

The Current State of Pediatric Drug Development

Lynne Yao, M.D.
Director, Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
U.S. FDA
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Disclosure Statement

- I have no financial relationships to disclose relating to this presentation
- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

Pediatric Drug Development

General Principles

- Pediatric patients should have access to products that have been appropriately evaluated
- Product development programs should include pediatric studies when pediatric use is anticipated

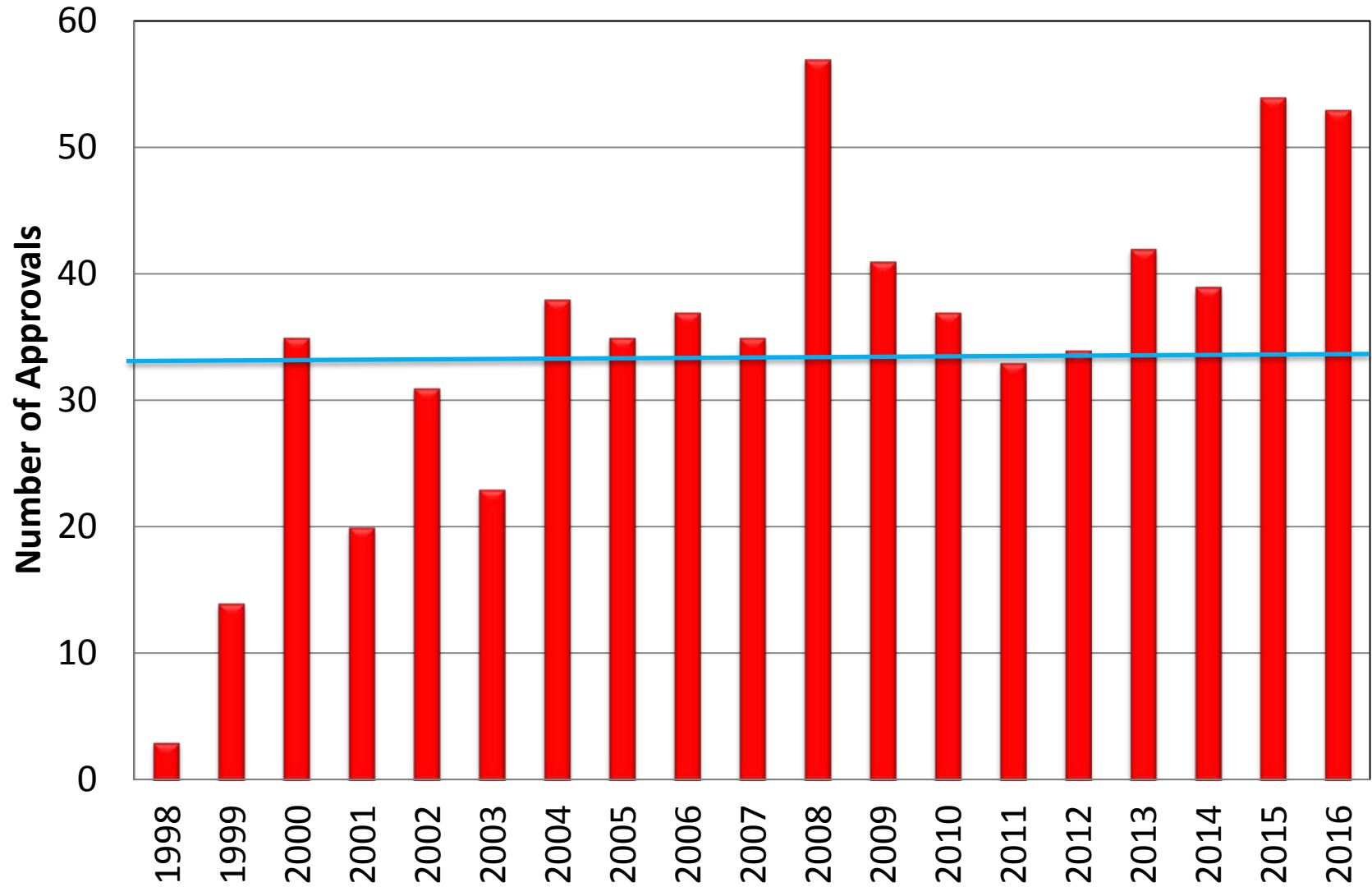
From FDA guidance to industry titled *E11 - Clinical Investigation of Medicinal Products in the Pediatric Population*, December 2000



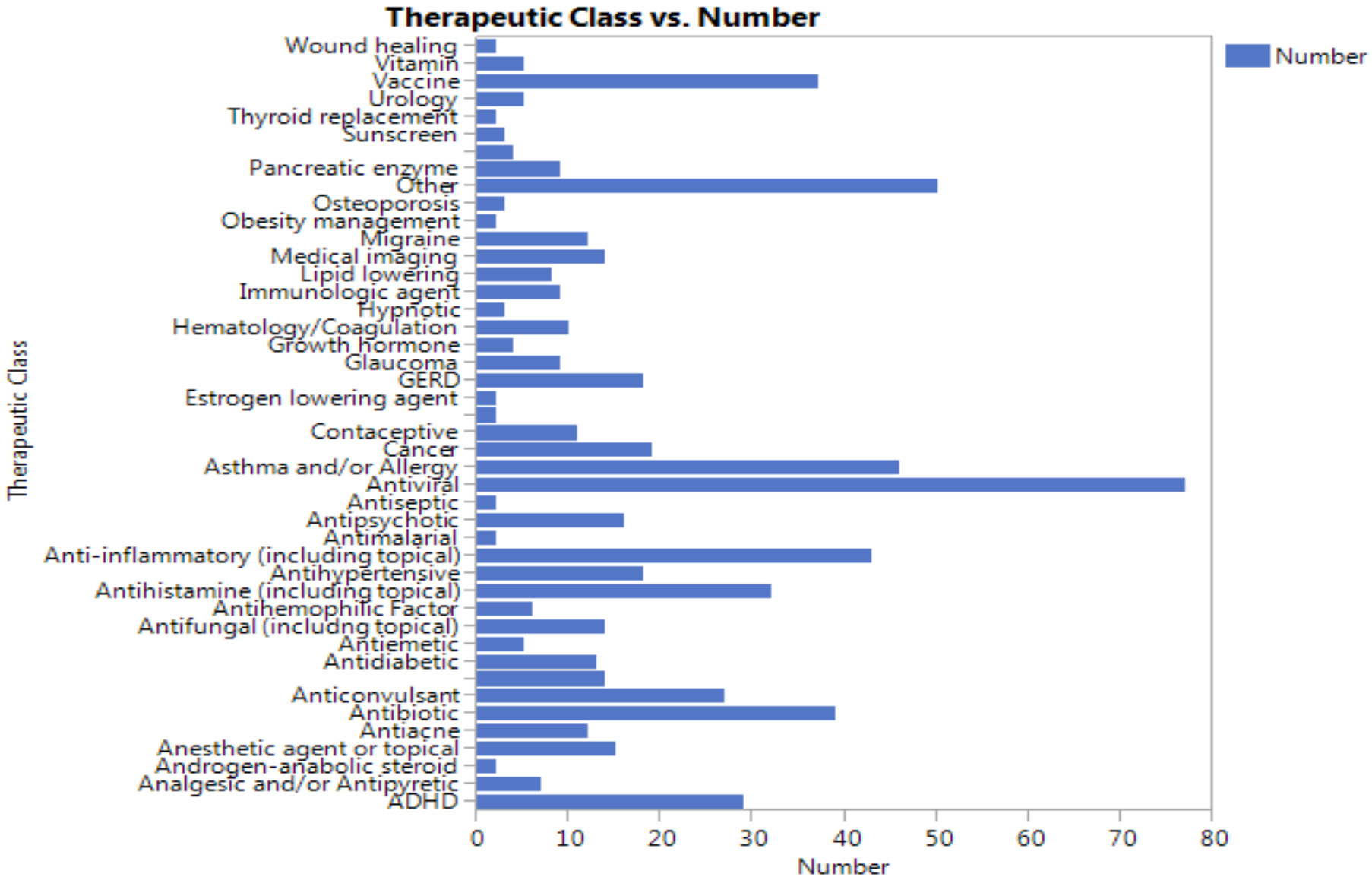
U.S. Pediatric Drug Development Laws

- Best Pharmaceuticals for Children Act (BPCA)
 - Section 505A of the Federal Food, Drug, and Cosmetic Act
 - Provides a financial incentive to companies to voluntarily conduct pediatric studies
 - FDA and the National Institutes of Health partner to obtain information to support labeling of products used in pediatric patients (Section 409I of the Public Health Service Act)
- Pediatric Research Equity Act (PREA)
 - Section 505B of the Federal Food, Drug, and Cosmetic Act
 - Requires companies to assess safety and effectiveness of certain products in pediatric patients
 - Products for indications that have received orphan designation are exempted from requirements under PREA

Pediatric Labeling Changes 1998-2016



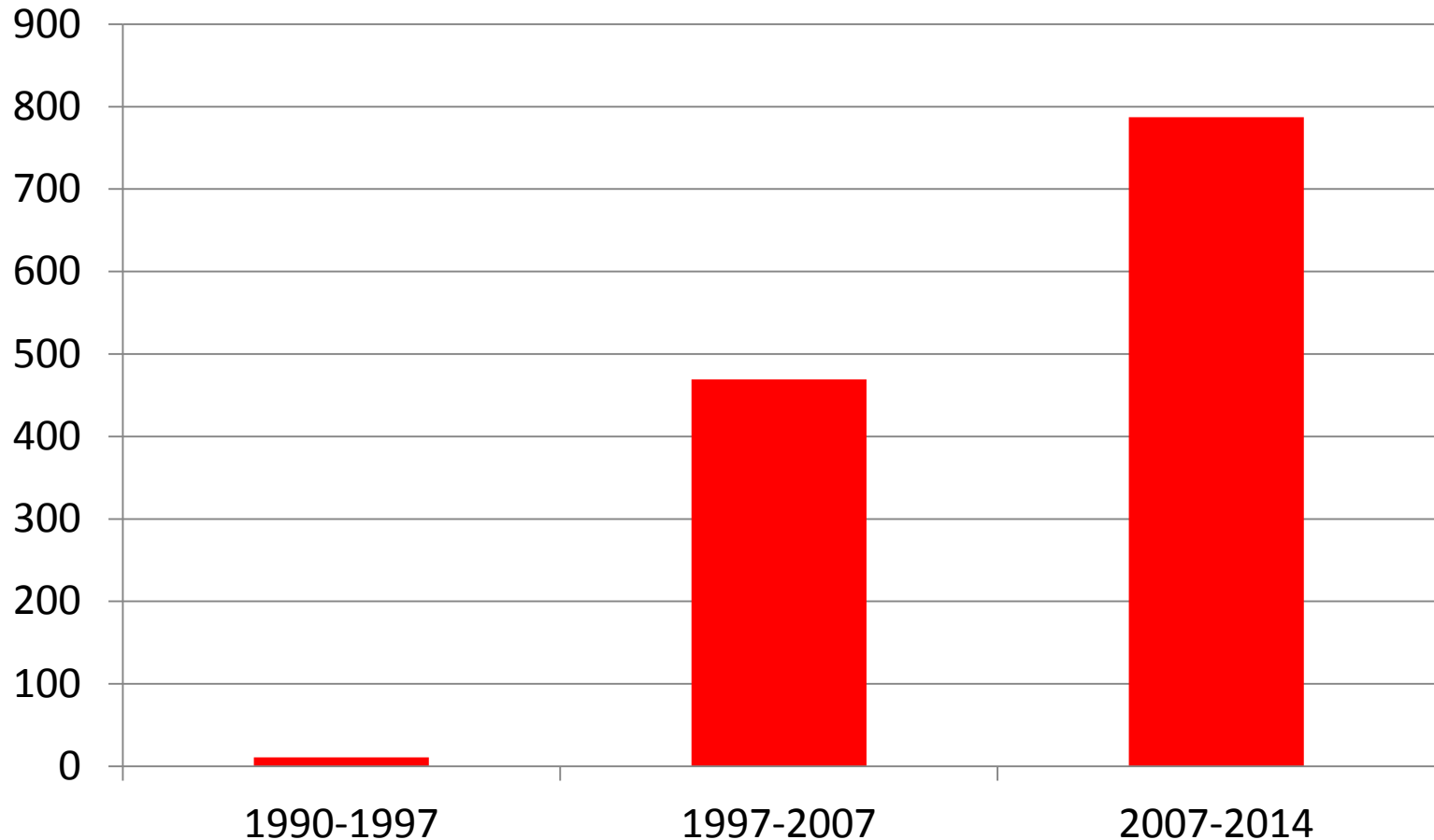
Pediatric Labeling Changes by Indication



Number of Studies Completed under BPCA and PREA



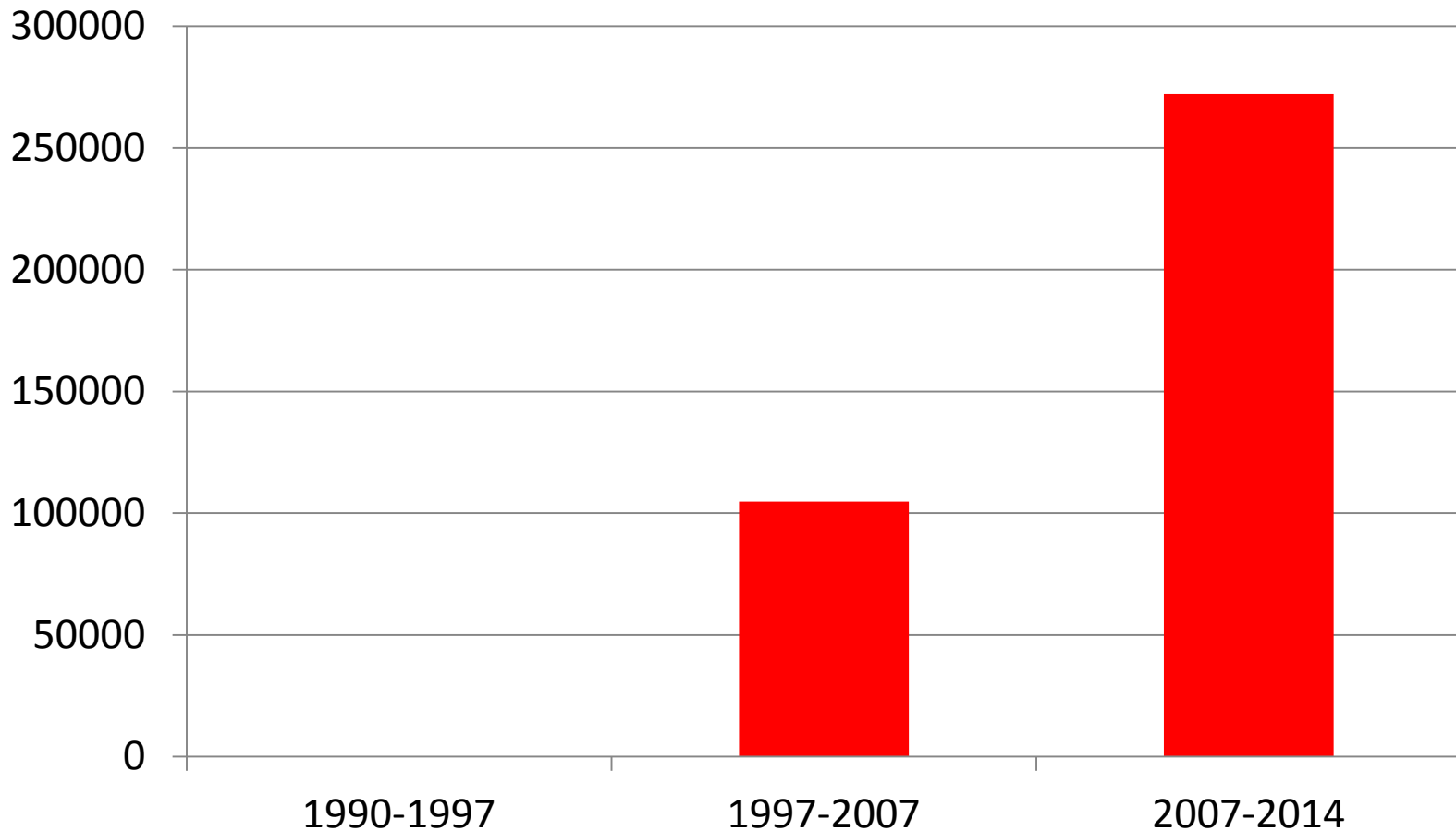
Number of clinical studies



Number of children enrolled in trials under BPCA and PREA



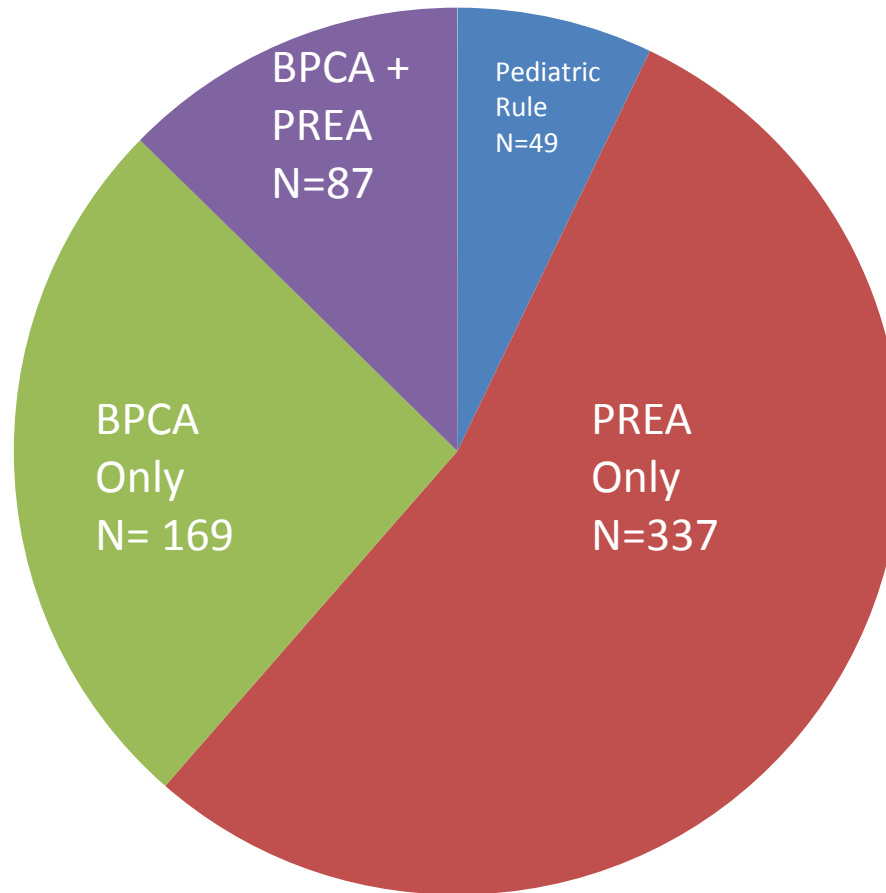
Estimated number of children enrolled in clinical trials



Pediatric Labeling Changes 1998-2017



N=699



Pediatric Product Development in 2017



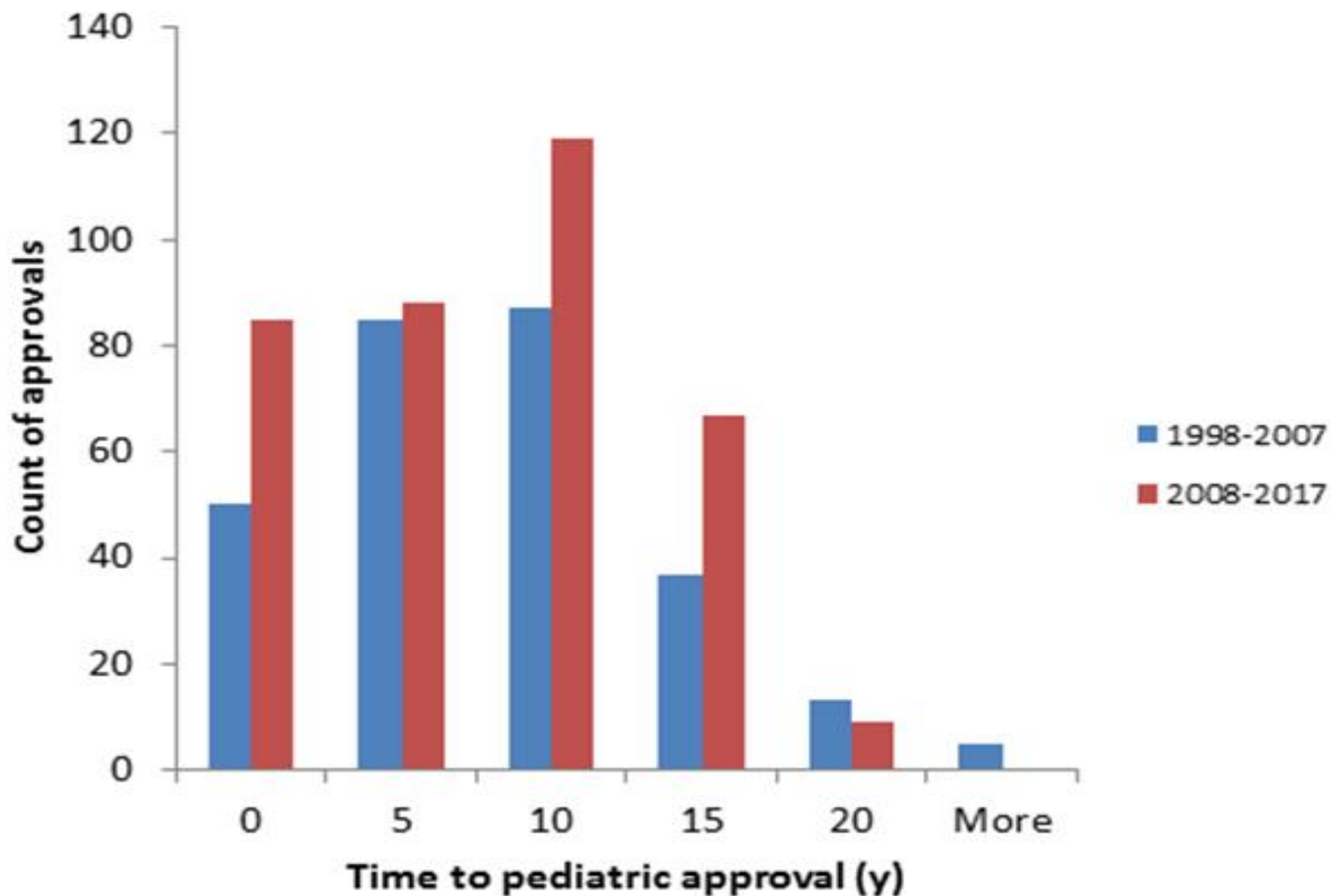
- Pediatric Product Development matured
- Increased experience and understanding of
 - Pediatric clinical trial design
 - Pediatric extrapolation
 - Pediatric formulations



Challenges in the 21st Century

- BPCA and PREA work together to accomplish goal of obtaining adequate pediatric efficacy and safety data for labeling
- Still time between adult approval and incorporation of pediatric information in labeling is substantial
- Pediatric-specific diseases
 - Neonates and premature infants
 - Cancer and Genetic diseases

Time to pediatric approval



Addressing Challenges

- Pediatric Extrapolation
- Innovative Clinical Trial Designs
- Real World Evidence
- Clinical Trial Networks
- Global Alignment

Innovative Clinical Trial Designs



- Improved framework for Pediatric Extrapolation
 - Review of evidence to support similarity of disease and response to therapy
 - Review of evidence needed to fill gaps in understanding
- Bayesian Strategies Applied to Pediatric Trials
- Use of Modeling and Simulation to Optimize the data already available to inform future clinical trials

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

Extrapolation and Bayesian Approaches



- Bayes' theorem is a method for calculating the validity of a hypothesis based on the best available evidence (e.g., observations, data, other information)
- Evidence (prior information) may include:
 - Adult Trial Data
 - Same disease with same treatment
 - Different population
 - Similar Pediatric Trial Data
 - Similar population
 - Same disease with similar treatment
 - Different indication with same treatment
 - PK/PD Data
 - Same population with same disease under same treatment
 - Different endpoint

Review of Prior Information



- Clinical input on whether prior information is reliable
- Similarity
 - Population
 - Baseline characteristics and demographic information
 - Disease progression
 - Baseline disease characteristics
 - Placebo information
 - Treatment effect (both disease and MOA)
 - Treatment group information
- Uncertainty regarding the validity prior information can be accounted for in Bayesian statistical modeling
- Sometimes Bayesian modeling will allow for fewer patients in a clinical trial but not always

Extrapolation and Modeling



- Modeling and Simulation
 - Clinical Pharmacology
 - Clinical Trial
 - Statistical
- Confidence in modeling depends on multiple factors
 - Quality and quantity of data used
 - Accuracy of assumptions made
- Does not replace the need for clinical trials but may increase efficiency
 - Confirmation of the assumptions requires clinical data
- Bayesian Modeling Applied to Pediatric Trials
 - Is a tool that make use of, or borrows, prior information in pediatric trials
 - Provides a formal approach for incorporating prior information into the planning and the analysis of the next study

Extrapolation and Modeling



- Modeling and Simulation strategies are not a replacement for extrapolation, but can be used to support an extrapolation approach
- Bayesian statistical modeling is NOT the same as Pharmacometric modeling and simulation
- Modeling and Simulation strategies can increase efficiency of product development
- Modeling and Simulation strategies must be tested and confirmed with clinical data

Extrapolation: The Next Chapter



- Pediatric extrapolation can be used to maximize the efficiency of pediatric product development while maintaining important regulatory standards for approval
- FDA continues to review assumptions about the acceptability of pediatric extrapolation approaches based on new knowledge gained.
- Use of innovative approaches to review assumptions and predict responses may further increase efficiency but these assumptions and predictions must be confirmed with clinical data
- Dosing and safety data relevant to applicable pediatric populations must always be collected

International Collaboration



- The US and EU now have permanent legislation that mandates plans for pediatric medical product development
- FDA and EMA to regularly share information related to the development of pediatric drug products.
- Monthly Pediatric Cluster Conference
 - European Medicines Agency (EMA); Japan Pharmaceuticals and Medical Devices Agency (PMDA); Health Canada (HC); Australia Therapeutic Goods Administration (TGA)
- Current ICH E11 guideline addendum completed
 - Updates on several topics including extrapolation, modeling and simulation, ethics, formulations
- New ICH guideline on Pediatric Extrapolation

FDARA Highlights

- PREA
 - Any original application for a new active ingredient that is intended for the treatment of an adult cancer and is directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer will be subject to PREA in 3 years
 - Must submit investigations that yield clinically meaningful pediatric study data
 - PREA will apply to orphan designated products as described above
 - FDA must publish a list of molecular targets and a list of automatic waivers for molecular targets within 1 year. The list should be developed in consultation with internal and external experts
 - FDA must convene a public meeting within 1 year to discuss plans for implementation
 - FDA must issue final guidance within 2 years
- BPCA
 - FDA is now required to respond to a sponsor's proposed pediatric study request (PPSR) within 120. FDA had previously maintained an internal goal date to respond within 120 days
 - The Pediatric Review Committee must review inadequate PPSR letters

Pediatric Product Development in the 21st Century



- Children are protected through research, not from it
 - Successes to date are noteworthy but we must continue to move forward and improve
- Commitment and collaboration to increase availability of safe and effective treatments for pediatric patients
- Advances in understanding of pediatric product development
 - Advancements in scientific and clinical knowledge of pediatric diseases and therapeutics
 - Increased understanding in design and conduct of pediatric clinical trials
 - Changes in regulatory requirements for pediatric product development
 - Better understanding of complexities related to pediatric product development
- FDA committed to working with external stakeholders to improve efficiency of pediatric clinical trials

Thank You