Pediatric Drug Development: Successes and Challenges

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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

Special Considerations for Pediatric Product 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 a prospect of direct therapeutic benefit, the risks to which a child would be exposed in a clinical trial must be "low"
  - Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care
- Feasibility considerations
  - The prevalence and/or incidence of a condition is often much lower compared to adult populations

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

PREA vs. BPCA

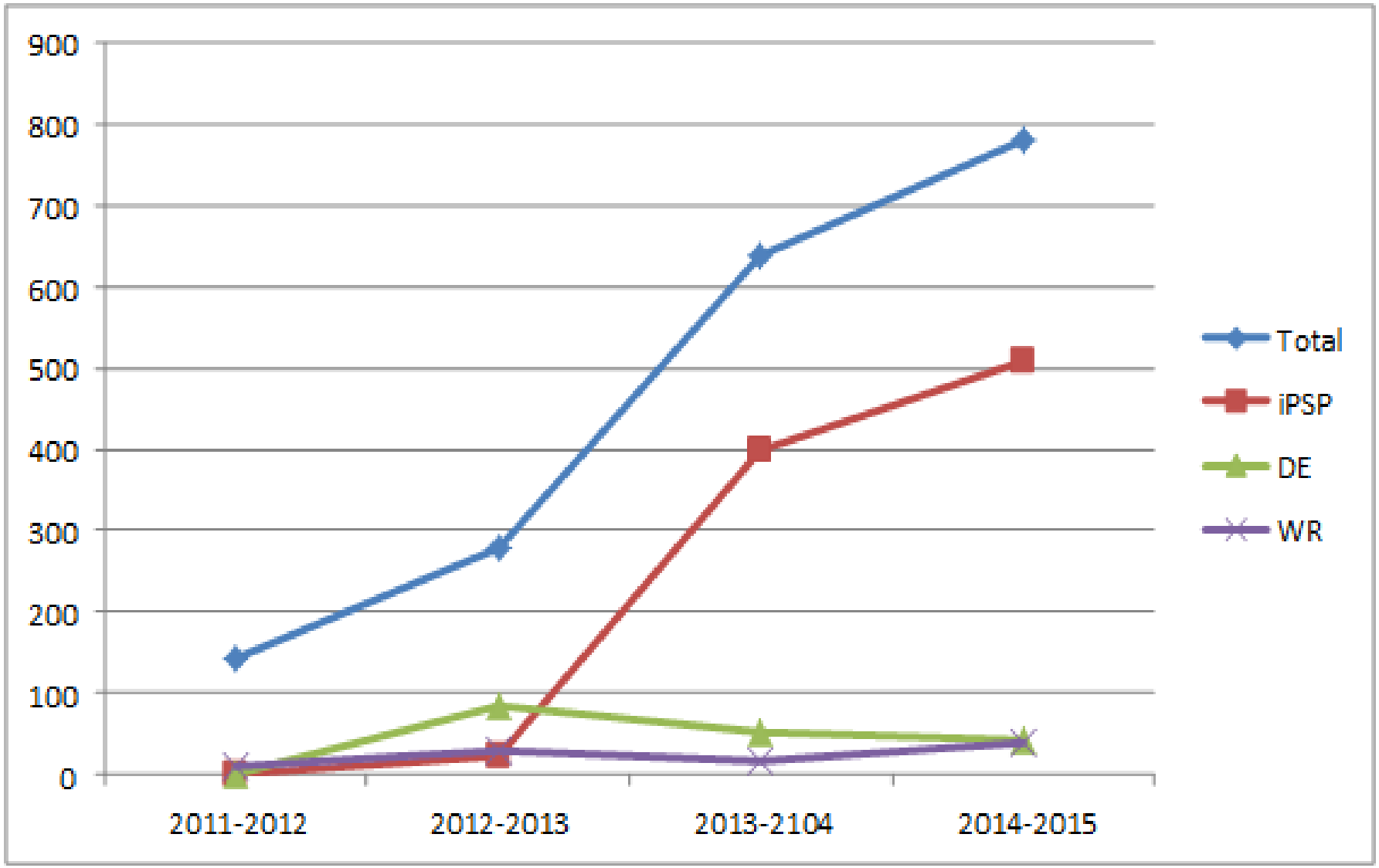
PREA

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

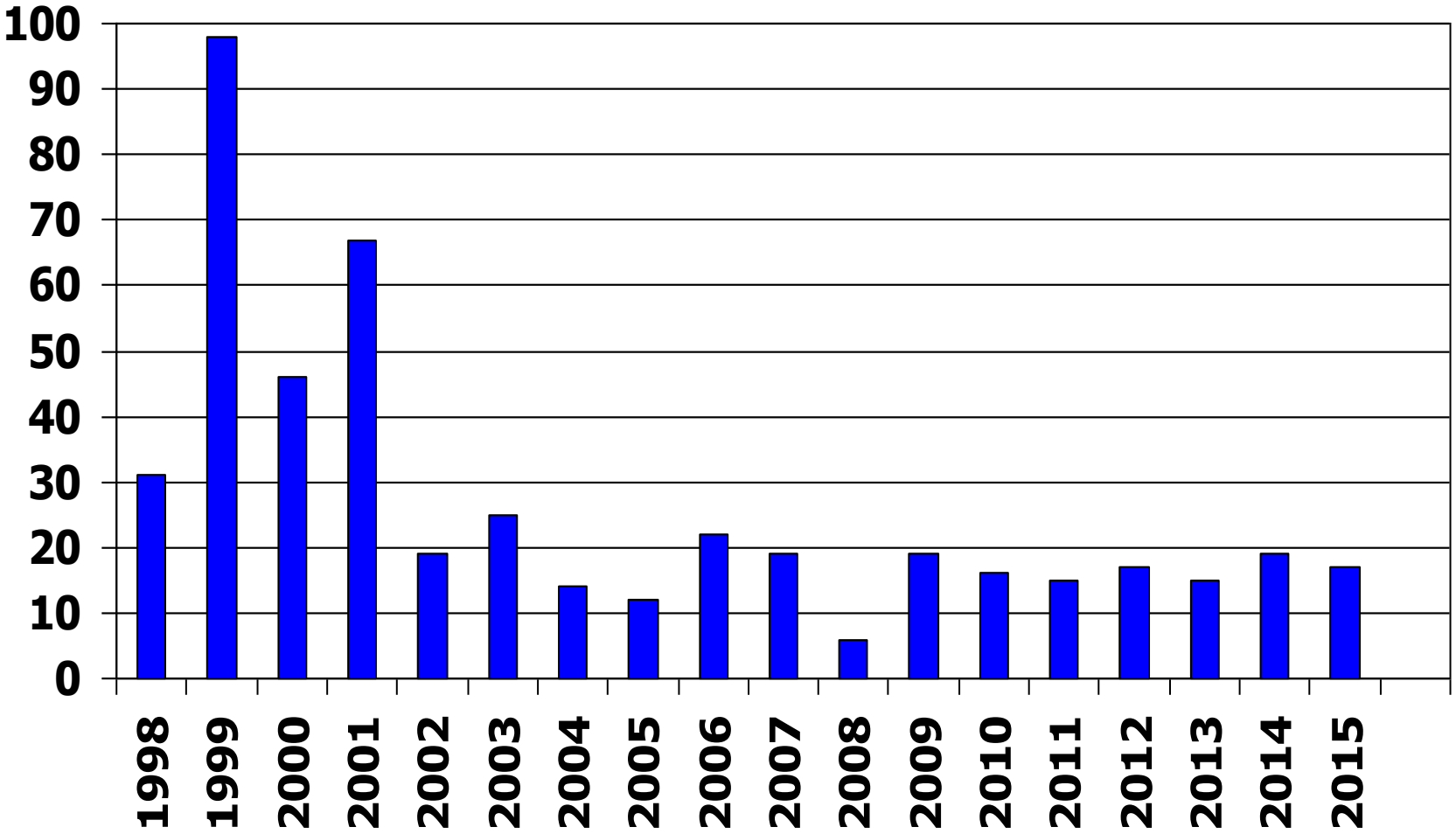
BPCA

- 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

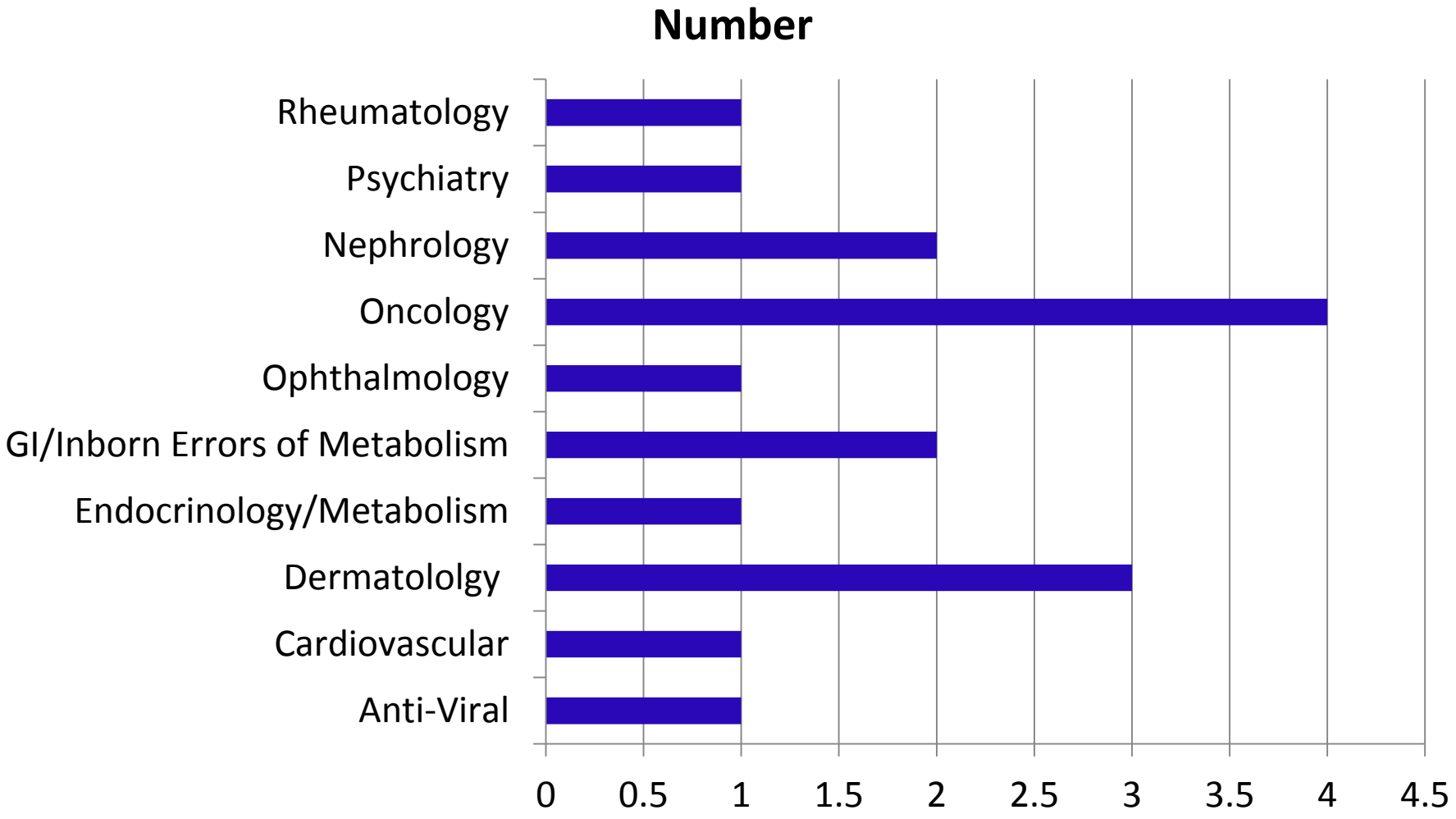
Pediatric Review Committee Activities



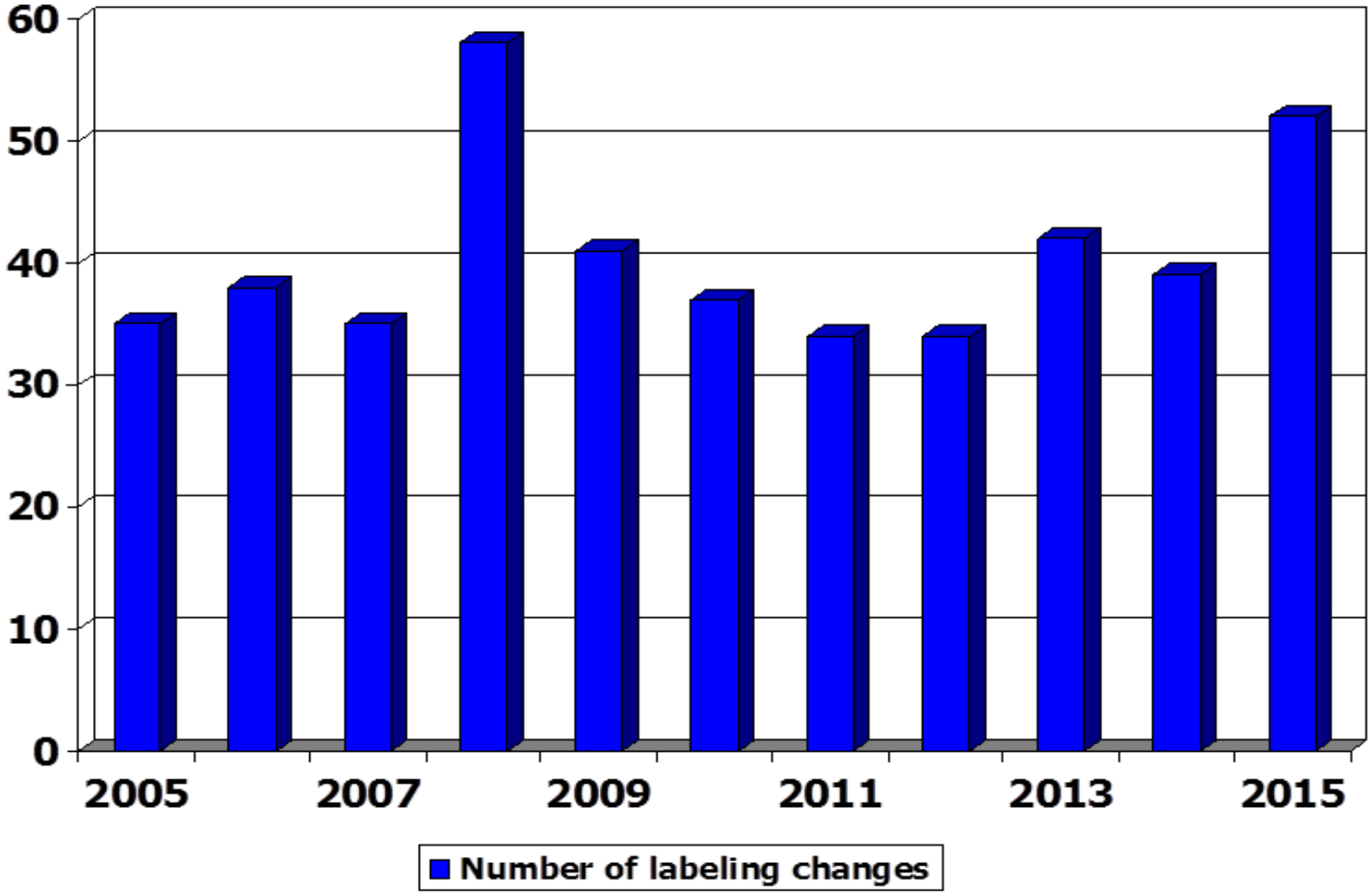
Written Requests Issued 1998-2015



Written Requests issued 2015



Pediatric Labeling Changes 2005-2015



Pediatric Product Development in 2016

- Pediatric Product Development matured
  - Over 600 products now labeled with pediatric-specific information
- Increased experience and understanding of
  - Pediatric clinical trial design
  - Pediatric extrapolation

Pediatric Extrapolation

- 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 of Approaches to Extrapolation 1998-2008

Extrapolation	Supportive Evidence Requested From Pediatric Studies	Products n/N (%)	New or Expanded Indication
None	Two adequate, well-controlled, efficacy and safety trials plus PK data.	19/166 (11)	7/19 (37)
	Oncology products only: sequential approach starting with phase 1/2. Do not proceed if no evidence of response.	10/166 (6)	3/10 (30)
Partial	Single, adequate, well-controlled, efficacy and safety trial (powered for efficacy) plus PK data.	67/166 (40)	35/67 (52)
	Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus PK data.	20/166 (12)	15/20 (75)
	Single exposure-response trial (not powered for efficacy) plus PK and safety data, PK/PD and uncontrolled efficacy plus safety data, or PK/PD plus safety data.	26/166 (16)	19/26 (73)
Complete	PK and safety data.	10/166 (6)	9/10 (90)
	Safety data only.	14/166 (8)	6/14 (43)

Review of Extrapolation

- First published review in 2011 based on 166 products with submitted pediatric studies between 1998-2008
- Recent review (just completed in 2016) based on 157 products with submitted pediatric studies between 2009-2014
  - Partial extrapolation decreased from 68% to 29%
  - Both Complete and "No" Extrapolation increased
- Changes in extrapolation based on:
  - Evolving science and knowledge from the pediatric trials that allow one to be more confident in assumptions
  - Failed pediatric trials and better understanding of the differences between adults and children
  - New science in the area of molecular or genetic biology

Challenges in the 21st Century

- Pediatric-specific diseases
  - Neonates and pre-term infants
  - Rare diseases, including pediatric cancers
- Long-term safety
  - Chronically administered drugs
  - Drugs administered during specific developmental periods
- Improving efficiency in pediatric product development
  - Coordinated global development programs
  - External and International collaborations
  - Clinical research networks
  - Innovate clinical trial designs

Pediatric Specific Diseases

- Pediatric Cancer
  - Traditionally understudied because PREA does not apply to many adult-only cancers
- Neonatal population
  - Only 35% of commonly used drugs in NICU are FDA approved*
  - Of 409 drugs with pediatric-specific labeling changes between 1997-2010, only 28 included information for use in neonates

*Hsieh EM et al., Medication Use in the Neonatal Intensive Care Unit Am J Perinatol 2014;31:811–822

Long-term Safety

- Pediatric long-term safety questions persist
- Many issues related to long-term safety of drugs used in children are unknown and not well studied
- Advancing Development of Pediatric Therapeutics (ADEPT)
  - ADEPT 1 held in June, 2014 discussed long-term bone health issues
  - ADEPT 2 held in April 2015 discussed evaluation of long-term neurocognitive and behavioral outcomes
  - ADEPT 3 held in April 2016 discussed long-term safety of drugs used in infants and children

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Strategies to Address Challenges

International Collaborations

- Monthly Pediatric Cluster Conference
  - European Medicines Agency (EMA); Japan Pharmaceuticals and Medical Devices Agency (PMDA); Health Canada (HC); Australia Therapeutic Goods Administration (TGA)
- ICH E11 (pediatrics) addendum
  - Updates on several topics including extrapolation, modeling and simulation, ethics

Pediatric Research Initiatives and Networks

- Critical path launched two pediatric network initiatives in 2014
  - International Neonatal Consortium (INC)
  - Pediatric Trials Consortium (PTC)—plan to advance to an independent non-profit (Institute for Advanced Clinical Trails for Children)
- European Research Network initiatives
  - European Network of Pediatric Research at EMA (Enpr-EMA)
  - GriP (Global Research in Paediatrics)
  - Consortium for Innovative Therapies for Children with Cancer (ITCC)
  - Paediatric European Network for Treatment of AIDS (PENTA)
  - UK Clinical Research Network (UK CRN)

Innovative Clinical Trial Designs

- Bayesian Modeling 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 the analysis of the next study
  - Bayesian statistical modeling is NOT the same as Pharmacometric modeling

Master Protocols

- One overarching protocol that includes one or more of the following:
  - Multiple diseases
  - Multiple treatments
  - Multiple molecular markers
- Master Protocols can increase efficiency of clinical trials
- Requires collaboration between academic investigators and/or industry sponsors with input from regulatory authorities

Pediatric Product Development in the 21st Century

- Children are protected THROUGH research, not from it
  - BPCA and PREA have led to incorporation of pediatric-specific labeling in over 600 products
- Commitment and collaboration to increase availability of safe and effective treatments for pediatric patients
- FDA committed to working with external stakeholders to improve efficiency of pediatric clinical trials
  - Extrapolation
  - Innovative clinical trial designs
  - Clinical trial networks