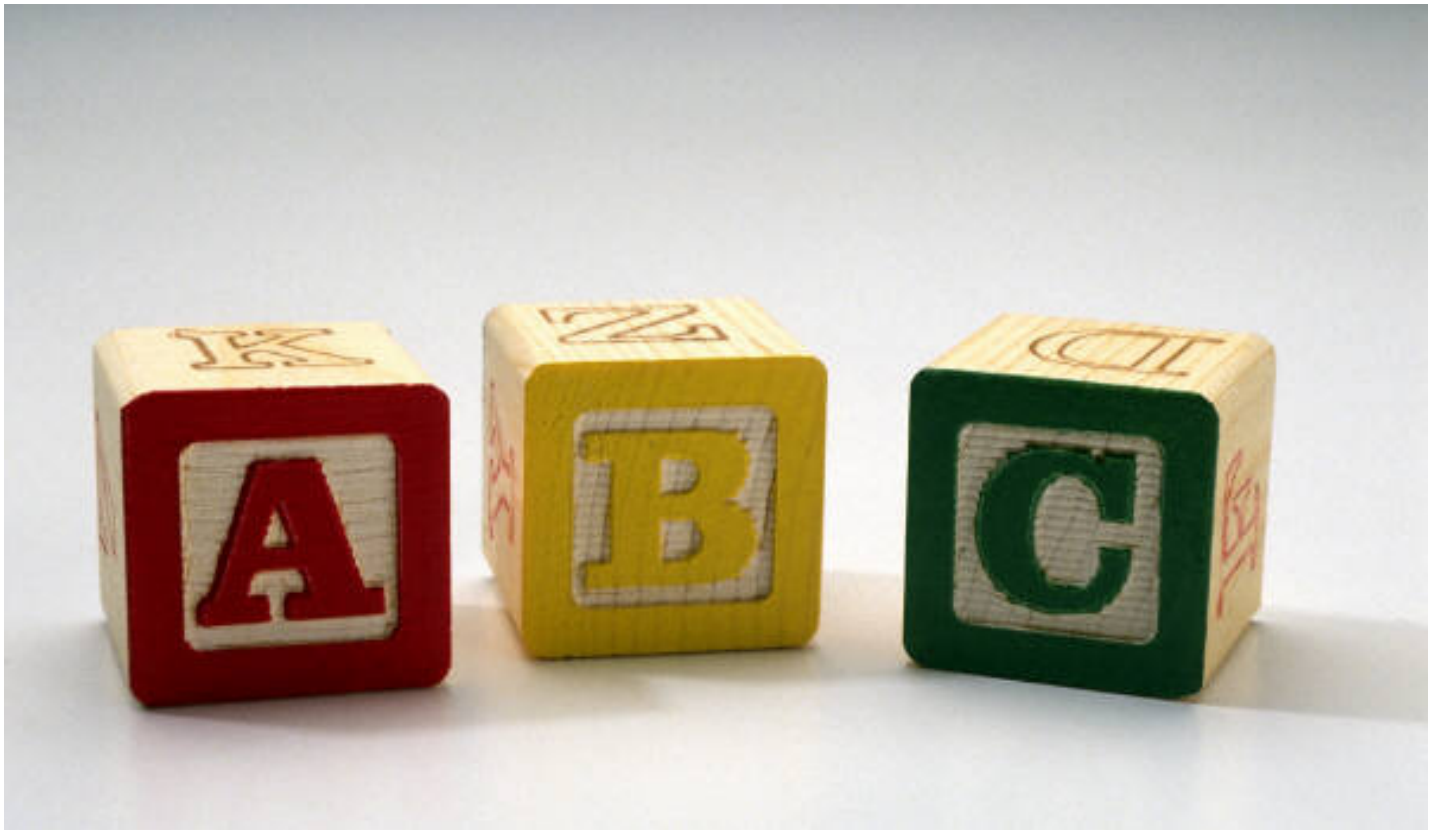
Pediatric Drug Regulation

Mona Khurana, MD
Pediatric Team Leader
Division of Pediatric and Maternal Health (DPMH)
Office of Drug Evaluation IV (ODE IV)
Office of New Drugs, CDER, FDA

Outline

- Define pediatric population
- Benchmark pediatric drug legislation
  - Pediatric Research Equity Act
  - Best Pharmaceuticals for Children Act
  - FDA Reauthorization Act

Who Are Pediatric Patients?



Regulatory Definitions: Pediatrics

- Prescription drug/biologic labeling regulations
  - Birth to 16 years of age inclusive [21 CFR 201.57(c)(9)(iv)]
- 2007 Pediatric Medical Device Safety and Improvement Act
  - Birth to 21 years [Section 303(E)(i)]
- Additional Safeguards for Children: 21 CFR 50 Subpart D
  - "Persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted" [21 CFR 50.3(0)]

Pediatric Drug Legislation Benchmarks

1997	Food and Drug Modernization Act
2002	Best Pharmaceuticals for Children Act
2003	Pediatric Research Equity Act
2010	Patient Protection and Affordable Care Act
2012	FDA Safety and Innovation Act
2017	FDA Reauthorization Act

1997 Food and Drug Modernization Act (FDAMA)

- Allowed FDA to issue a Written Request (WR) outlining studies needed for a specific drug for one or more indications
  - Could grant 6 months marketing exclusivity to sponsor who completes these studies

Pediatric Drug Legislation

- 2002 Best Pharmaceuticals for Children Act (BPCA)
  - Awards financial incentive to companies that **voluntarily** conduct FDA-requested pediatric studies of a drug for all indications which could provide health benefit
- 2003 Pediatric Research Equity Act (PREA)
  - **Requires** companies to assess safety and effectiveness of new drugs/biologics in pediatric patients for same indication being developed or approved in adults
- 2010 Patient Protection and Affordable Care Act
  - Extended financial incentive outlined under BPCA to biologics
- 2012 FDA Safety and Innovation Act (FDASIA)
  - Permanently reauthorized BPCA and PREA

PREA Requirements

PREA Requirements

- Gave FDA authority to require a **pediatric assessment**
  - Data gathered from pediatric studies using appropriate formulations to assess safety and efficacy and to support dosing and administration of a drug or biological product in all relevant pediatric subpopulations for same indication(s) being sought in adults – unless requirement is waived or deferred
- Requires companies to develop age-appropriate formulation to conduct required studies but does **not** require companies to market the formulation
- Provides specific criteria for when study requirements could be waived
- Do not apply to products granted orphan designation

PREA: Study Requirements

Pediatric study requirements under PREA apply whenever the product being developed contains any of the features:

- New indication
- New dosage form
- New dosing regimen
- New route of administration
- New active ingredient

PREA: Initial Pediatric Study Plan (iPSP)

- Statement of intent describing planned or ongoing pediatric studies (e.g., PK/PD, safety, efficacy) that will comprise the pediatric assessment
- Should address development of age-appropriate formulation if applicable
- Must contain timeline for study(ies) completion

PREA: Initial Pediatric Study Plan (iPSP)

- Must be submitted
  - Within 60 days of end-of-phase 2 meeting; OR
  - No later than 210 calendar days before planned submission of marketing application
- Must be reviewed and agreed upon by FDA
- Agreed iPSP must be included in NDA, BLA, or supplemental application
  - Failure to include could be refuse-to-file issue

PREA: Deferrals

- Sponsors may request deferral of some or all of assessment until a specified date after adult approval
  - Drug/biologic is ready for approval in adults before pediatric studies are completed; OR
  - Pediatric studies should be delayed until additional safety or effectiveness data have been collected; OR
  - There is another appropriate reason for deferral (e.g., scientific issues exists regarding study design or endpoints)
- Include evidence justifying deferral request in iPSP

PREA: Waivers

Sponsors may request full (all pediatric ages) or partial (subset of pediatric population) waiver of required assessments:

1. Necessary studies are impossible or highly impracticable; OR
2. Evidence strongly suggests the drug/biologic would be ineffective or unsafe; OR
3. Drug/biologic does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used by a substantial number of pediatric patients; OR
4. Reasonable attempts to produce a pediatric formulation necessary for that age group have failed (partial waiver only)

PREA: Timelines

- Based on when sufficient information available to support dosing and preliminary safety and NOT tied to adult approval
- Formulation development and juvenile toxicology studies can begin while adult studies are ongoing
- Consider enrolling pediatric patients in adult program
  - Experience with active moiety or class
  - Approval of product or ongoing trials for another pediatric indication

PREA: Post-Marketing Requirements

- FDA grants deferral and waivers requested in an Agreed iPSP during review of marketing application
- FDA issues post-marketing requirements (PMRs) under PREA for deferred pediatric studies
  - Final protocol submission date
  - Study completion date
  - Final study report submission date

https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

PREA: Non-Compliance Letters

- Sent to sponsors who have failed to:
  - Submit their pediatric assessments required under PREA by the final study report submission due date
- Publicly posted: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm343203.htm
  - 31 letters have been posted as of October 15, 2018

BPCA Incentive Provisions

BPCA: Written Request (WR)

- Authorizes FDA to issue WR requesting a company voluntarily conduct pediatric studies for all approved and unapproved indications for which active moiety may have health benefit in pediatric patients
  - Can be issued for on and off-patent products
- Legal contract between sponsor and FDA
- WR are publicly posted
  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049997.htm

BPCA: WR Process for On Patent Drugs

- Sponsor can submit a Proposed Pediatric Study Request (PPSR) to OND Review Division seeking a WR from FDA
  - Address every indication applicable to pediatric patients
  - Propose studies in all appropriate age groups
- FDA can issue Inadequate Letter outlining deficiencies

2012-2017: 27 Inadequate Letters and 19 WR/year

2017-2018: 35 Inadequate Letters and 20 WR

BPCA: WR Process for Off Patent Drugs

- Established partnership between FDA and NIH to conduct studies on older, off-patent drugs to inform pediatric labeling
- Request must be issued to all application holders
  - If declined by all holders of an application, NIH may complete studies
- The process for submission, review and labeling of studies submitted by NIH is unique and outlined under section 409I of BPCA

BPCA: Financial Incentive

- Sponsors who complete the requested studies as outlined in the WR may be awarded additional 6 months of marketing exclusivity (**pediatric exclusivity**)
  - Attaches to all existing marketing exclusivities and patents for the active moiety
  - Does not require positive pediatric studies

Pediatric Review Committee (PeRC)

- Established by legislation to carry out the activities described under PREA and BPCA
- Intended to increase the consistency of implementation of provisions of PREA and BPCA across FDA
- Committee membership
  - Required to have expertise in Pediatrics, Neonatology, Pediatric Ethics, Biopharmacology, Statistics, Chemistry, and Law
  - Appropriate expertise pertaining to the product under review

2017 FDA Reauthorization Act (FDARA)

- BPCA
  - Earlier discussion of PPSRs and WRs with sponsors
  - Earlier issuance of WRs (e.g. during IND phase for serious, life-threatening diseases)
  - New requirement to respond to PPSRs and requests to amend WR's within 120 days
  - New requirement for PeRC to review inadequate PPSRs
  - Reauthorized off patent process through 2022
- PREA
  - New requirement to establish and publish a list of oncology molecular targets and a list of automatic waivers for those targets

2017 FDARA

- Requires evaluation of molecularly targeted drugs and biologics "intended for treatment of adult cancers and directed at a molecular target substantially relevant to growth and progression of a pediatric cancer"
- Eliminated orphan exemption of PREA study requirements for cancer drugs directed at relevant molecular targets
  - iPSPs, deferrals, waivers, and extrapolation of data all apply to these investigations
  - Pediatric study(-ies) of dosing, safety and preliminary efficacy to inform potential pediatric labeling

1983 Orphan Drug Act (ODA)

- Incentivizes sponsors to develop drugs for rare diseases and conditions
- Pediatric subpopulation designation
  - FDA historically granted orphan designation to drugs for indications with US prevalence > 200,000 in total population but < 200,000 in pediatric population
    - Pediatric UC, pediatric HIV
  - No longer necessary to promote pediatric studies
  - Created unintended loophole by exempting these sponsors from conducting required studies under PREA
  - 2017 draft Guidance conveys FDA's intent to no longer grant this designation unless drug meets other criteria

Pediatric Drug Legislation

PREA

- Drugs and biologics
- **Mandatory** studies
- Requires studies **only for indication(s) under review or being developed in adults**
- Does **not** apply to orphan indications
- Pediatric studies must be labeled

BPCA

- Drugs and biologics
- **Voluntary** studies
- Studies relate to entire active moiety and **may include other indications**
- Studies **may be requested** for orphan indications
- Pediatric studies must be labeled

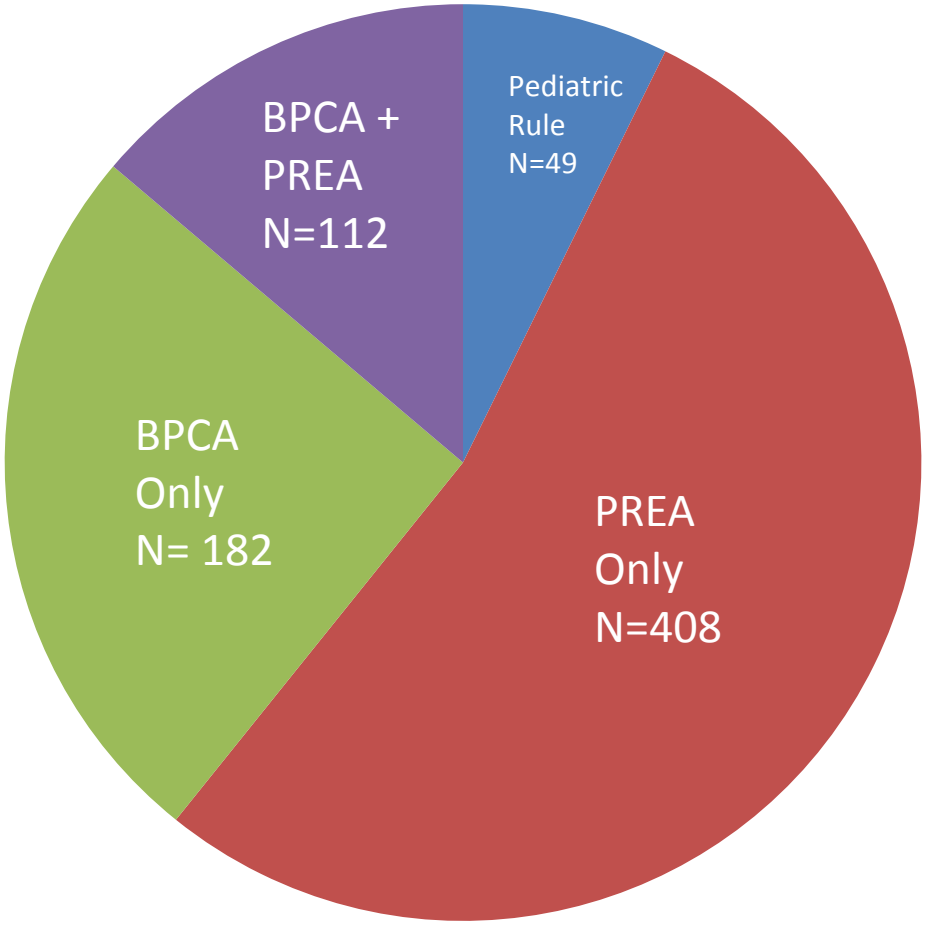
Ultimate Goal of PREA and BPCA

New Pediatric Labeling

to encourage appropriate use of drugs and biologics to treat pediatric patients

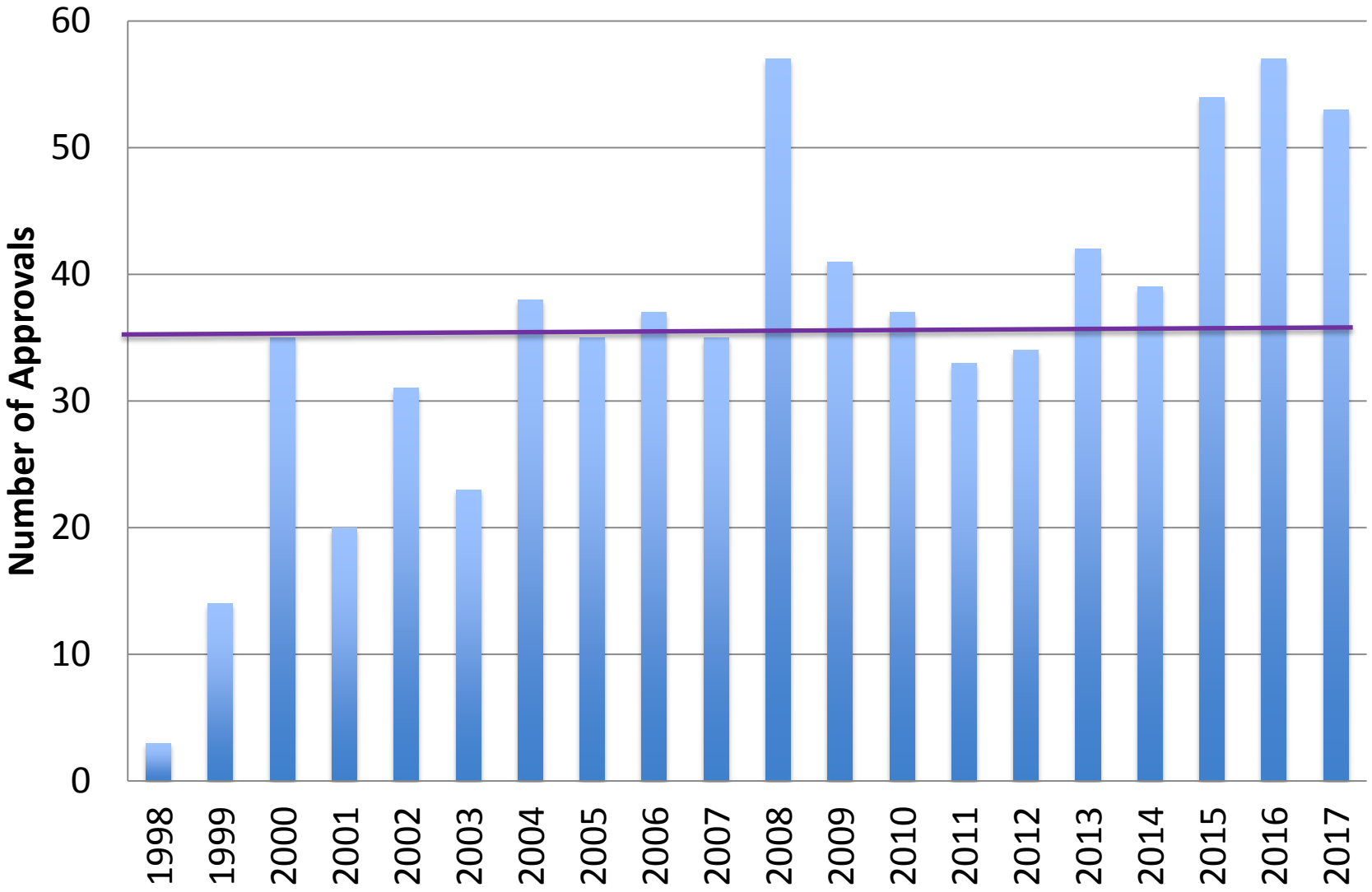
Pediatric Labeling Changes

N=751 as of October 12, 2018



New Pediatric Information Labeling Database accessed 10/12/18:
https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase

Pediatric Labeling Changes 1998- 2017



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Thank You!