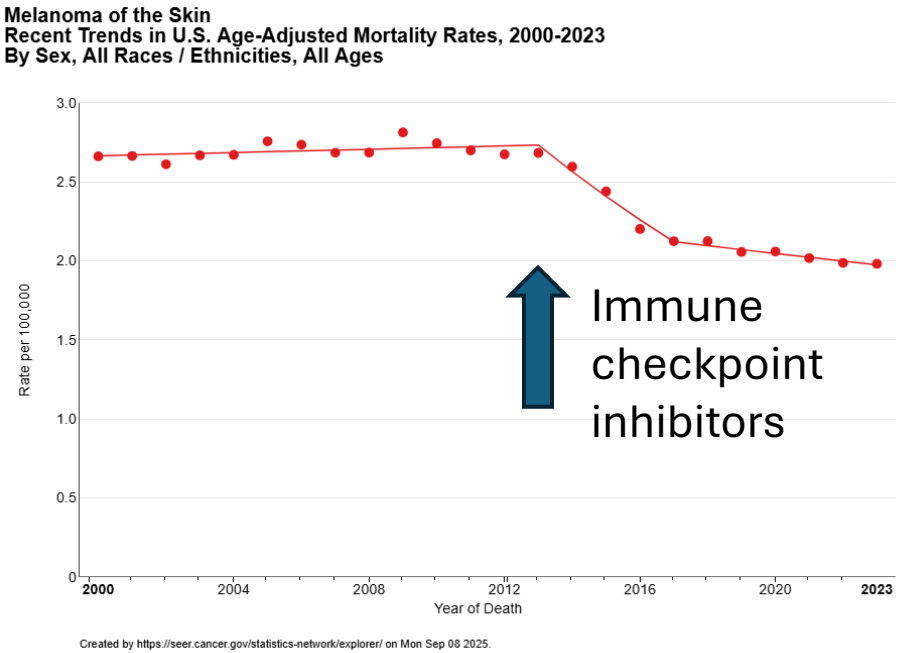
Bone Cancers

CNS Tumors

- MAPK pathway inhibitors

Mortality rates for chronic myeloid leukemia (CML) and melanoma



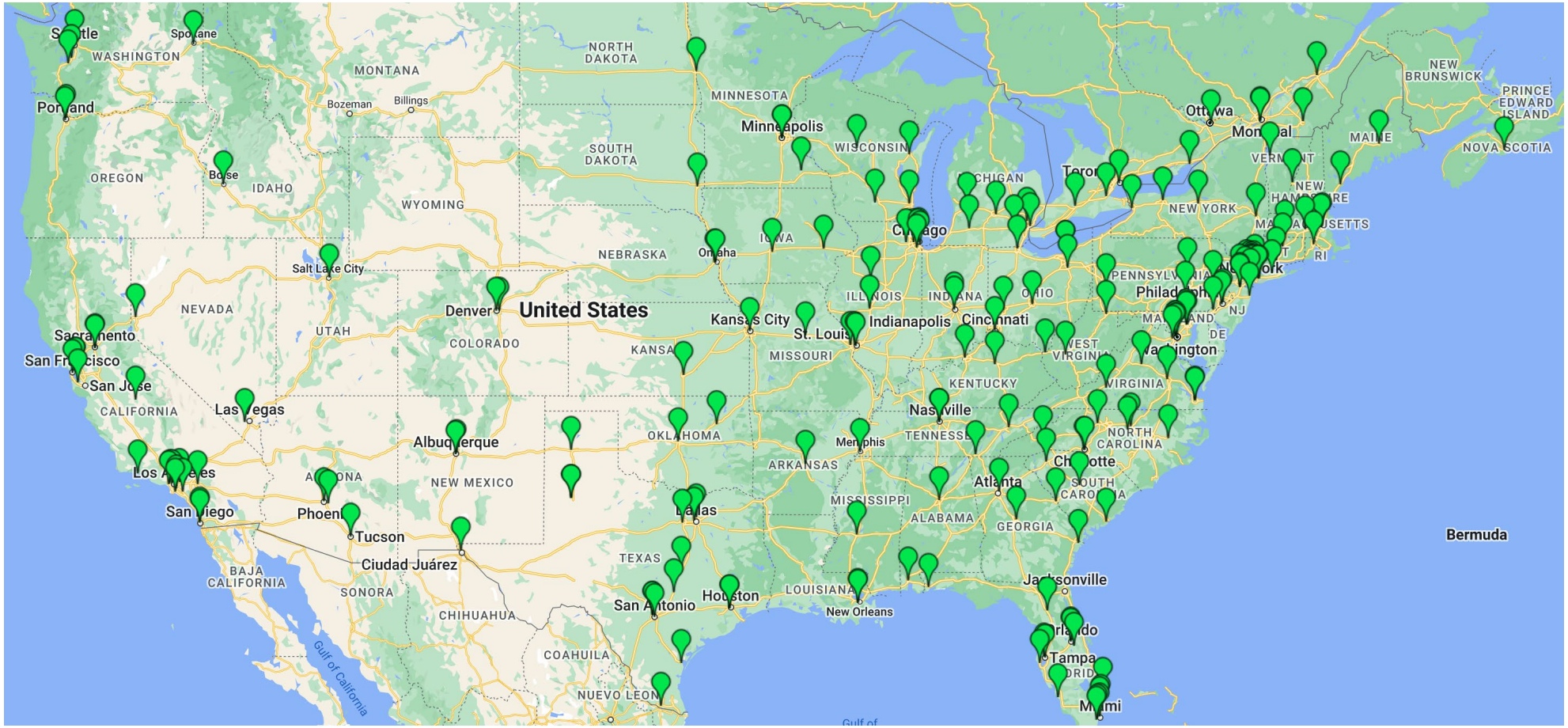


Chronic myeloid leukemia

Melanoma

SEER*Explorer

What Childhood Cancer Researchers Need



"We need active new agents, not …"

Challenges of Identifying Active New Agents for Children with Cancer

In the precision oncology era, agents are more effectively targeted to adult cancer characteristics, many of which are not shared with childhood cancers

Many agents developed for adults with cancer have little/no pediatric cancer relevance

Other challenges

1)Small populations limit number of agents that can be tested

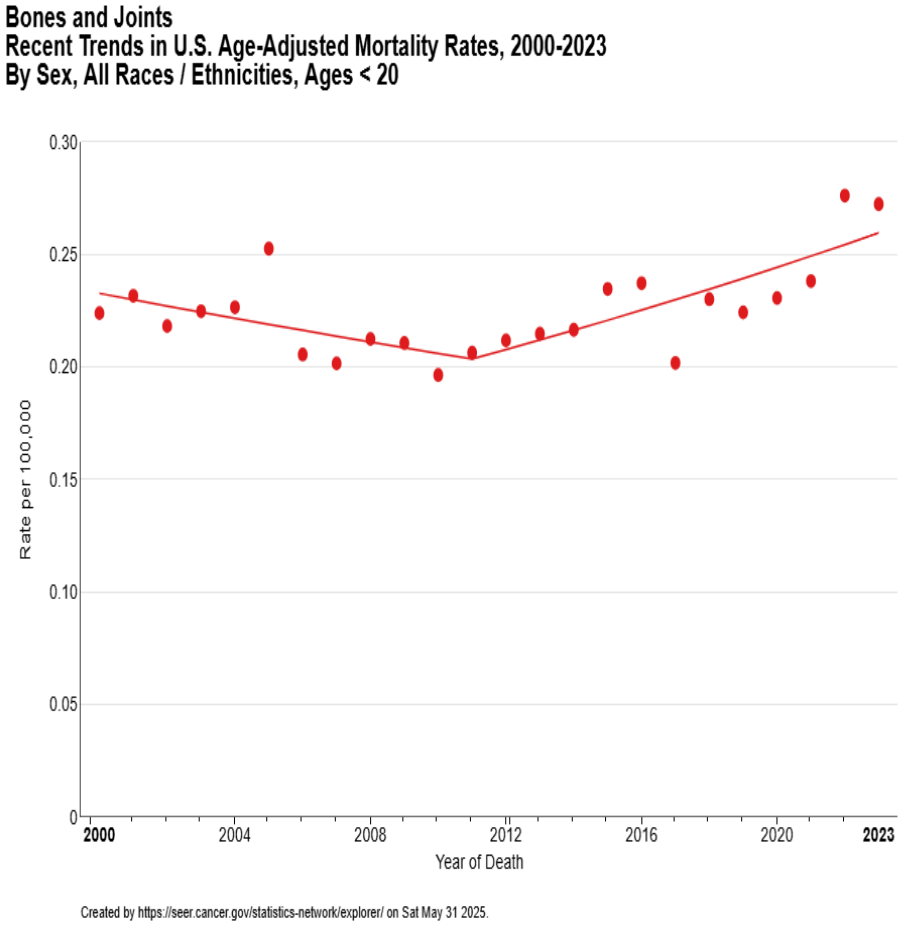
2) Multiple agents in class

3) Risk of agent's development being stopped

Pharma timeline for pediatric development is driven by adult cancer milestones

Agents that are high priority for one or more pediatric cancers may be delayed in entering testing in children

Acting with a sense of urgency to identify active new agents

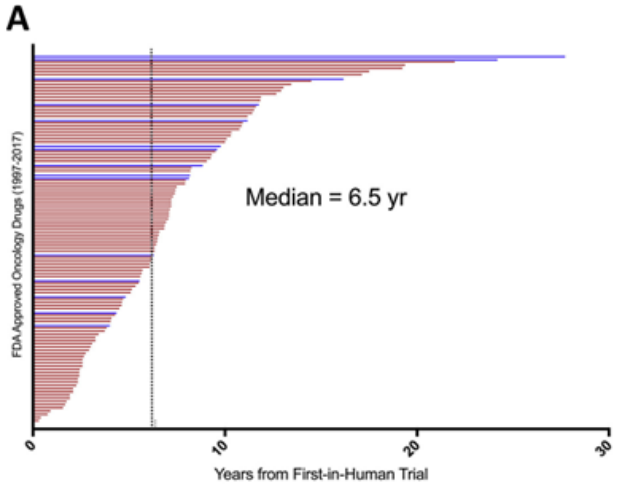


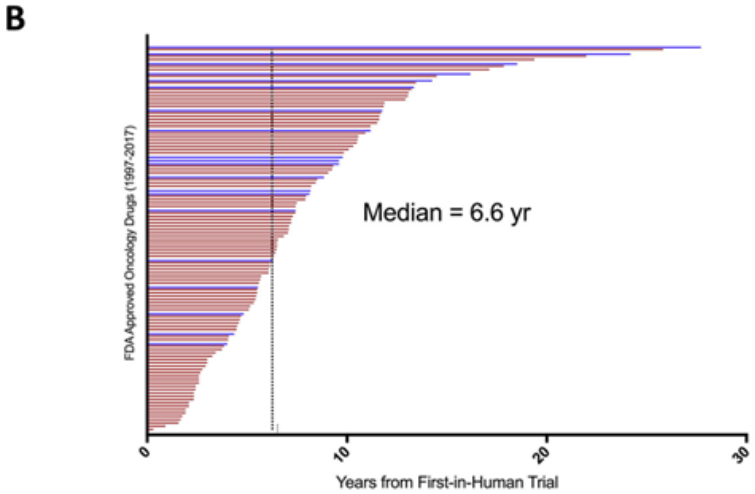
Bone Cancers

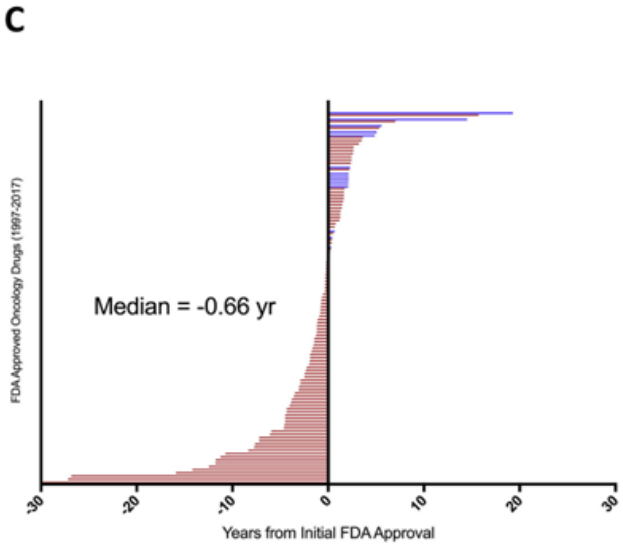
- Without active new agents, it is challenging to improve outcome
- Sense of urgency needed for bringing the most promising new agents into clinical testing for children with bone cancers (and CNS tumors and soft tissue cancers)

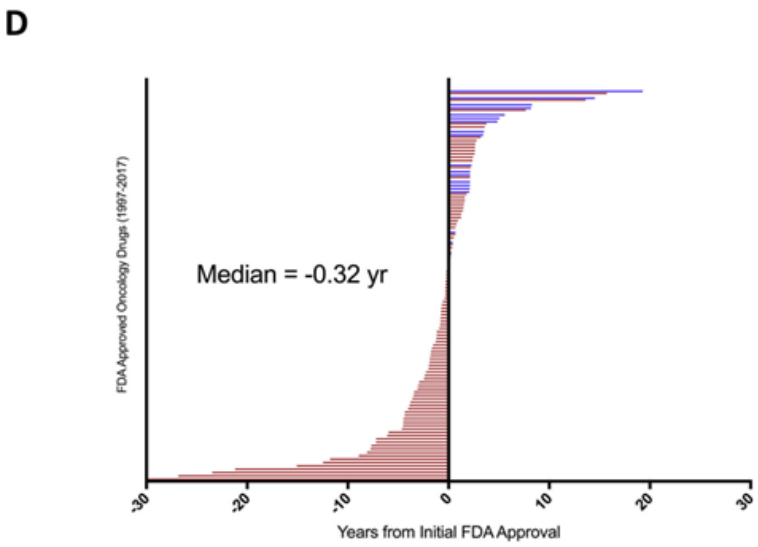
Time to Pediatric Trial After Initiation of First Clinical Trial for Adults

- Clinical trials from 1997 to 2017







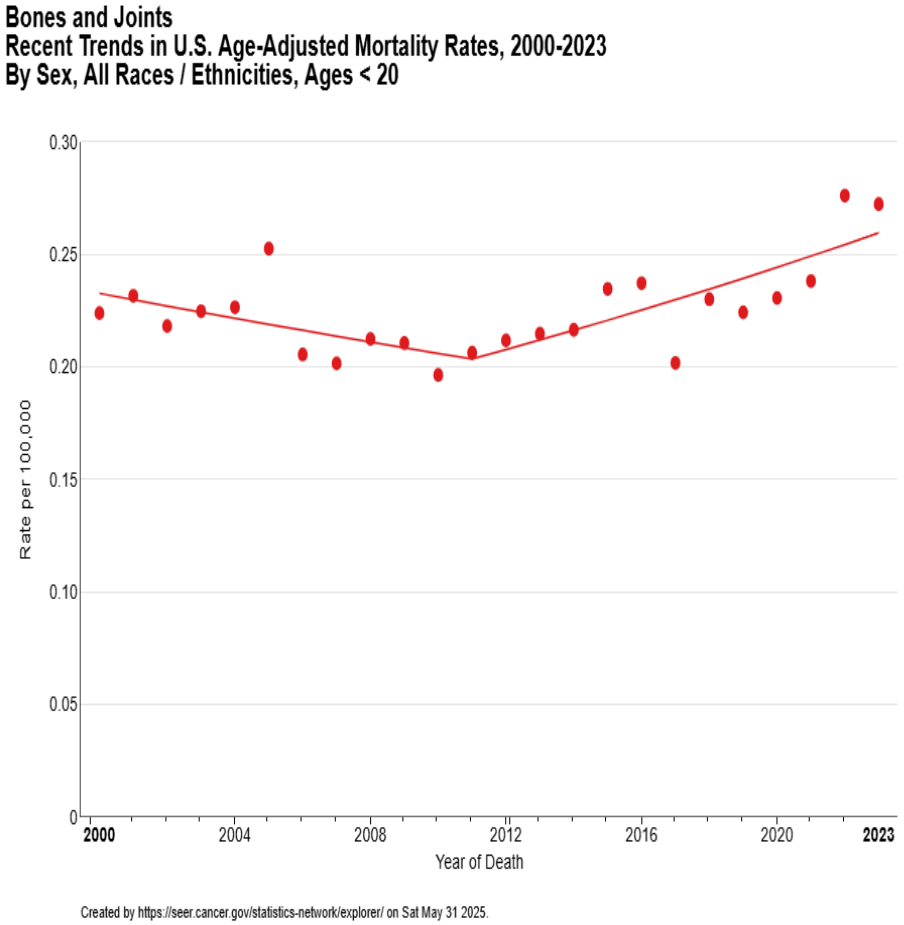


European Journal of Cancer 112 (2019) 49e56

A final challenge for pediatric investigators is to ensure that new agents continue to be available for evaluation in children at appropriate stages of the agents' development. Since the relatively small number of children with cancer limits their importance to pharmaceutical sponsors as a commercial market, pediatric investigators must continuously advocate for the access of their patients to new agents. Agents that have completed phase I trials in adults and that have shown activity against pediatric tumors in xenograft systems or have shown promising antitumor activity against adult tumors should be available for evaluation in children.

Smith M, et al. *J Clin Oncol 16:966-978, 1998* Conduct of Phase I Trials in Children With Cancer

Acting with a sense of urgency to identify active new agents



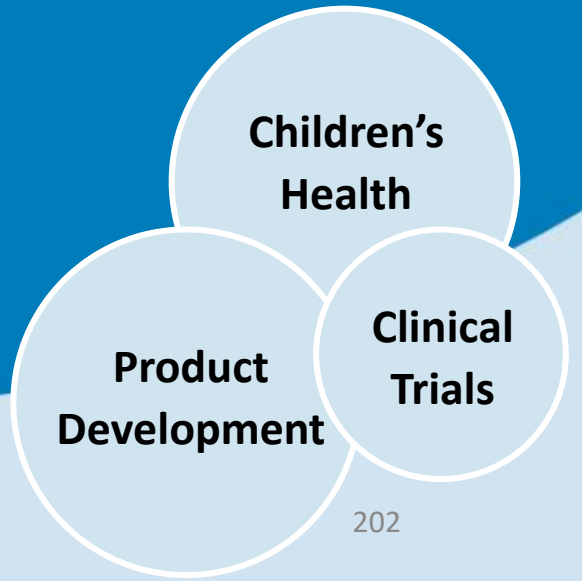
Bone Cancers

- Without active new agents, it is challenging to improve outcome
- Sense of urgency needed for bringing the most promising new agents into clinical testing for children with bone cancers (and CNS tumors and soft tissue cancers)

- Dedicated public servants at FDA who do critical work ensuring the safety and effectiveness of the drugs that we use
- NCI colleagues who work tirelessly to build and maintain the clinical trials infrastructure that is required for COG and other consortia
- Pharma/Biotech research teams working to bring new agents to testing in children
- Patient advocates who educate themselves on topics they never wanted to learn about so that they can have the biggest impact for policies that will help children
- Families who allow their children to participate in the clinical trials that will define more effective treatments for new generations of children

Kids v. Cancer

Nancy Goodman, JD



Interested Parties Meeting:
Implementation of BPCA and PREA

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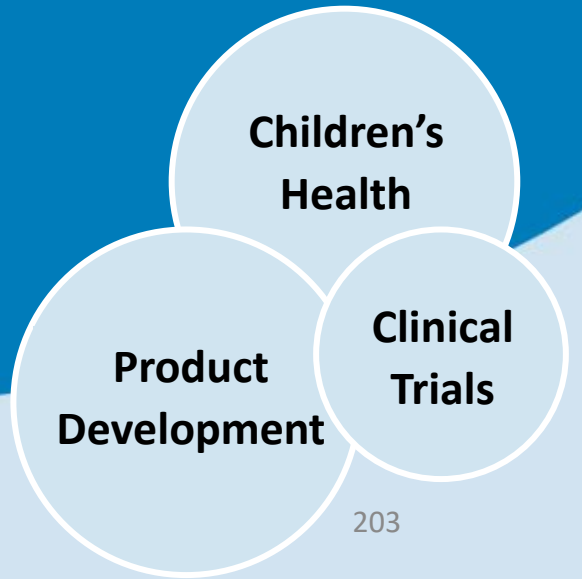
Break



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

FDA

Interested Parties Meeting for Pediatrics

Provide your feedback on implementation of the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA)

Children's Health

Product Development

Clinical Trials

September 15, 2025

9:00 a.m. to 4:30 p.m. ET

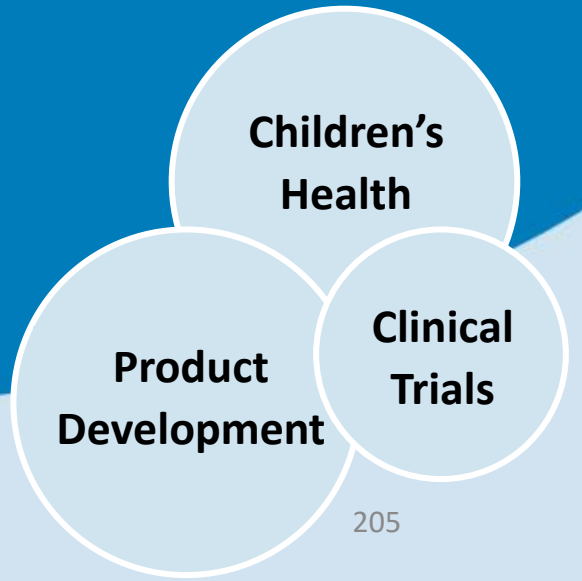
FDA Great Room
White Oak Campus
Silver Spring, MD

Virtual option available

Submit comments to the public docket number FDA-2024-N-5784 until 11:59 p.m. Eastern Time, September 30, 2025

Visit https://www.regulations.gov

Open Public Comment Period



Interested Parties Meeting:
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September 15, 2025

Open Public Comment

Speaker One

Interested Parties Meeting:
Implementation of BPCA and PREA

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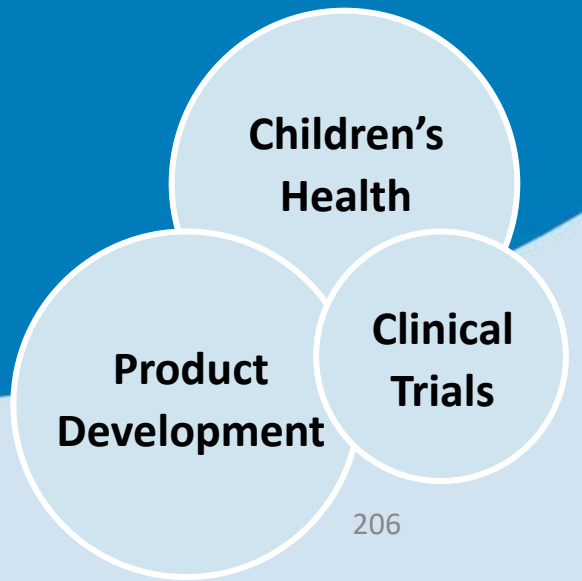


Albert J. Allen, MD, PhD

Training: child psychiatrist, pharmacologist, clinical research

Career focus: pediatric drug development, safety and ethics

Experience: former academic clinician and researcher, retired from Lilly (21+ years) and I-ACT, current consultant and pediatric advocate

Indianapolis, IN

DrAJAllen@gmail.com

Observations Re: Pediatric Drug Development Ecosystem

- **Celebrate our many successes! A joint effort of government, academia, clinicians & researchers, families, advocates and more!!**
  - Even as we recognize we were **far from perfect** (lots of mistakes and failures to learn from)
  - **Pediatric drug development is more challenging than adult drug development**…and that "isn't rocket science, it is harder than rocket science"
- Resources are scarce in pediatrics…and getting scarcer…so **cooperation and collaboration** between FDA, NIH, CDC, pediatric clinicians & researchers (whatever setting), families, advocates, industry, economists, investors, and others – in the US **and internationally** is essential for success.
  - All have unique knowledge, resources, and perspectives to share…and we all need to listen to each other
  - Historically, **cooperation and collaboration has occurred, but limited by multiple issues of trust between different groups**

Observations Re: Pediatric Drug Development Ecosystem (continued)

- **Industry and private funding for pediatric drug development is limited, and this creates significant challenges for small companies, families, clinicians & researchers, and government when such funding falters – example, LGMD and Sarepta**
- Historically, **pediatric drug development as relegated to the last stages of development for a molecule…just before patent expiration**
  - **Created a "wild west" between launch of adult indications/data and pediatric indications/datad ("pediatric gap")**
    - **Off-label prescribing**
      - Concerns about efficacy
      - Concerns about safety
      - Concerns about how to use (dose, dosing frequency, formulations, etc.)
  - **Created research inefficiencies and challenges by treating pediatric drug development as an after thought to adult drug development**
    - **Still the prevailing approach with many development teams**

Observations Re: Pediatric Drug Development Ecosystem

- Despite the successes of the last 25+ years since the passage of what became BPCA, and then PREA, **it feels like we are losing ground**
  - **Policy/legislative/regulatory: PREA limits and lacks real teeth ("misbranding" is problematic in practice)** , **BPCA incentives have largely lost their value** (biologics limited by ACA, small molecules limited by IRA), PPRVs expired in 2024. In addition, limits re: **outcomes that may be incentivized under BPCA have handcuffed FDA**
  - **Research infrastructure:** Loss of Federal funds supporting critical pediatric research infrastructure – both directly and indirectly. Example: **Loss of pediatric brain tumor consortium – supports government funded research and trains new generation of pediatric researchers, and also a resource for industry clinical trials** (study sites).
  - **Funding: Pediatrics already is a money loser** for most healthcare systems and the **pediatric research infrastructure is in a fragile state**. Pediatric clinical programs and hospitals are **heavily dependent on Medicaid and CHIP, as well as other sources of Federal funding, all of which are being cut back**.
  - **Industry infrastructure:** In the last couple years, a number of companies that had dedicated pediatric groups have **eliminated or cut back those groups for a number of reasons**, possibly including the loss of incentives for pediatric drug development
    - **Loss of pediatric perspective in industry is a loss of pediatric expertise and advocacy for pediatric patients in industry**

Recommendations Re: Pediatric Drug Development Ecosystem

- **Pediatric Drug Development is not easy, and it requires a complex pediatric research infrastructure and ecosystem to be successful – but this is an increasingly fragile, and in some cases collapsing – research infrastructure and ecosystem**
  - It must be thoroughly grounded in **good, ethical scientific methods that systematically generate hypotheses to be tested via clinical trials**
    - **A central tenet of pediatric drug development must be evaluating new treatments in terms of both benefits and risks.** The benefit/risk balance, whether a drug has the potential to do more good than harm (not just harm alone), is central to clinical care.
  - **The pediatric research infrastructure and ecosystem exists for the benefit of all children, including American children, and it deserves and requires adequate support from all stakeholders, including the US government. This must be a consideration in future funding and policy decisions.**

Recommendations Re: Pediatric Drug Development Ecosystem (continued)

- **Increasingly, pediatric drug development needs to be integrated with adult drug development and begin earlier, rather than treated as a separate after thought to adult drug development**
  - **FDA can model this strategic change** in approach via its expectations and requirements of industry
  - As a start, **rethink the original IND to include more details from the start on all populations (including pediatric, if appropriate) with a given indication.** Not a full initial pediatric study plan, but some discussion of pediatric needs and planned preclinical safety studies, pharmacology studies and formulation work to support a pediatric clinical program if appropriate.
  - **Include pediatric patients earlier in clinical trials when appropriate, both based on age and stage of drug development**
    - **For progressive diseases, pediatric patients often have the most to gain from new treatments that may prevent or slow future loss of function**

Recommendations Re: Pediatric Drug Development Ecosystem (continued)

- **For multiple reasons, ranging from possible incentives to the financial challenges of pediatric drug development and how that impacts patients and families, we need to better understand the economics of pediatric drug development across multiple settings** - clinical care, research infrastructure, academic medical centers, biotechs, small pharma, large pharma, industry development teams vs. leadership, etc.
  - FDA, perhaps together with NIH or other groups, can **lead this work by engaging economists to work with other stakeholders to better understand the economics of pediatric drug development**

Recommendations Re: Pediatric Drug Development Ecosystem (continued)

- Remember what we know about behavior modification! **Need both requirements (PREA) and incentives (BPCA), but…positive rewards generally are more effective than negative penalties at modifying behaviors**
  - Consider desired outcomes carefully…not just "conduct clinical trials in kids," really **about drug development for pediatric patients**
  - **The value of an incentive are in the eye of the beholder**…and if it doesn't have value to the target group (e.g., a development team, a company), it won't change behaviors **– engage economists in discussions**
  - **The value of drugs increases as the phase of development increases** (look at the deals companies make)
  - **More flexibility for FDA re: desired outcomes (e.g., speed to completion of studies, pediatric infrastructure in industry) might be helpful**
  - **PREA needs more realistic teeth** ("misbranding" is a problematic consequence)

Thank You!

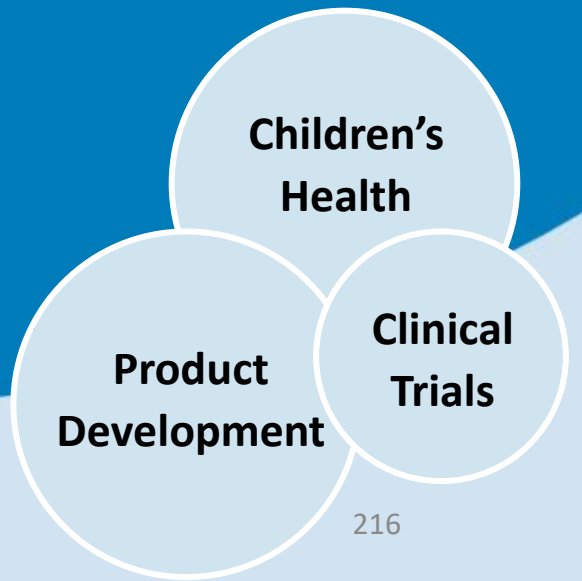
DrAJAllen@gmail.com

Open Public Comment

Speaker Two

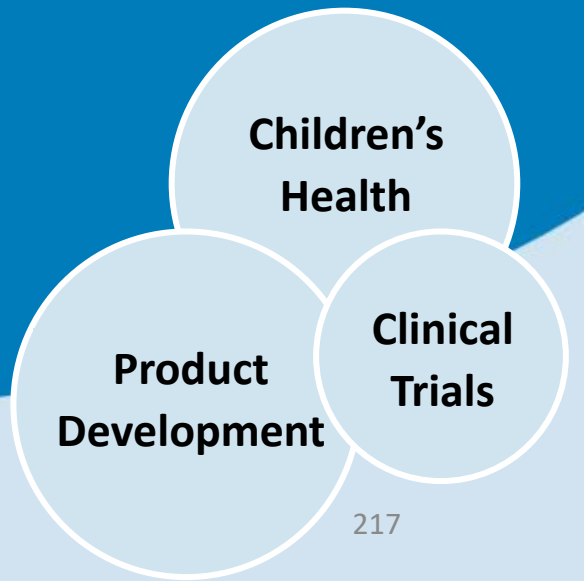
Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025



Open Public Comment

Speaker Three



Interested Parties Meeting:
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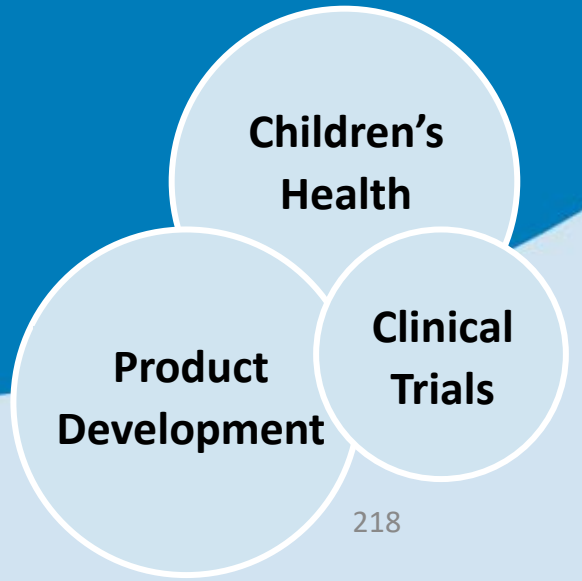

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Implementation of BPCA and PREA

September 15, 2025

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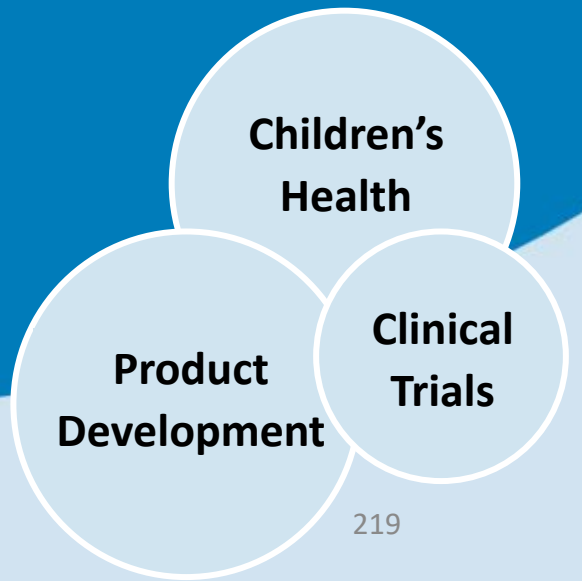
Speaker Four

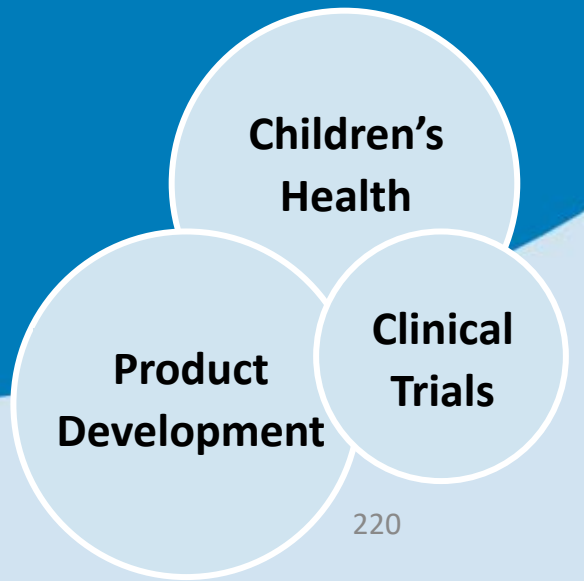
Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025



Open Public Comment

Speaker Five



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

PORTAL
Program on Regulation, Therapeutics, And Law

DoPE

Interested Parties Meeting: Implementation of the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act

Ian Liu, MD, JD, MPH, MS
Aaron Kesselheim, MD, JD, MPH

Program On Regulation, Therapeutics, And Law
Division of Pharmacoepidemiology and Pharmacoeconomics
Department of Medicine
Brigham and Women's Hospital

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

BRIGHAM HEALTH
BWH
BRIGHAM AND WOMEN'S HOSPITAL

Overview

- PREA's goal was to "make certain that children are no longer a therapeutic afterthought by ensuring that all new drugs are studied for pediatric use at the time a drug comes to market." [1]

- PREA applies to all new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration.

1. 149 Cong. Rec. S3883-01, S3898.

Exceptions

- Exempt indications
  - with an Orphan Drug Act designation

- Waivers
  - For 1 of 3 statutory reasons
  - May be complete or partial

Rare disease exemptions, more common

- Over time, rare disease exemptions have become more common
- 15% of new drugs approved from 1999 to 2003[1]
- 23% of new approvals from 2003 to 2012[2]
- 47% of new drugs approved from 2015 to 2021[3]

1. Coté T, Kelkar A, Xu K, Braun MM, Phillips MI. Orphan products: an emerging trend in drug approvals. *Nature Reviews Drug Discovery*. 2010 Jan;9(1):84.
2. Hudgins JD, Bacho MA, Olsen KL, Bourgeois FT. Pediatric drug information available at the time of new drug approvals: a cross-sectional analysis. *Pharmacoepidemiol Drug Saf*. 2018;27(2):161-167.
3. Liu ITT, Hwang TJ, Kesselheim AS. Testing of New Drugs Approved From 2015 to 2021 under the US Pediatric Research Equity Act. *JAMA*. 2024;332(17):1482–1484.

Congressional action

- In 2019, the RACE Act was passed
- Eliminated rare disease exemption for certain pediatric cancer drugs
- In a study, we found that the RACE Act was associated with earlier initiation of pediatric trials (around 2.8 years)[1]
- Can only be changed via Congressional action

1. Liu ITT, Kesselheim AS. The RACE Act and Pediatric Trials of Adult Cancer Drugs. *Pediatrics*. 2024;154(4):e2024066920.

Waivers

- 22% of new drugs approved between 2015 to 2021 were granted complete PREA waivers[1]

- In unpublished research, we have found that 50% of drugs granted complete pediatric testing waivers have observable pediatric use within 3 years of approval[2]

1. Liu ITT, Hwang TJ, Kesselheim AS. Testing of New Drugs Approved From 2015 to 2021 under the US Pediatric Research Equity Act. *JAMA*. 2024;332(17):1482–1484.
2. Manuscript on file with authors. Currently under review at *Pediatrics.*

Delays

- Almost 6 years after approval, only 28% of required PREA studies were completed[1]

- Federal spending on drugs with delayed or deferred pediatric trials is significant
  - Estimated at over $27 billion over 7 years[2]

1. Liu ITT, Hwang TJ, Kesselheim AS. Testing of New Drugs Approved From 2015 to 2021 under the US Pediatric Research Equity Act. *JAMA*. 2024;332(17):1482–1484.
2. Liu ITT, Kesselheim AS. US Government Spending on New Drugs with Incomplete and Postponed Mandatory Pediatric Trials, 2015-2022. *JAMA Pediatrics*. Published online September 02, 2025.

Suggestions

- FDA should consider a firmer stance towards pediatric trial delays
  - Especially for trial delays plausibly within a manufacturer's control
- Use non-compliance letters to encourage timely trials
- Ensure that PREA waivers—especially those granted for "impossible or highly impracticable" trials—are supported by high-quality evidence

BPCA

- Adds 6 month of market exclusivity for manufacturers that complete voluntary trials

- Appears successful at generating valuable pediatric labeling information[1]
  - 97% of drugs had new efficacy information
  - 31% expanded a pediatric indication

1. Liu ITT, Raymakers AJN, Sarpatwari A, Kesselheim AS. Pediatric Exclusivity-Associated Revenues and Labeling Changes, 2013-2023. *Journal of Pediatrics*. 2025;284(1):114660.

BPCA - cont'd

- However, label changes occur on average 8.83 years after approval[1]

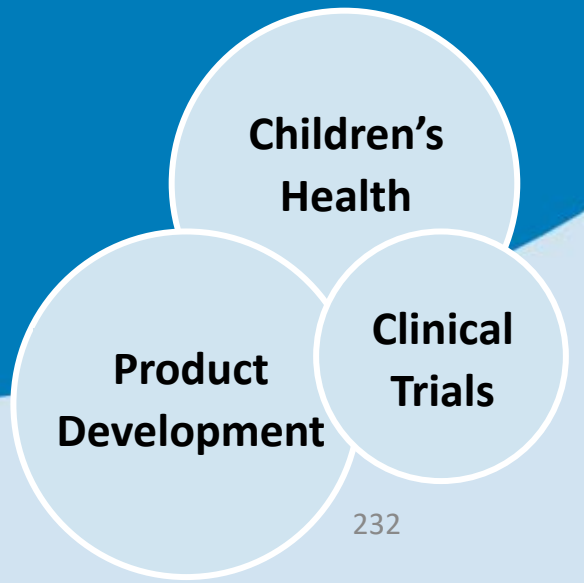
- FDA has the authority to request earlier trial deadlines, and should do so to make valuable clinical data available earlier for children

1. Liu ITT, Raymakers AJN, Sarpatwari A, Kesselheim AS. Pediatric Exclusivity-Associated Revenues and Labeling Changes, 2013-2023. *Journal of Pediatrics*. 2025;284(1):114660.

Thank you for your time.

Open Public Comment

Speaker Six



Interested Parties Meeting:
Implementation of BPCA and PREA

September 15, 2025

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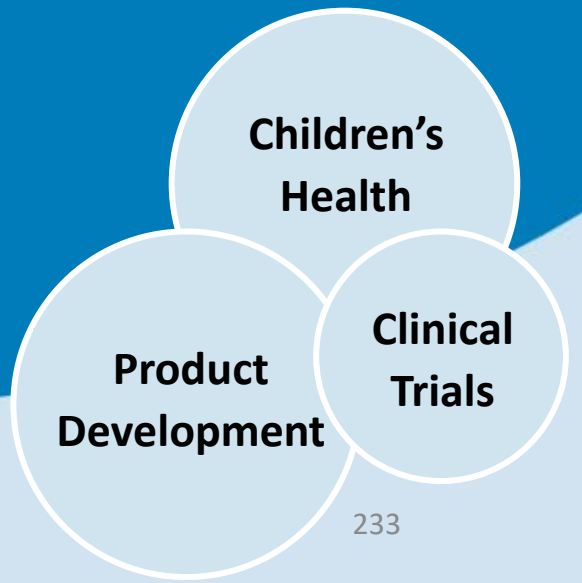
Speaker Seven

Interested Parties Meeting:
Implementation of BPCA and PREA

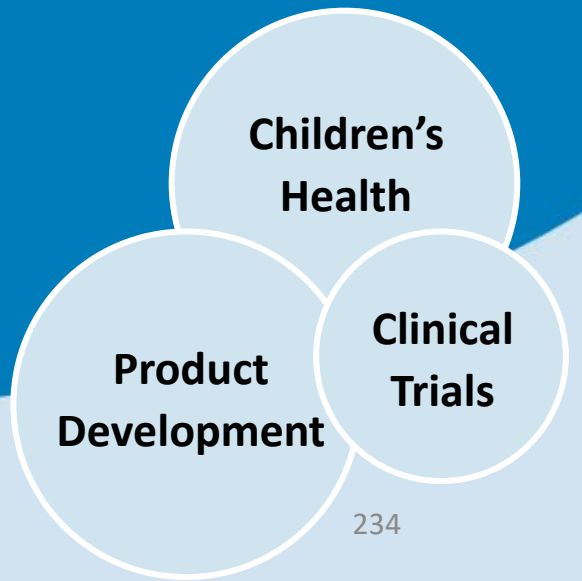
September 15, 2025



Thank you for participating!

Submit comments to the public docket number **FDA-2024-N-5784** until 11:59 p.m. Eastern Time, **September 30, 2025**

Visit https://www.regulations.gov



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