Regulatory Landscape for Pediatric Drug Development Including Extrapolation

Food and Drug Administration (FDA) and
University of Maryland - Center of Excellence in Regulatory Science and Innovation (M-CERSI)
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Carolyn L. Yancey, MD
Senior Clinical Reviewer, Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
U. S. FDA

Disclosure Statement

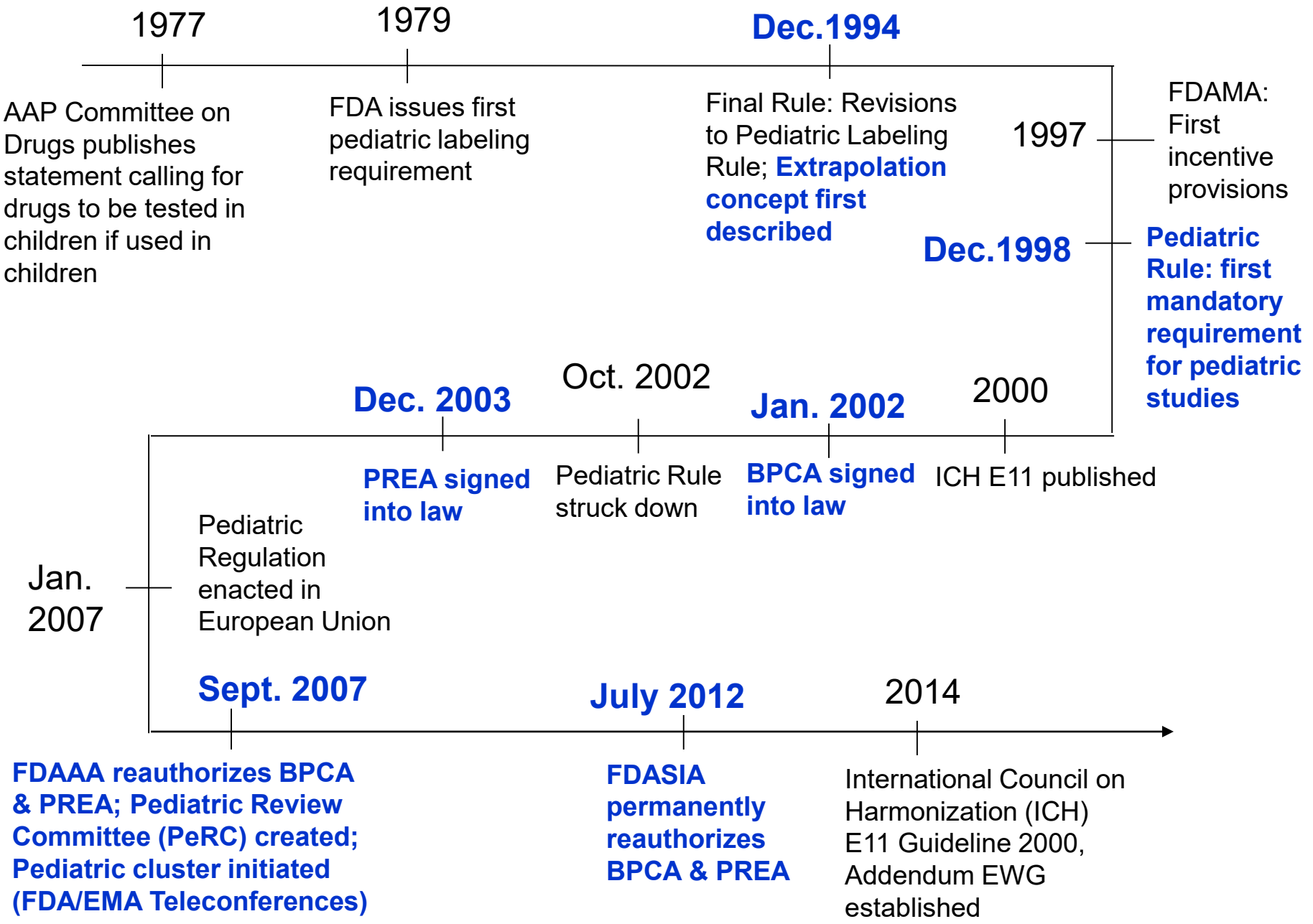
- I have no financial interests or conflicts of interest with any pharmaceutical company to disclose relating to this presentation.

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Agenda

- Historical Timeline - Pediatric Drug Development
- U. S. Standards for Product Approval
- Special Considerations for Pediatric Drug Development
- Legislation on Pediatric Drug Development
  - Best Pharmaceuticals for Children Act (BPCA)
  - Pediatric Research Equity Act (PREA)
- An initial Pediatric Study Plan (iPSP)
- Pediatric Extrapolation
  - Similarity in disease and response to treatment
  - Pharmacokinetics
  - Extrapolation and Bayesian statistical approach
- Summary

History of Pediatric Drug Development



U. S. Evidentiary Standard of Approval

- A product approved for children must demonstrate substantial evidence of clinical benefit/effectiveness
  - Clinical benefit:
    - Improvement or delay in progression of clinically meaningful aspects of the disease
  - Evidence of effectiveness:
    - Consists 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 labeling.
- Adequate safety information must be included in the application to allow for appropriate risk benefit analysis.

Special Considerations: Pediatric Drug Development

- **Ethical considerations**
  - Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults)
  - Absent the prospect of direct therapeutic benefit, the risks to which a child would be exposed in a clincial trial must be “low”
  - Ethical considerations do play a role in the need to correctly apply pediatric extrapolation
- **Feasibility considerations**
  - The prevalence and/or incidence of a pediatric condition is generally much lower compared to adult populations
  - Feasibility, alone, is not a scientific justification for use of extrapolation

Pediatric Drug Development Laws

- Best Pharmaceuticals for Children Act (BPCA)
  - Passed by Congress in 2002
  - Provides a financial incentive (marketing exclusivity) to pharmaceutical companies to voluntarily conduct pediatric studies by way of a Written Request (WR) issued by FDA.
  - Sponsors who "fairly meet" the terms of the WR may be eligible to receive 6 months of pediatric exclusivity on the moiety.

Pediatric Drug Development Laws

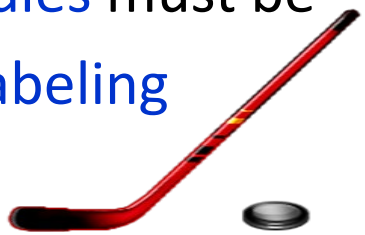
- Pediatric Research Equity Act (PREA)
  - Passed by Congress in 2003
  - Requires pharmaceutical companies to assess safety and effectiveness of certain products in pediatric patients (pediatric assessment)
  - PREA requirements do not apply to drugs or biologics with indications granted orphan designation

- Goal of both programs BPCA and PREA → increase the number of approved therapies for pediatric subjects

PREA versus BPCA

PREA

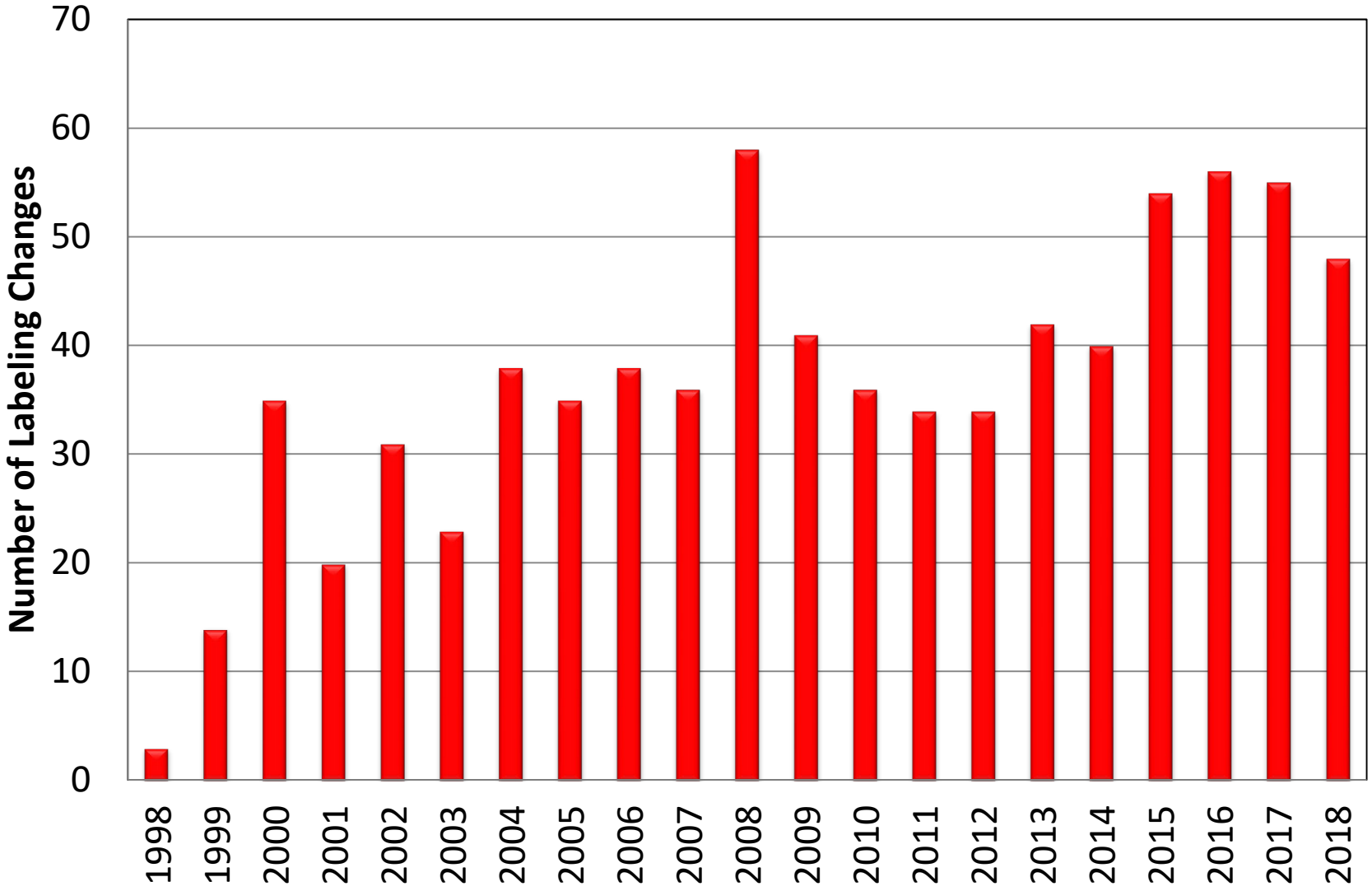
- Drugs and biologics
- Required studies
- Studies may only be required for approved indications
- Orphan designation/ indications are exempt from PREA required study
- Pediatric studies must be included in labeling



BPCA

- Drugs and biologics
- Voluntary studies
- Studies relate to the moiety and may expand pediatric indication(s)
- Studies may be requested via WR for products with orphan designation
- Pediatric studies must be included in labeling

BPCA and PREA Pediatric Labeling Changes 1998-2018



Applications subject to PREA

- A sponsor planning to submit a marketing application for a drug/biologic will be subject to PREA if one or more of the following are part of their application:
  - New active ingredient
  - New indication
  - New dosage form
  - New dosing regimen
  - New route of administration

initial Pediatric Study Plan (iPSP)

- Sponsors planning to submit a new drug application (NDA), biologics license application (BLA), or supplemental NDA/BLA subject to PREA need to submit an iPSP early in the clinical development process, i.e. within 60 days of the End-of-Phase 2 meeting with FDA.

- iPSP includes:
  - Criteria for plans to request a partial waiver, full waiver, and/or a deferral of required pediatric studies

iPSP Content

1. Overview of the Disease Condition in the Pediatric Population
2. Overview of the Drug or Biological Product
3. Overview of Planned Extrapolation of Effectiveness to Specific Pediatric Populations
4. Planned Request for Drug-Specific Waiver(s)
5. Plan to Request Deferral of Pediatric Studies
6. Tabular Summary of Planned Non-clinical and Clinical Studies
7. Age-Appropriate Formulation Development
8. Non-clinical Studies (juvenile animal studies)
9. Clinical Data to Support Design and/or Initiation of Studies in Pediatric Patients
10. Planned Pediatric Clinical Studies
    - 10.1 Pediatric Pharmacokinetic Studies
    - 10.2 Clinical Effectiveness and Safety Studies
11. Timeline of the Pediatric Development Plan
12. Agreements for Pediatric Studies with Other Regulatory Authorities

Guidance for Industry: Pediatric Study Plans: Content of and Process for submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans (dated March 2016)

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 FDA 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 → pediatric patients if the disease course and response to therapy (exposure-response) are sufficiently similar
  - Dosing cannot be fully extrapolated but can be supported by adult dosing data
  - Safety cannot be fully extrapolated though adult safety data may inform on reported risks

Disease Similarity and Response to Therapy

- The assessment is not a simple “yes or no”
- Quantitative assessment of differences between target and source population
  - Evidence of common pathophysiology and natural history
  - Similarity in response to treatment assessed by similar endpoints, mode of action, or biological pathway, experience with drugs in the same therapeutic class
- What assumptions or uncertainties exist in the assessment?
  - Quantity of evidence
  - Quality of evidence
- Degree of confidence in similarity of disease will affect the information needed to support efficacy

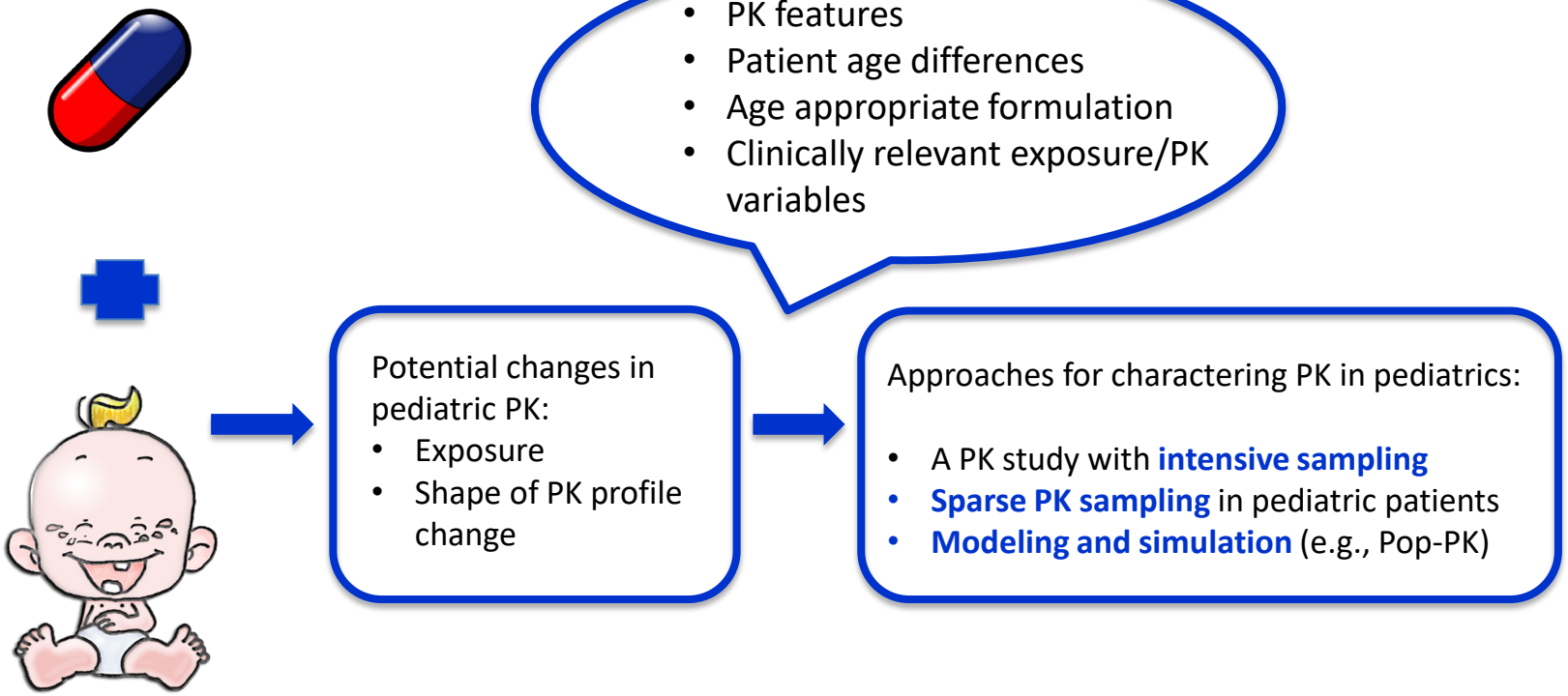
Prior Information

- Clinical input on whether prior information is reliable
- Similarity
  - Patient population
    - Baseline characteristics and demographic information
  - Disease progression
    - Baseline disease characteristics, morbidities over time
    - Placebo/active/historical control information
  - Treatment effect (disease and mechanism of action)
    - Treatment group information
- Uncertainty regarding the validity of 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 Bayesian Approach

- Bayesian Approach Applied to Pediatric Trials
  - Make use of or borrow prior information in pediatric trials
  - Provides a formal approach for incorporating prior information into the planning and analysis of the next study
  - Bayesian statistical modeling is not the same as pharmacometric modeling
- Prior information may include:
  - Adult Trial Data
    - Same disease with same treatment
    - Different population with same treatment
  - Similar Pediatric Trial Data
    - Similar population
    - Same disease with similar treatment
    - Different indication with same treatment
  - Pharmacokinetic (PK)/Pharmacodynamic (PD) Data
    - Same population with same disease under same treatment
    - Different endpoint(s)

Characterization of PK in Pediatrics



Value of PK in Pediatric Clinical Development

Drug Development

- **Efficacy Extrapolation based on PK-matching**
- **Dose Optimization using PK Information**
- **Clinical Trial Design based on PK in Pediatrics**

Research and Policy Development

- **Efficacy Extrapolation**
- **Joint Efficacy and Safety Trial with Adults**

FDA Experience - Pediatric Extrapolation

- Recent analysis of products with new pediatric labeling between 3/1/2009 - 12/31/2014
- Compared to FDA pediatric extrapolation publication (Dunne, et al.) with new pediatric labeling between 2/1/1998 - 2/2009

Extrapolation Category	Current Data Numbers of Products (%)	Dunne's Reference Numbers of Products (%)
Complete	53 (34)	24 (14)
Partial	46 (29)	113 (68)
No	58 (37)	29 (18)

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Summary

- Advances in our understanding of basic pathophysiology and natural history of disease are critically important
- Leverage efficacy in other disease conditions to understand exposure-response data in adults to explore applicability to pediatric disease
- Pediatric extrapolation:
  - can be used to maximize the efficiency of pediatric product development while maintaining important regulatory standards for approval
  - has matured over the last 20 years
  - increases our understanding of disease mechanisms and progression
- FDA continues to review assumptions about the acceptability of pediatric extrapolation approaches based on new knowledge gained

References

- *Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans (dated March 2016)* *http://www.fda.gov/downloads/Drugs/GuidanceComplianceREgulatoryInforamtion/Guidances/UCM360507.pdf*
- International Council on Harmonization Guideline, Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population, E11 (R1) dated August 2016 *www.ich.org/.../ICHProducts/Guidelines/.../E11/ICH_E11_R1_Step_2_25Aug2016*
- Drugs@FDA: FDA Approved Drug Products https://www.accessdata.fda.gov/scripts/cder/daf
- *Automatic Waiver List: Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics* *https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm*

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