FDA OVERVIEW OF THE PEDIATRIC LEGISLATION

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Stakeholder Input on Pediatric Legislation Public Meeting

November 21, 2019

Disclaimer

- The views presented here are personal and do not necessarily reflect the views of the Agency
- All specific drug development questions should be discussed with the relevant review division

Agenda

- History of Pediatric Legislation
- FDASIA Report
- BPCA/PREA Experience
- NICHD/BPCA Experience
- RACE for Children Act
- Pediatric Labeling of Orphan Products
- Rare Pediatric Disease Priority Review Voucher Program
- Pediatric Advisory Committee
- International Pediatric Therapeutic Development
- Patient Focused Drug Development
- Extrapolation
- Summary

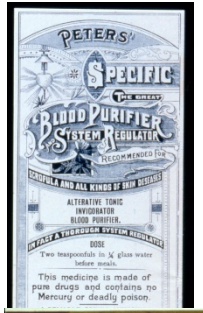
Adulterated Drugs

Cantharides (Spanish Flies) used chiefly as a blistering agent was adulterated with other insects and even beads. Drug Importation Act, 1848

Early Safety

1890 Effective antitoxin for diphtheria from serum of animals injected with diphtheria toxin. In 1901, five year old girl died of tetanus after receiving diphtheria antitoxin. Biologics Control Act of 1902

Pre-1906 Patent Medicines

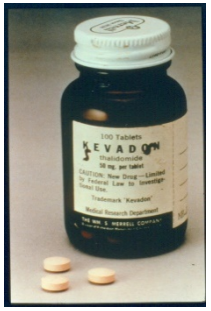


Peters' Specific Blood Purifier claimed much but divulged little if any of its contents, quite legally before 1906. Mrs. Winslow's Soothing Syrup for teething and colicky babies, unlabeled yet laced with morphine, killed many infants. 1906 Pure Food and Drugs Act

Sulfanilamide

Elixir of Sulfanilamide introduced in September 1937. Compounded with an untested solvent, diethylene glycol (chemically related to antifreeze). Caused 107 deaths including many children. Food, Drug and Cosmetic Act, 1938

Thalidomide



1962 Kefauver-Harris Amendment that manufacturers had to prove efficacy as well as safety

Historical Milestones and Legislation

- **1902** The Biologics Control Act enacted following the death of 22 children from tainted anti-toxins
- **1938** FD&C Act: Drugs must be Safe: enacted after 100 deaths, many in children, after use of Elixir Sulfanilamide
- **1962** Following thalidomide tragedy in Europe; Kefauver–Harris amendments require effectiveness
- **1962** The FD&C Act amended: Drugs not tested in children should not be used in children
- **1974** AAP Committee on Drugs issues guidelines for evaluating drugs for pediatric use
- **1977** AAP issues guidelines for ethical conduct in pediatric studies
- **1979** FDA requires sponsors to conduct pediatric clinical trials before including pediatric information in the labeling
- **1992** Agency proposed Pediatric Labeling Rule and proposes extrapolation of efficacy from other data
- **1994** Final Rule on Pediatric Labeling. Formalizes Extrapolation of Efficacy; manufacturers to update labeling if pediatric data existed; HOWEVER, it allowed a disclaimer to the labeling for drugs not evaluated in children
- **1994** Pediatric Plan to encourage voluntary development of pediatric data
- **1997** FDAMA creates pediatric exclusivity provision **(voluntary**), provides 6-month exclusivity incentive
- **1998** Pediatric Rule **(mandatory):** products are required to include pediatric assessments if the drug is likely to be used in a ‘‘substantial number of pediatric patients’’ (50,000) or if it may provide a ‘‘meaningful therapeutic benefit’’
- **2002** Pediatric Rule declared invalid by DC Federal Court; the rule exceeded FDA’s authority
- **2002** FDAMA reauthorized as BPCA. Maintains 6-month exclusivity added to patent life of the active moiety. Creates Office of Pediatric Therapeutics (including ethicist). Mandates pediatric focused safety reviews
- **2003** PREA re-establishes many components of the FDA’s 1998 pediatric rule. Orphan products are exempted
- **2007** FDAA Reauthorizes BPCA & PREA for 5 years: Pediatric Review Committee (PeRC) formed
  Studies submitted will result in labeling. Negative and positive results of pediatric studies will be placed in labeling
- **2012** FDASIA legislation makes **permanent** BPCA and PREA; PAC was permanently reauthorized under section 507

Food and Drug Administration Safety and Innovation Act (FDASIA)

- The Food and Drug Administration Safety and Innovation Act (FDASIA), enacted in 2012, required in section 508 that the Secretary of Health and Human Services report by July 9, 2016, and every 5 years thereafter, on various activities resulting from the implementation of sections 505A and 505B of the Federal Food, Drug, and Cosmetic Act. The 2016 report, submitted in accordance with that provision, contains a brief discussion of various pediatric drug development laws, regulations, and guidances; an assessment of the pediatric programs; as well as suggestions for improving pediatric research
- At least 180 days prior to the submission of each report under subsection (a), the Secretary shall consult with representatives of patient groups (including pediatric patient groups), consumer groups, regulated industry, academia, and other interested parties to obtain any recommendations or information relevant to the report including suggestions for modifications that would improve pediatric drug research and pediatric labeling of drugs and biological products

Best Pharmaceuticals for Children Act and Pediatric Research Equity Act

- BPCA (505A) and PREA (505B)
- FDASIA permanently authorized sections 505A and 505B but only authorized funding for section 409I of the Public Health Service Act for 5 years (part of BPCA which authorizes testing of pediatric therapeutic products by NIH – development and funding of the Pediatric Trial Network (PTN) by NICHD)
- 505B does not apply to any drug for an indication for which orphan designation has been granted under section 526 of the FD&C Act – amended by the RACE for Children Act in 2017

PREA vs. BPCA

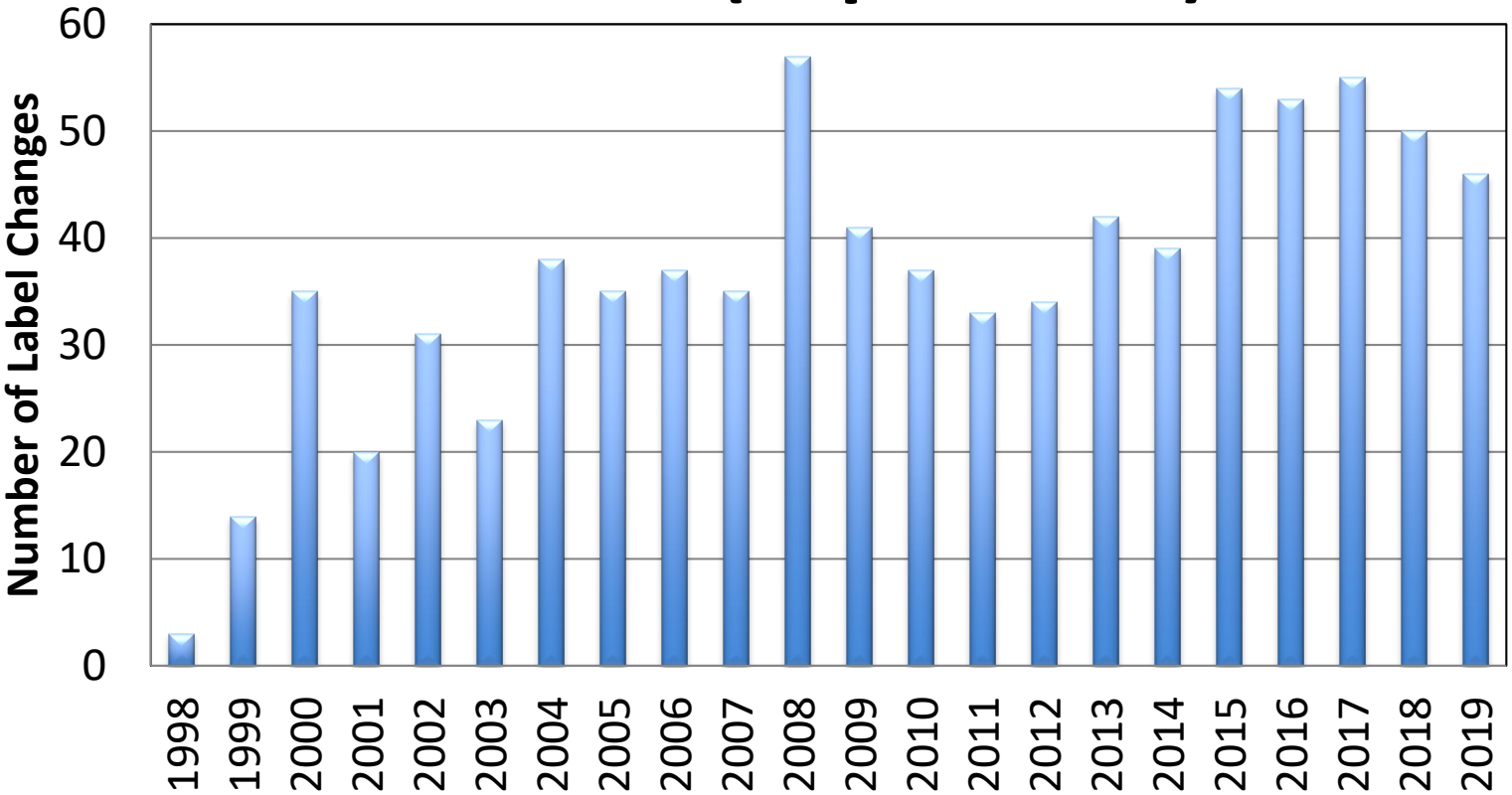
PREA

- Drugs and biologics
- **Required studies**
- Studies may only be required for approved indication(s)
- Products with orphan designation are exempt from requirements except molecular targets relevant to pediatric cancers
- Pediatric studies must be labeled

BPCA

- Drugs and biologics
- **Voluntary studies**
- Studies relate to entire moiety and may expand indications
- Studies may be requested for products with orphan designation
- Pediatric studies must be labeled

Pediatric Labeling Changes 1998-2019 (September)



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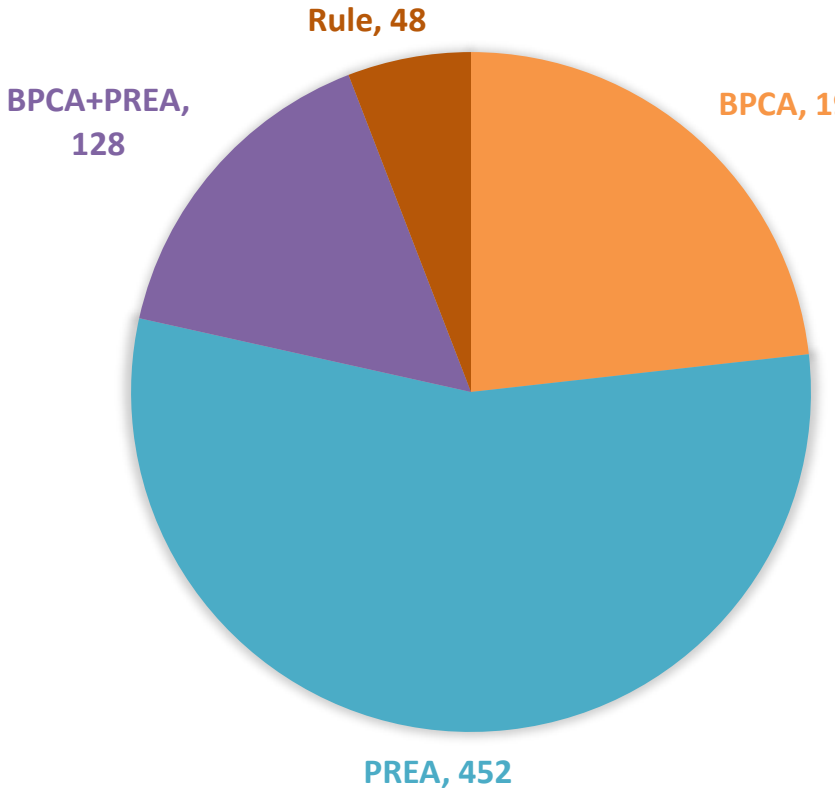


Total Pediatric Labeling Changes = 818

(CDER=738; CBER=80)

NICHD/BPCA

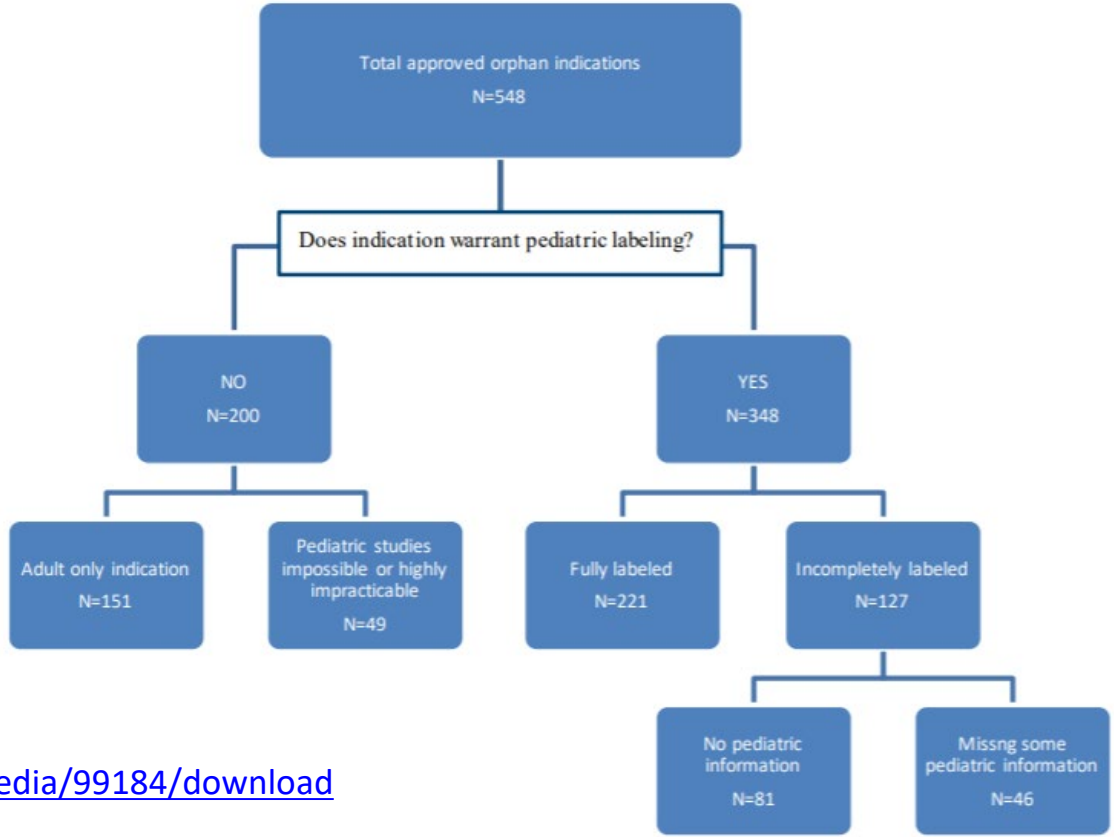
- 2002 BPCA legislation provisions for off-patent drugs
- Authorized a research program through the Department of Health and Human Services with implementation through NICHD
  - Responsible for developing a priority list of needs in pediatric therapeutics in consultation with FDA and pediatric experts
  - Sponsorship of relevant pediatric clinical trials
  - Submission of resulting data to FDA for pediatric labeling changes
- Priority list for pediatric therapeutics (2018-2019) published https://www.nichd.nih.gov/sites/default/files/inline-files/2018PriorityList-Feb19.pdf
- NICHD/BPCA has funded more than 30 clinical trials and has produced 11 labeling changes (2 of which are devices)
- Pediatric Trials Network established in 2010
  - Part of the NICHD/BPCA program
  - Coordinated by the Duke Clinical Research Institute

RACE for Children Act

- Incorporated as Title V of the FDA Reauthorization Act (FDARA), enacted August 18, 2017 (Research to Accelerate Cures and Equity (RACE) for Children Act)
- Requires evaluation of new molecularly targeted drugs and biologics "intended for the treatment of adult cancers and directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer"
- Molecularly targeted pediatric cancer investigation: clinically meaningful study data, "using appropriate formulations, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling." [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)]
- Elimination of orphan exemption for pediatric studies for cancer drugs directed at relevant molecular targets

Courtesy of Dr. Gregory Reaman

Pediatric Labeling of Orphan Drugs



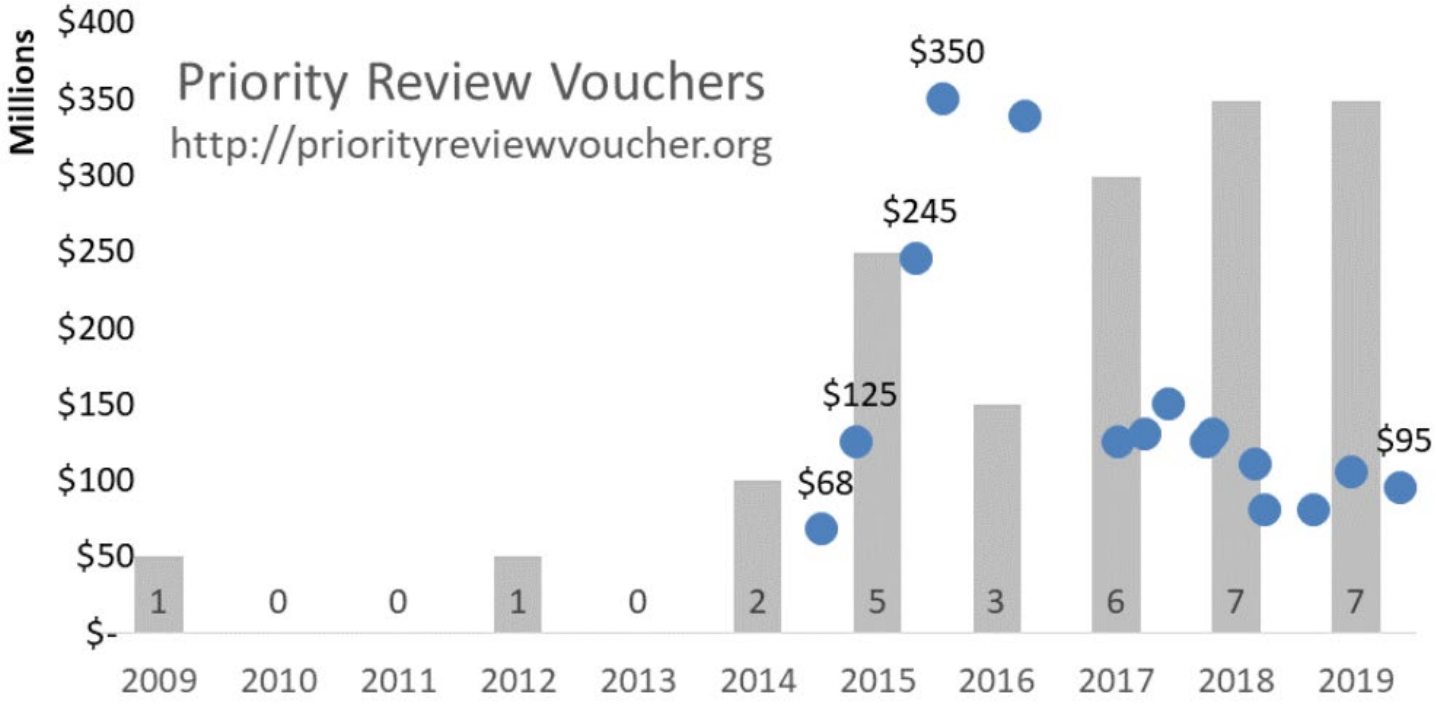
Report to Congress
https://www.fda.gov/media/99184/download

Rare Pediatric Disease Priority Review Voucher Program

- FDA may award a priority review voucher to the sponsor of a rare pediatric disease product application upon approval which entitles the holder to priority review for a subsequent application
- In effect starting October 2012 and sunsets September 2020 (at that time FDA may only award a voucher if the drug has rare pediatric disease designation granted by September 30, 2020)
- OPT collaborating with OOPD on reviews starting in May 2017
- Designations (as of November 2019)
  - Total = 199
  - Since May 2017 = 128
- Vouchers (as of November 2019)
  - First Priority Review Voucher issued February 14, 2014 for Vimizim (elosulfase alfa) for treatment for Mucopolysaccharidosis Type IVA (Morquio A Syndrome)
  - Total = 19
- New definition of rare pediatric disease (Advancing Hope Act of 2016 – September 30, 2016)
  - *disease is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents.*

Priority Review Voucher Programs

Includes neglected tropical diseases, rare pediatric diseases and medical countermeasures



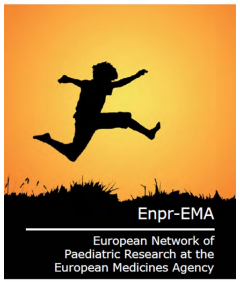
Pediatric Advisory Committee (PAC)

- Beginning on September 27, 2007, during the 18-month period beginning on the date a labeling change is made pursuant to subsection (g), the Secretary shall ensure that all adverse event reports that have been received for such drug (regardless of when such report was received) are referred to the Office of Pediatric Therapeutics. In considering such reports, the Director of such Office shall provide for the review of such reports by the Pediatric Advisory Committee, including obtaining any recommendations of such committee regarding whether the Secretary should take action under this chapter in response to such reports
- First safety presentation to the PAC on June 12, 2003
- To date, there have been 506 products presented to the PAC for safety review
- The first web posting of safety reviews was done on September 12, 2016
- To date, there have been 135 product reviews posted to the web
  - CDER = 105
  - CBER = 14
  - CDRH = 16

International Pediatric Therapeutic Development – Pediatric Cluster

- Established in 2007
- At least monthly informal discussions between regulators, which currently includes FDA, EMA, Health Canada, Japan's PMDA and Australia's TGA
- September 2007 through October 2019, 149 teleconferences with discussion of 537 products and 177 general topics (e.g. safety concerns pertaining to a product class) and, since October 2012, completion of 38 Common Commentaries
- Frequently discussed issues include scope of pediatric development, safety, trial design and study population
- Convergence on approaches have been achieved for 72% of the issues discussed in the past 3 years

Collaborative International Pediatric Therapeutic Development



Medical Product Development: Incorporating Patient Input

- Patient-Focused Drug Development Program Staff in CDER are the liaison for the Externally-Led Patient-Focused Drug Development Program using the FDA-Led Patient Focused Drug Development Public Meetings as a model https://www.fda.gov/industry/prescription-drug-user-fee-amendments/externally-led-patient-focused-drug-development-meetings
- Patient Affairs Staff in the Office of the Commissioner coordinate the Patient Listening Sessions https://www.fda.gov/patients/learn-about-fda-patient-engagement/patient-listening-sessions
- Advancing the Development of Pediatric Therapeutics (ADEPT 6): Pediatric Clinical Trial Endpoints for Rare Diseases with a Focus on Pediatric Patient Perspectives – November 12, 2019

Pediatric Extrapolation

- 1994: Final Regulation: Pediatric Labeling Rule
- "A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted"
- Efficacy may be extrapolated from adequate and well-controlled studies in adults to pediatric patients if:
  - The course of the disease is sufficiently similar
  - The response to therapy is sufficiently similar
- Dosing cannot be fully extrapolated
- Safety cannot be fully extrapolated

Summary

- Children are protected through research, not from it
  - Successes to date are noteworthy but we must continue to move forward and improve
- FDA's role
  - Ensure protection of human subjects during all phases of therapeutics development
  - Review adequacy of data to support approval of therapeutics
  - Promote collaboration to increase the availability of approved therapies for children
- Scientific and regulatory advances have broadened the types, collection methods, and analyses of data that can be used to support approval of products for use in children
- All the stakeholders play an important role in the development of safe and effective therapies for children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