

American Course on Drug Development and Regulatory Sciences

Pediatric Drug Development Workshop

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University of California, San Francisco
Schools of Pharmacy and Medicine
Department of Bioengineering
and Therapeutic Sciences

Pediatric Drug Development : Moving Toward the Best Pharmaceuticals for Children

Presentation Developed By...

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Disclosures, Affiliations, and Acknowledgements

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- Debbie Avant, R.Ph.; Haihao Sun, M.D.; Jean Temeck, M.D.; Susie McCune, M.D.; Office of Pediatric Therapeutics, FDA
- Pamela L. Simpkins, MBA, Johnson and Johnson
- Dianne Murphy, M.D.

Disclosures

- 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



Harry C. Shirkey, M.D.

- Famous for the quote, “By an odd and unfortunate twist of fate, infants and children are becoming therapeutic or pharmaceutical orphans.”
 - Given at the Conference of Professional and Scientific Societies, Chicago, June 27-28, 1963 (sponsored by the Commission on Drug Safety, Chicago, Illinois).
- Born in 1916 in Cincinnati, Ohio
- Received a B.Sc. in Pharmacy from University of Cincinnati in 1939 and received his M.D. at the University of Cincinnati School of Medicine
- Lived in and was a noted pediatrician and pediatric pharmacologist
- Professor and Chairman, Department of Pediatrics, Tulane University School of Medicine

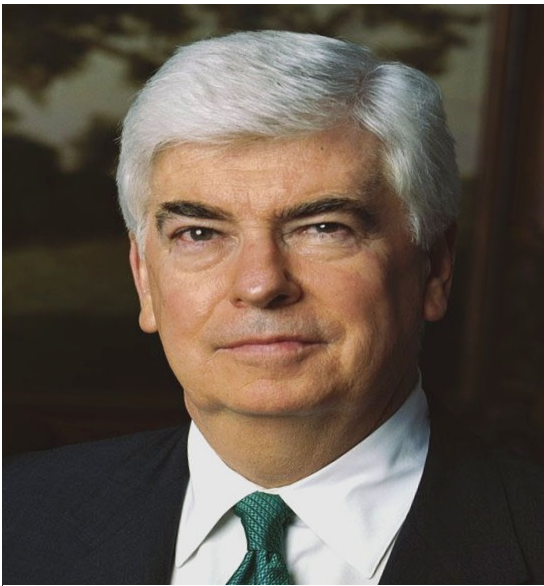
Harry C. Shirkey, M.D.

- Edited a textbook on Pediatric Therapy
 - First edition 1964-Sixth edition 1980
- Became medical director of the Children's Hospital in Birmingham Alabama in 1958
- Chair of Department of Pediatrics at Hawaii School of Medicine
- Returned to Cincinnati in 1997 and retired in 1984
- His body was donated after his death to the University of Cincinnati School of Medicine



Nancy Kassebaum

- Nancy Kassebaum, Republican senator from Kansas 1978-1997
- Introduced the “Better Pharmaceuticals for Children Act” in 1992, 1994, and 1996 but failed to pass each time
- First woman elected to a full term in the Senate without her husband having previously served in Congress
- Daughter of Alf Landon, Governor of Kansas, and Republican Presidential candidate in 1936 (lost in a landslide to FDR)
- Chair of the Senate Health, Education, Labor, and Pensions (HELP) Committee 1995-1997
- Strong advocate for children’s health issues
- Retired after completing her 4th term in the Senate in 1996



Chris Dodd, D-CT



Mike DeWine, R-OH



Jim Greenwood, R-PA



Henry Waxman, D-CA

Who are these men, and why are they all on the same slide?

Better Pharmaceuticals for Children Act

- Introduced in the Senate in 1997 by Chris Dodd and Mike DeWine
- Introduced in the House by Jim Greenwood and Henry Waxman
- Passed as part of FDAMA in November, 1997
 - Chris Dodd is now the CEO of the Motion Picture Association of America
 - Mike DeWine is now the Attorney General of the State of Ohio
 - Henry Waxman served from 1975-2015. Chose not to seek a 21st term in 2014
 - Jim Greenwood has been the President and CEO of BIO since 2004.



Hillary Rodham Clinton

- US Senator from New York from 2001-2009
- Originally introduced PREA in 2002 and passed out of committee but was not passed by the Senate
 - Hillary Clinton and Mike DeWine (R-OH) re-introduced the Pediatric Research Equity Act in March, 2003
 - Jim Greenwood, Anna Eshoo (D-CA), and Deborah Pryce (R-OH) introduce the legislation in the House of Representatives
- PREA passed both houses of Congress and became law on December 3, 2003.
- PREA should not to be confused with the Prison Rape Elimination Act, also passed by Congress and signed into law in 2003.

Pediatric Product Development in 2017

- Pediatric Product Development matured
 - 674 products now labeled with pediatric-specific information
- Increased experience and understanding of
 - Pediatric clinical trial design
 - Pediatric extrapolation
 - Pediatric formulations
 - Policies and practices developed under BPCA and PREA

How should success be measured?

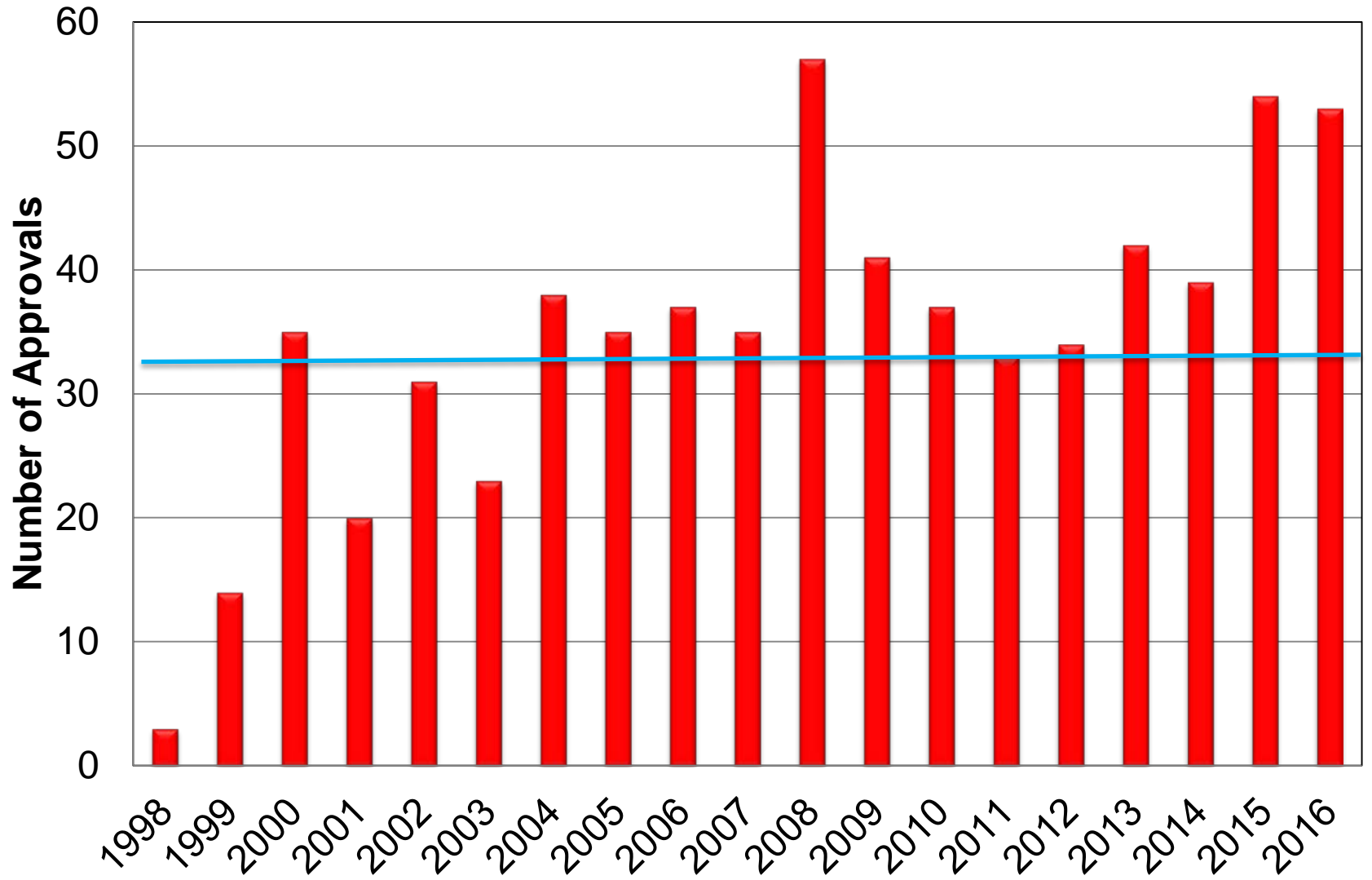
Number of labeling changes?

Number of pediatric patients in clinical trials?

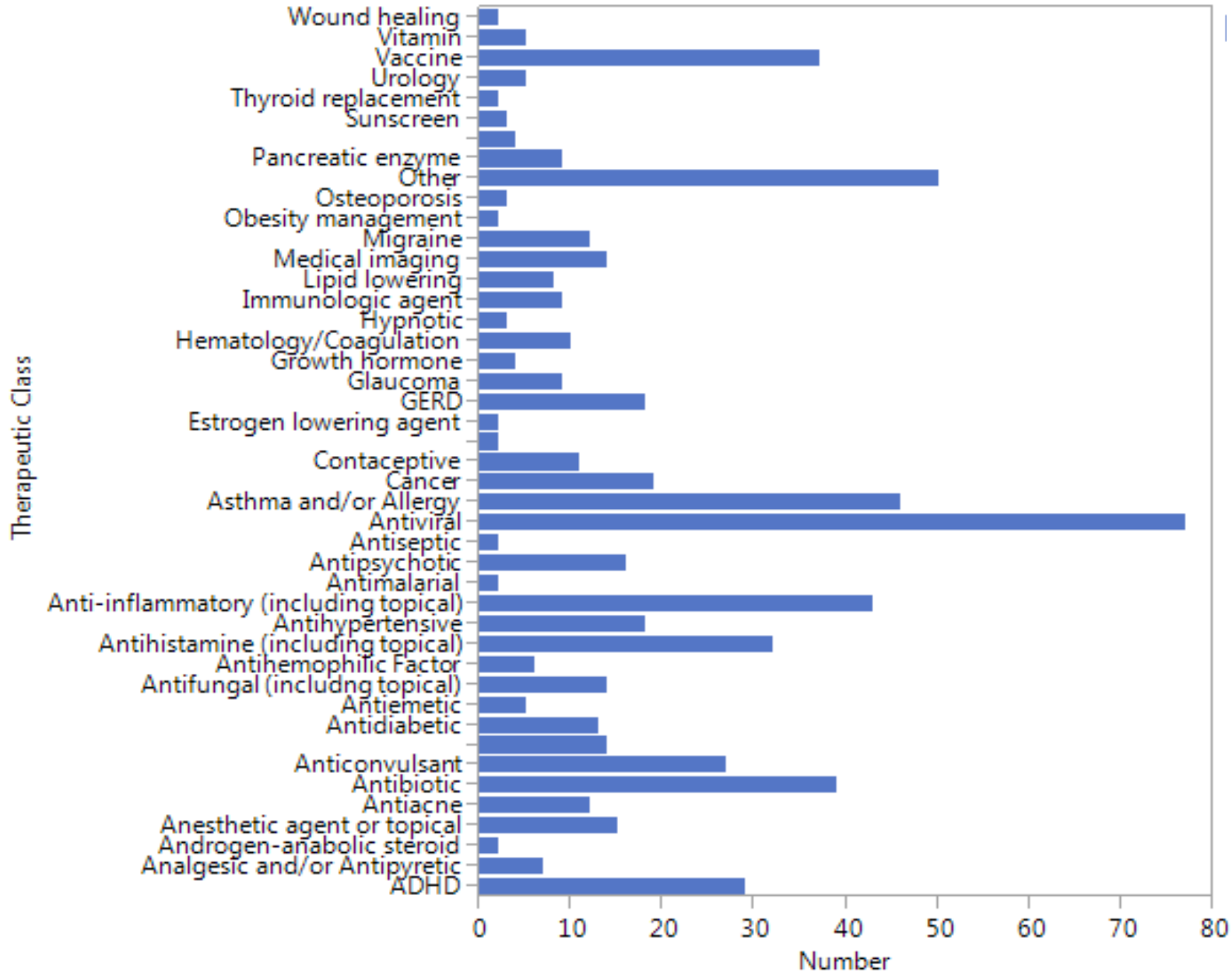
Number of studies completed under BPCA
and PREA?

Speed of time from original approval to
pediatric labeling?

Pediatric Labeling Changes 1998-2016

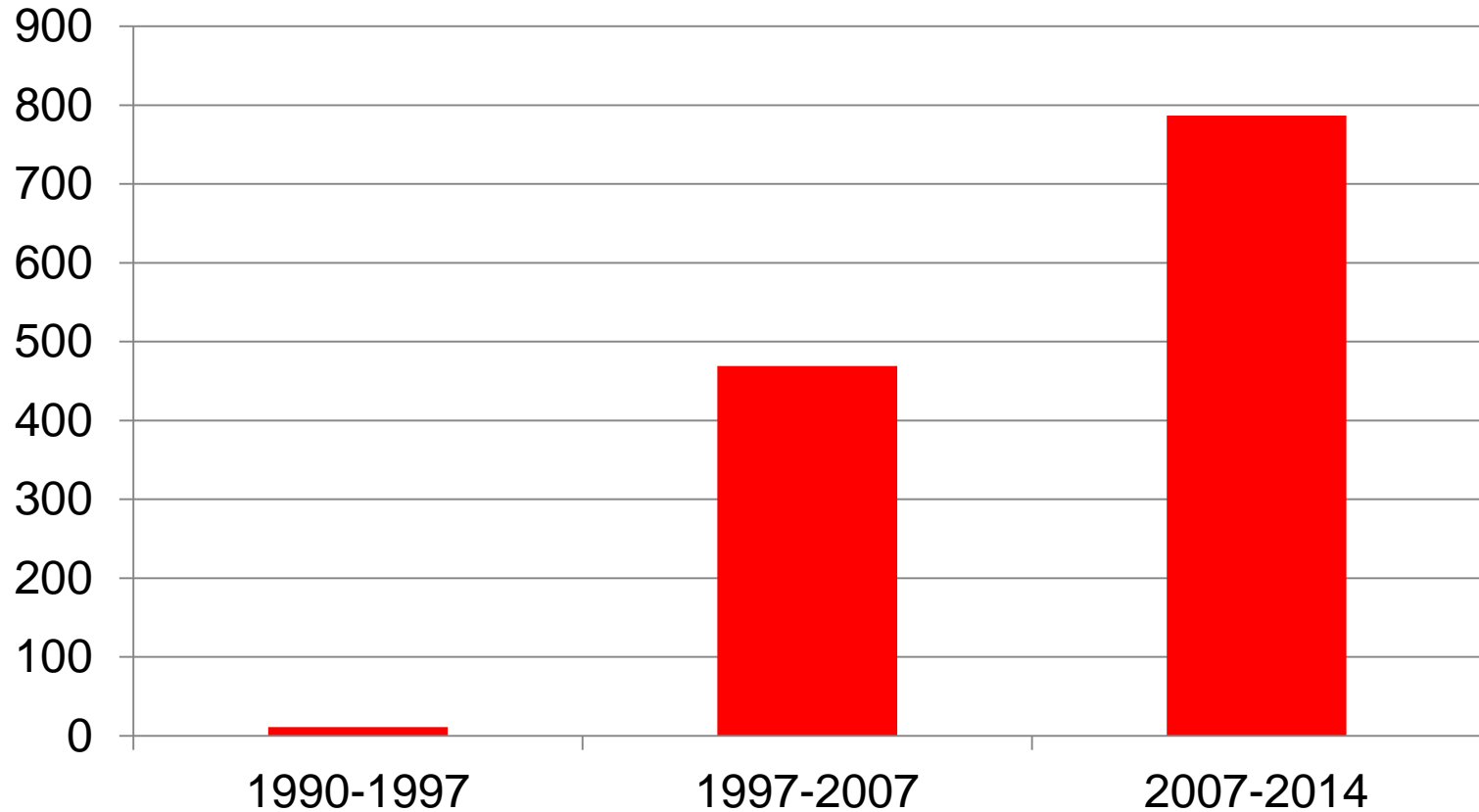


Pediatric Labeling Changes by Indication



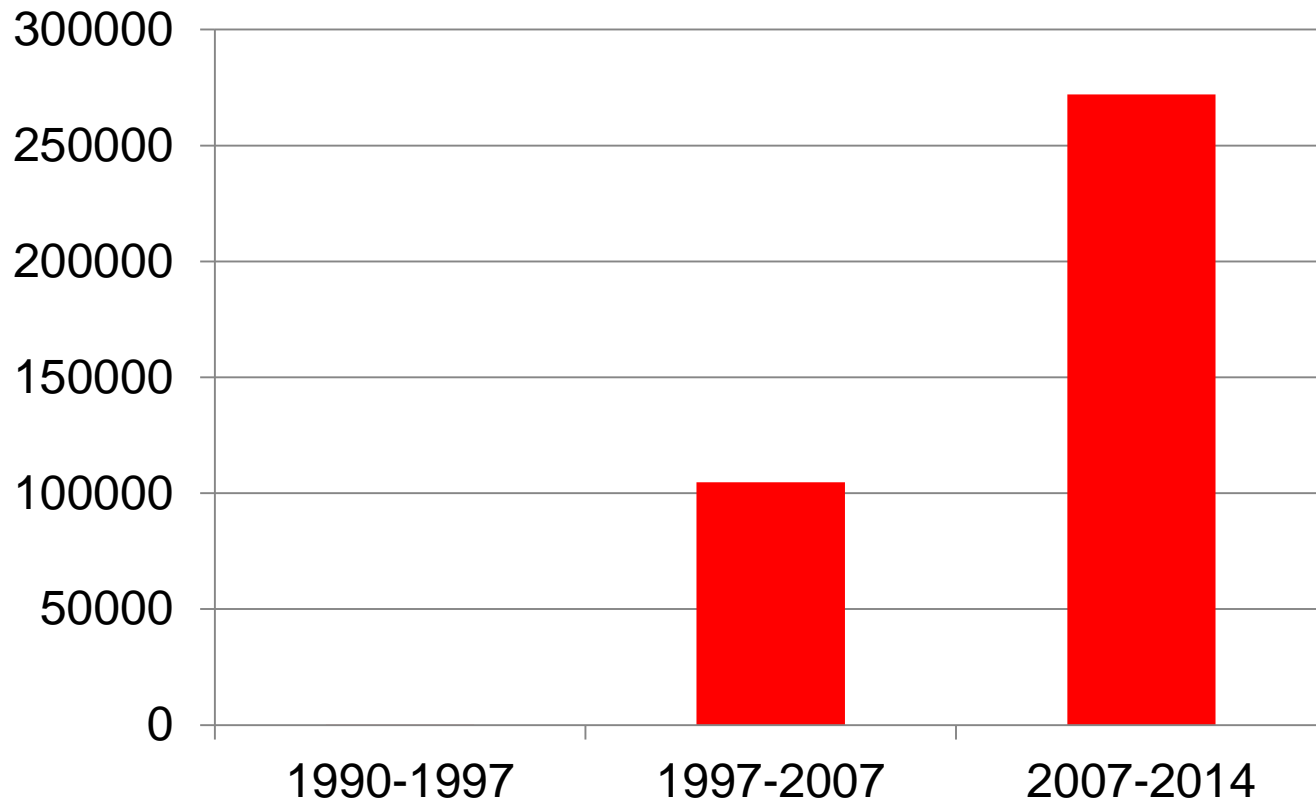
Number of Studies Completed under BPCA and PREA

Number of clinical studies



Number of children enrolled in trials under BPCA and PREA

Estimated number of children enrolled in clinical trials



Time between Adult Approval and Pediatric Labeling

Time Lapse (in years)		
Difference between Adult NDA and Pediatric Label		
1998–2003	2004–2009	2010–2013
9.64	9.32	9.09
<i>n=31</i>	<i>n=49</i>	<i>n=38</i>

Sources: Analysis was completed using this data set: Drugs@FDA.gov (adult NDA) and FDA New Pediatric Labeling Information Database (pediatric label changes). Accessed June 2014. Sample size N = 118 pediatric labels randomly selected

On average, it takes 9 years from the time of a product's approval for use in adults until the label is updated to include pediatric data.

Off-label use occurs during this time period.

Long Time Lapse Between Initial Adult Label and Pediatric Label Updates

Average Time Lapse (in years)

Difference between Adult NDA Date and First Pediatric Label Date

2001 & Earlier	2002–2006	2007–2011	2012–2016
7.03	9.84	7.06	9.68
N=17	N=35	N=34	N=28

Source: P.L. Simpkins, Unpublished, 2017. Analysis was completed using data from Evaluate Pharma, [Drugs@FDA.gov](https://www.drugs@fda.gov) (label) and FDA New Pediatric Labeling Information Database (pediatric label changes). Accessed February 2017. Sample size N = 114 pediatric labels. Rx products only (excludes OTC products).

On average, it takes 9 years from the time of a product's approval for use in adults until the label is updated to include pediatric data.

Off-label use occurs during this time period.

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

**Can we do better?
How do we get to “the
Best”?**

Areas to Consider

- Pediatric Extrapolation and Innovative Clinical Trial Designs
- Big Data
- Clinical Trial Networks
- Global Alignment

Pediatric Extrapolation: The Traditional Paradigm

- 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
- Degrees of confidence in extrapolation
 - No extrapolation
 - Partial extrapolation
 - Full extrapolation
- First published review in 2011 based on 166 products with submitted pediatric studies between 1998-2008
 - 68% of products relied upon partial extrapolation
 - 17% no extrapolation
 - 14% full extrapolation

(Dunne, et al., *Pediatr.*,2011)

Review of Extrapolation

- 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

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

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)
 - Prior knowledge about the value of a quantity of interest based on evidence not derived from the study
 - Summary of the information based on data collected in the study
 - Posterior distribution (probability) of the event occurring

Extrapolation and Bayesian Approaches

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 Use 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 modelling 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

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
- Master protocols in pediatric cancer are being implemented now
 - Limited to identification of molecules that could be moved into confirmatory trials

Big Data

- Real World Data vs. Real World Evidence
 - Development of framework to evaluate large, often proprietary databases
 - Real World Data may not translate into Real World Evidence
 - Will need to consider experts in analysis and modeling
- How much data are enough to draw conclusions or make clinical/scientific/regulatory decisions?
 - Both quality and quantity of data must be considered

Pediatric Research Initiatives and Networks

- Critical path launched two pediatric network initiatives in 2014
 - International Neonatal Consortium (INC)
 - Pediatric Trials Consortium (PTC)—now an independent non-profit (Institute for Advanced Clinical Trials 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)

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)

International Collaborations

- 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
- Current ICH E11 guideline being revised based on scientific, clinical, and regulatory advancements
 - Updates on several topics including extrapolation, modeling and simulation, ethics, formulations

Pediatric Product Development in the 21st Century

- Children are protected through research, not from it
 - Successes to date are noteworthy but we must strive for the best
- 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
 - Innovative clinical trial designs (efficacy and safety)
 - Use of big data
 - Improved framework for pediatric extrapolation
 - Clinical trial networks
 - International collaborations



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Thank you!