FDA and BPCA

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

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 requirie also 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
- **1990** Institute of Medicine holds workshop regarding the lack of labeling for pediatric drugs
- **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 505**A** 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. Biological products not eligible. Creates Office of Pediatric Therapeutics. 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

U.S. Pediatric Drug Development Laws

- Best Pharmaceuticals for Children Act (BPCA)
  - Section 505A of the Federal Food, Drug, and Cosmetic Act
  - Provides an incentive in the form of marketing exclusivity to companies to **voluntarily** conduct pediatric studies for therapies with potential public health benefit in children
  - 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
  - PREA does not apply to any drug for an indication for which orphan designation has been granted
- **Goal of both programs is to increase the number of approved therapies for children**

PREA vs. BPCA

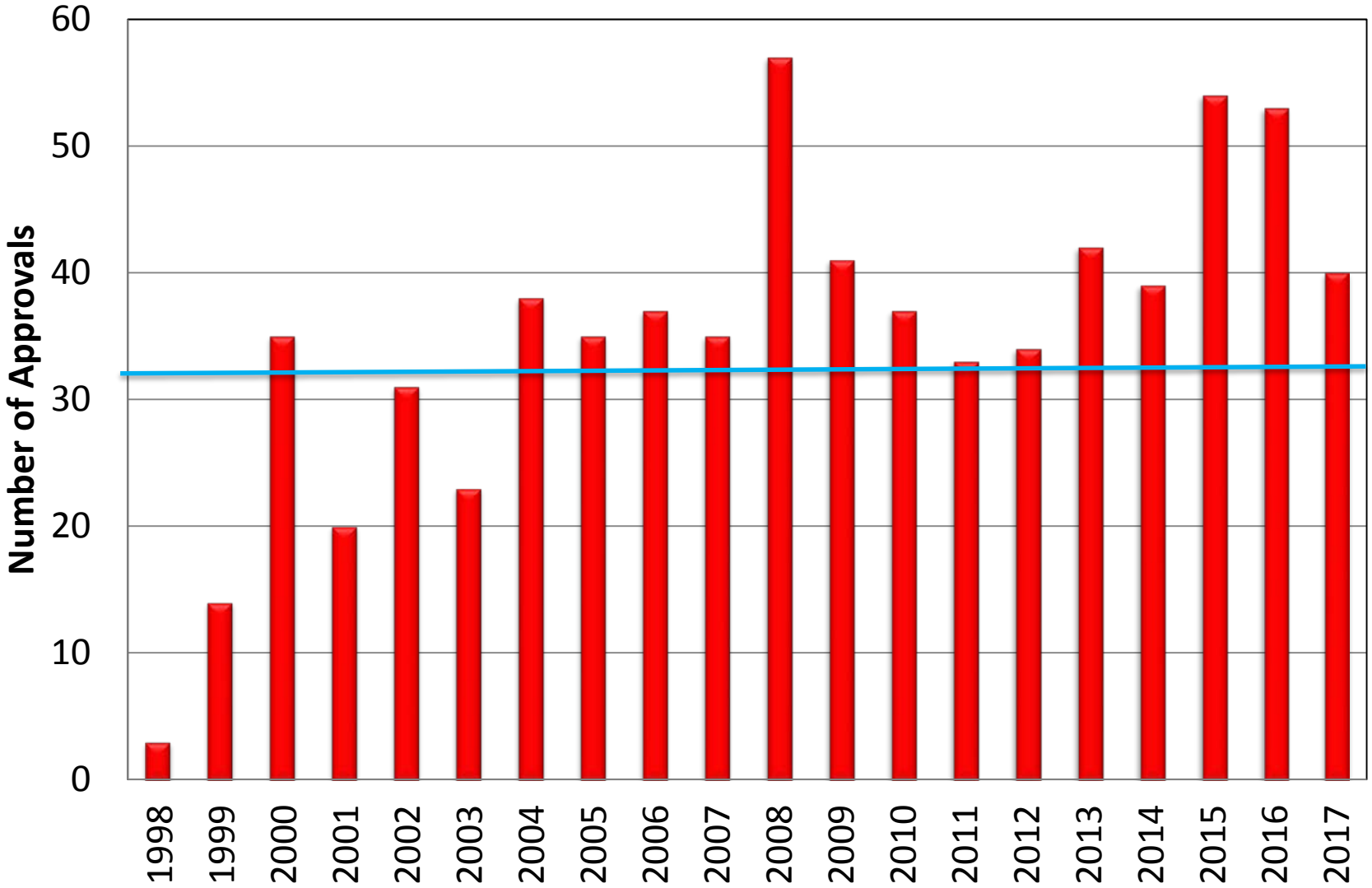
PREA

- Drugs and biologics
- **Required** studies
- Studies may only be required **for approved indication(s)**
- Orphan drug exemption (with exception of molecular targets for cancer)
- Pediatric studies must be labeled

BPCA

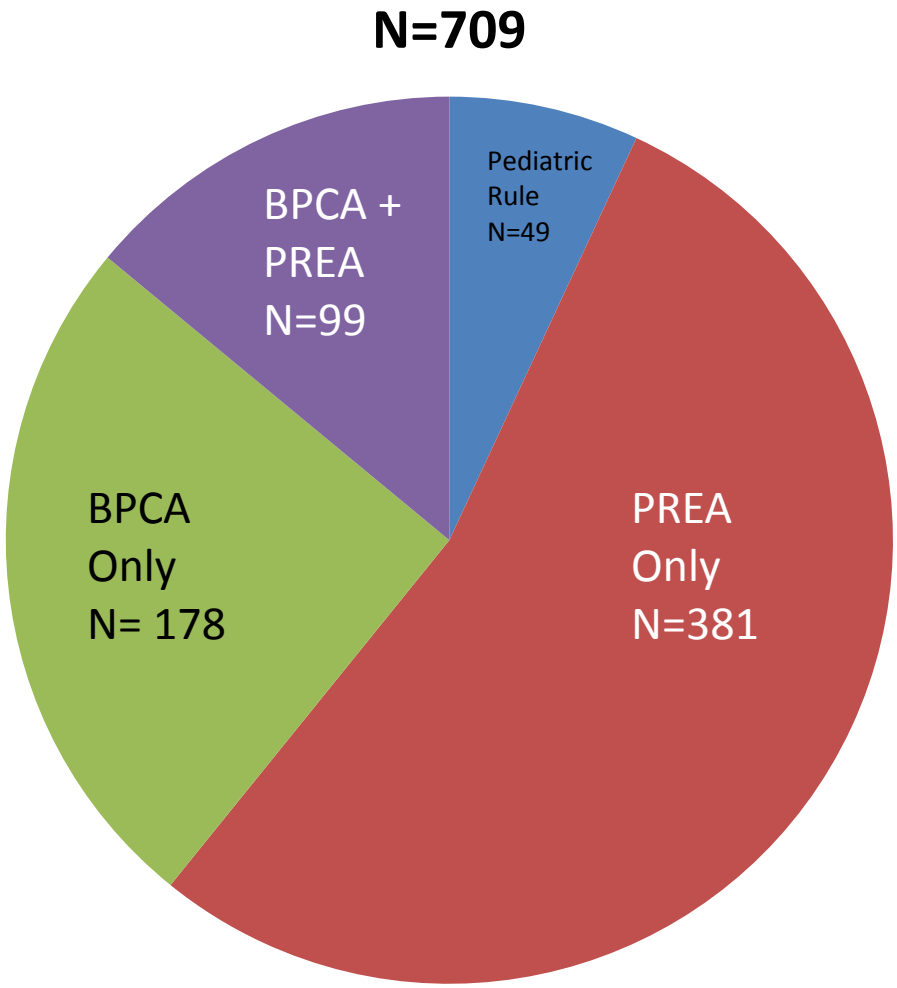
- Drugs and biologics
- **Voluntary** studies
- Studies relate to entire moiety and **may expand indications**
- Studies may be requested for products with orphan designation
- Pediatric studies must be labeled

Pediatric Labeling Changes 1998-Current*



* Through September, 2017

Pediatric Labeling Changes 1998-Current



U.S. Evidentiary Standard for Approval

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

Differences in Regulatory Approval Paths

- Pediatric patients are considered a distinct population from adults
  - Historically viewed as “little adults”
  - Differences in metabolism, development, ontogeny of organ systems
  - Efficacy can be different
  - Dosing and safety must be established
- Pregnant patients are still considered to be adults
  - Efficacy established in non-pregnant patients supports efficacy in pregnancy
  - Dosing and safety may be different
- **Approval pathway for drugs in pediatric and pregnant patients is different**

Research Gaps

- Pregnant patients have access to an approved therapy once the product is approved in adults
  - Exception is for drugs intended to treat a pregnancy-specific indication or condition (e.g., eclampsia,
- Need for additional information on dosing and safety in pregnant and lactating patients
- Safety information
  - Can this information be collected outside a larger controlled trial in non-pregnant patients?
  - Can big data sources or real-world evidence be used?
- Dosing information
  - Can this information be collected outside a larger controlled trial in non-pregnant patients?
  - Are there opportunities for modeling and simulation to aid in obtaining this information?
- Development of pregnancy-specific pharmacodynamic markers may be important for both safety and dosing
- Development of *in silico, in vitro,* and animal models may also be considered

Conclusions and Recommendations

- Goal of BPCA and PREA is to increase the number of approved therapies for children
- ***Goal of this task force is to identify gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women***
- Collection of data to provide adequate information to support the appropriate dose and safety of drugs used during pregnancy is a critically important public health issue
  - Use of novel methodologies, including model-informed drug development, opportunistic PK studies, and sources of big data may be leveraged
  - Inclusion of pregnant women in clinical trials should also be considered
- Use of legislative mandates to collect information to address these gaps is premature
- Any legislative or regulatory changes should be considered only ***after*** the appropriate scientific strategies for collection of needed data are established