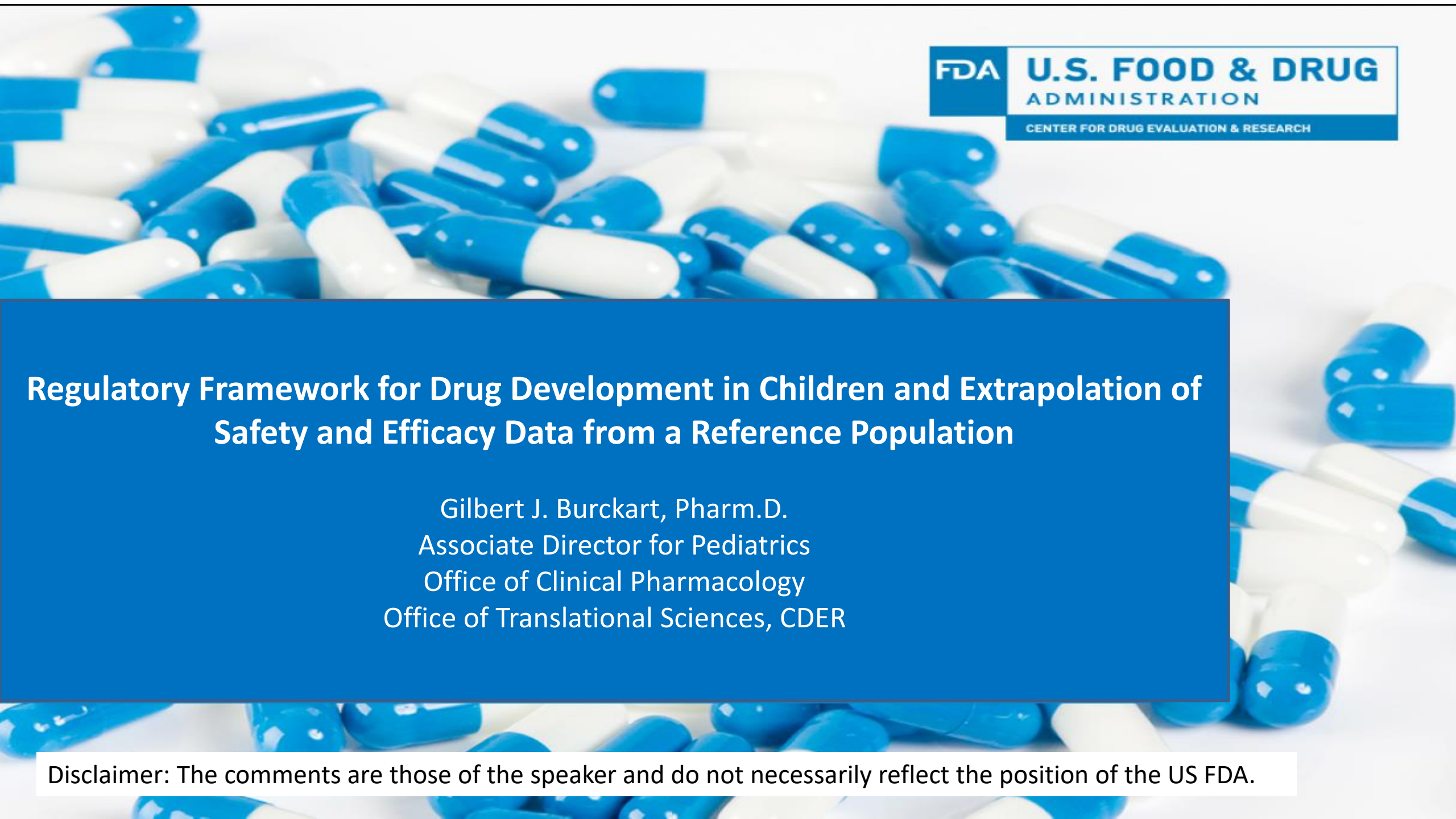


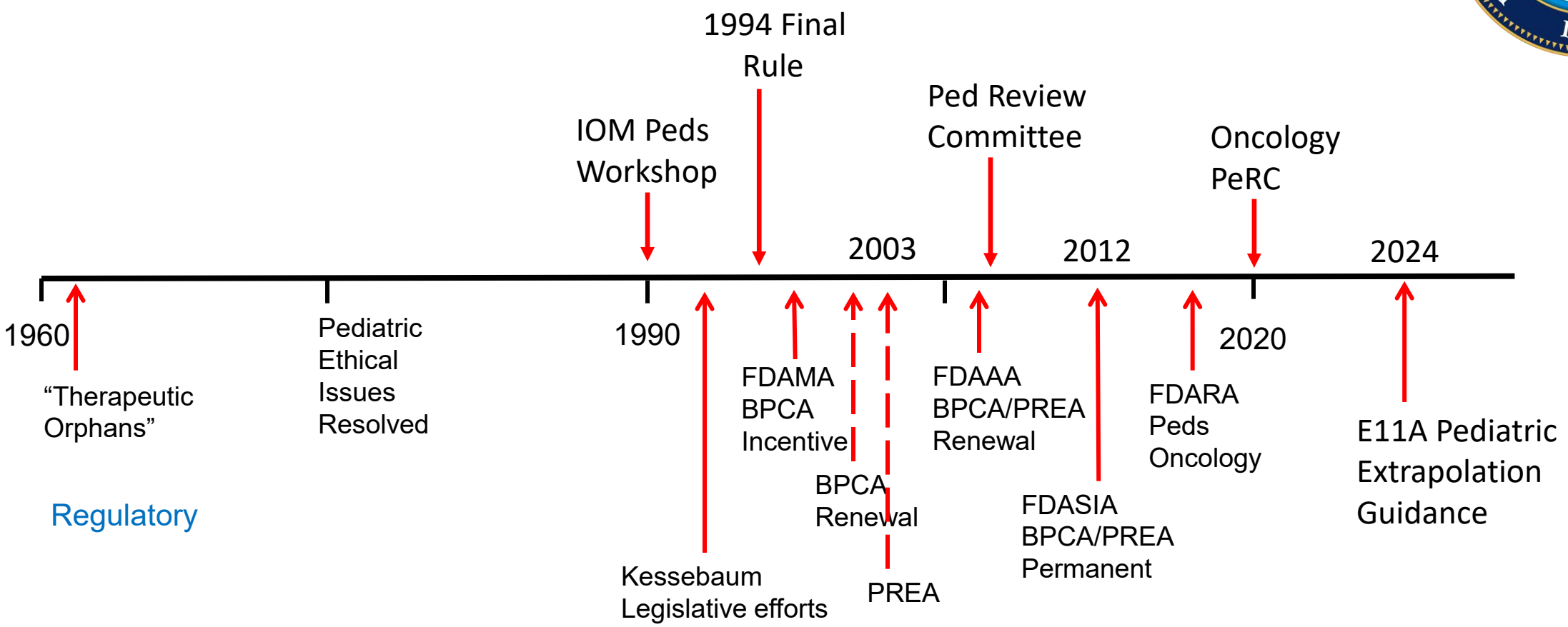
FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH

Regulatory Framework for Drug Development in Children and Extrapolation of Safety and Efficacy Data from a Reference Population

Gilbert J. Burckart, Pharm.D.
Associate Director for Pediatrics
Office of Clinical Pharmacology
Office of Translational Sciences, CDER

Disclaimer: The comments are those of the speaker and do not necessarily reflect the position of the US FDA.

TIMELINE FOR PEDIATRIC DRUG DEVELOPMENT



Initiation of Pediatric Extrapolation - 1

April, 1990 **Institute of Medicine Workshop** on Drug Development and Pediatric Populations; Recommendations:

1. FDA explore innovative ways to encourage labeling of drugs for pediatric patients;
2. NIH provides funding for training in pediatric pharmacology;
3. Congress pass legislation to mitigate the disincentives of pediatric drug development; and
4. Industry develop the infrastructure and expertise to conduct pediatric trials to support pediatric labeling.

Initiation of Pediatric Extrapolation - 2

FDA's 1994 Final Rule

"A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency 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."

Unfortunately, companies did not have pediatric data and academic studies did not meet standards, so this Rule produced very little at the time.

Reviews of FDA's Experience with Pediatric Extrapolation

2011

Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs

WHAT'S KNOWN ON THIS SUBJECT: Extrapolation of efficacy, an approach first proposed in 1994, can increase the efficiency of pediatric drug development. Little has been published on its practical application and whether it can achieve the objectives of increased efficiency and increased pediatric drug labeling

AUTHORS: Julia Dunne, MD, FRCP,[a] William J. Rodriguez, MD, PhD,[a] M. Dianne Murphy, MD,[a] B. Nhi Beasley, PharmD,[b] Gilbert J. Burckart, PharmD,[c] Jane D. Filie, MD,[d] Linda L. Lewis, MD,[e] Hari C. Sachs, MD,[f] Philip H. Sheridan, MD,[g] Peter Starke, MD,[h] and Lynne P. Yao, MD[i]

Pediatrics 2011; DOI: 10.1542/peds.2010-3487

2017

Extrapolation of Efficacy in Pediatric Drug Development and Evidence-based Medicine: Progress and Lessons Learned

Haihao Sun, MD, PhD[1], Jean W. Temeck, MD[1], Wiley Chambers, MD[2], Ginger Perkins, AAS[1], Renan Bonnel, PharmD, MPH[1], and Dianne Murphy, MD[1]

Ther Innov Regul Sci 2017; doi:10.1177/2168479017725558

2022

Pediatric Efficacy Extrapolation in Drug Development Submitted to the US Food and Drug Administration 2015–2020

The Journal of Clinical Pharmacology
2022, 0(0) 1–7
Published 2022. This article is a U.S. Government work and is in the public domain in the USA.
DOI: 10.1002/jcph.2160

J Clin Pharmacol 2022; DOI: 10.1002/jcph.2160

Sherbet Samuels, PhD[1], Kyunghun Park, PharmD[1], Varsha Bhatt-Mehta, PharmD[1], Haihao Sun, PhD[2], Yeruk Mulugeta, PharmD[3], Lynne Yao, MD[3], Dionna J. Green, MD, FCP[2], and Gilbert J. Burckart, PharmD, FCP[1]

Pediatric Antihypertensive Drugs Prior to 2011

Pediatric Antihypertensive Trial Failures

Analysis of End Points and Dose Range

Daniel K. Benjamin, Jr, P. Brian Smith, Pravin Jadhav, Jogarao V. Gobburu, M. Dianne Murphy, Vic Hasselblad, Carissa Baker-Smith, Robert M. Califf, Jennifer S. Li

Hypertension 2002; 51:834-840

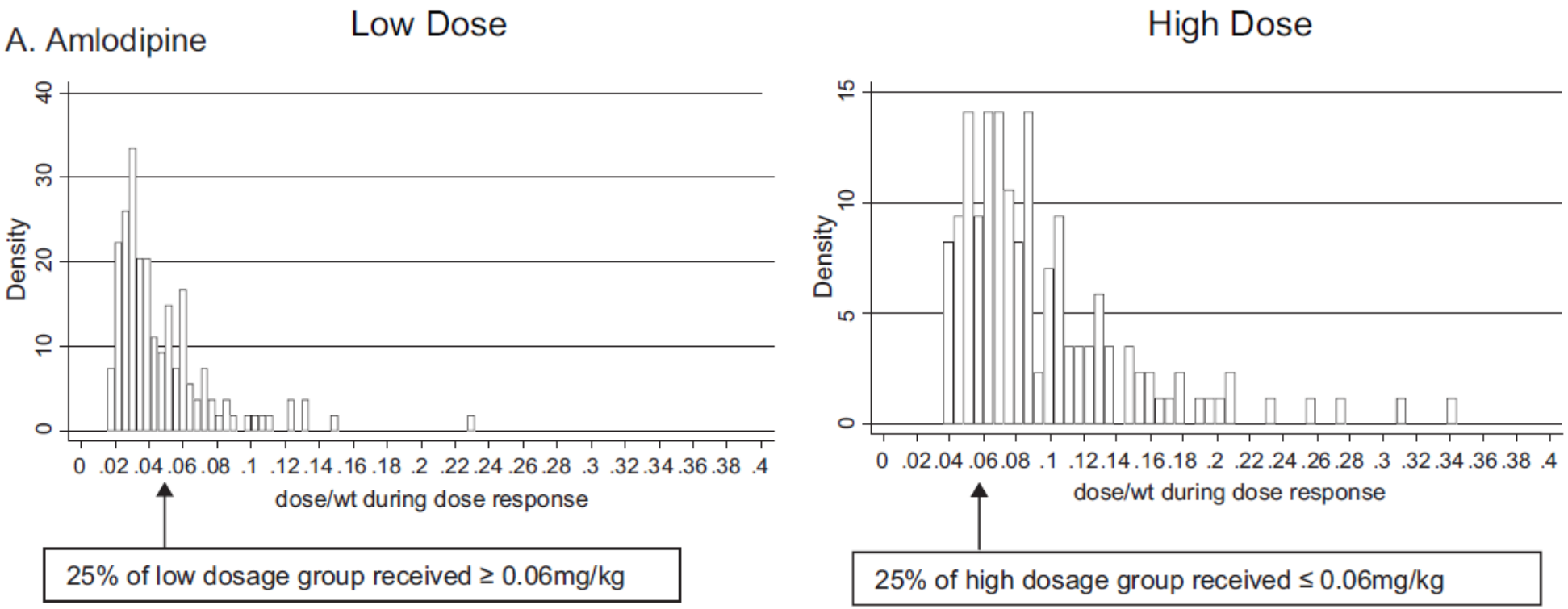
Three drugs gained pediatric approval (enalapril, lisinopril, losartan) and three failed (amlodipine, fosinopril, irbesartan); Investigators concluded that "**poor dose selection**, lack of acknowledgement of differences between adult and pediatric populations, and **lack of pediatric formulations** to be associated with failures."

Dunne report, 2011 for "Hypertension":

Extrapolation was used to label enalapril for use down to age of 1 mo on the basis of consistent pharmacokinetic data across pediatric (2 mo to 16 y) and adult age groups and positive controlled, dose-response study results for patients 6–16 y of age. However, FDA changed this approach after receiving data on antihypertensive drugs that showed no efficacy in pediatric age groups despite similar pharmacokinetic characteristics for pediatric and adult populations. Antihypertensive drugs now receive pediatric labeling only for age groups for which efficacy is confirmed.

Lack of Dose Ranging in Pediatric Antihypertensive Trials

Hypertension 2002; 51:834-840



More about dose-ranging
In pediatric trials:

Dose Ranging in Pediatric Drug Development Trials Submitted to the US FDA 2012–2020

The Journal of Clinical Pharmacology
2025, 0(0) 1–6
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DOI: 10.1002/jcph.70016

Pediatric Research Equity Act (PREA, 2003)

Requires pediatric studies for:

- **new active ingredient,**
- **new indication,**
- **new dosage form,**
- **new dosing regimen,**
- **new route of administration**

Therefore we can get a second chance for drugs, such as antihypertensive agents, that have previously failed in pediatrics.

- **Classic example:**

Migraine Therapeutics in Adolescents

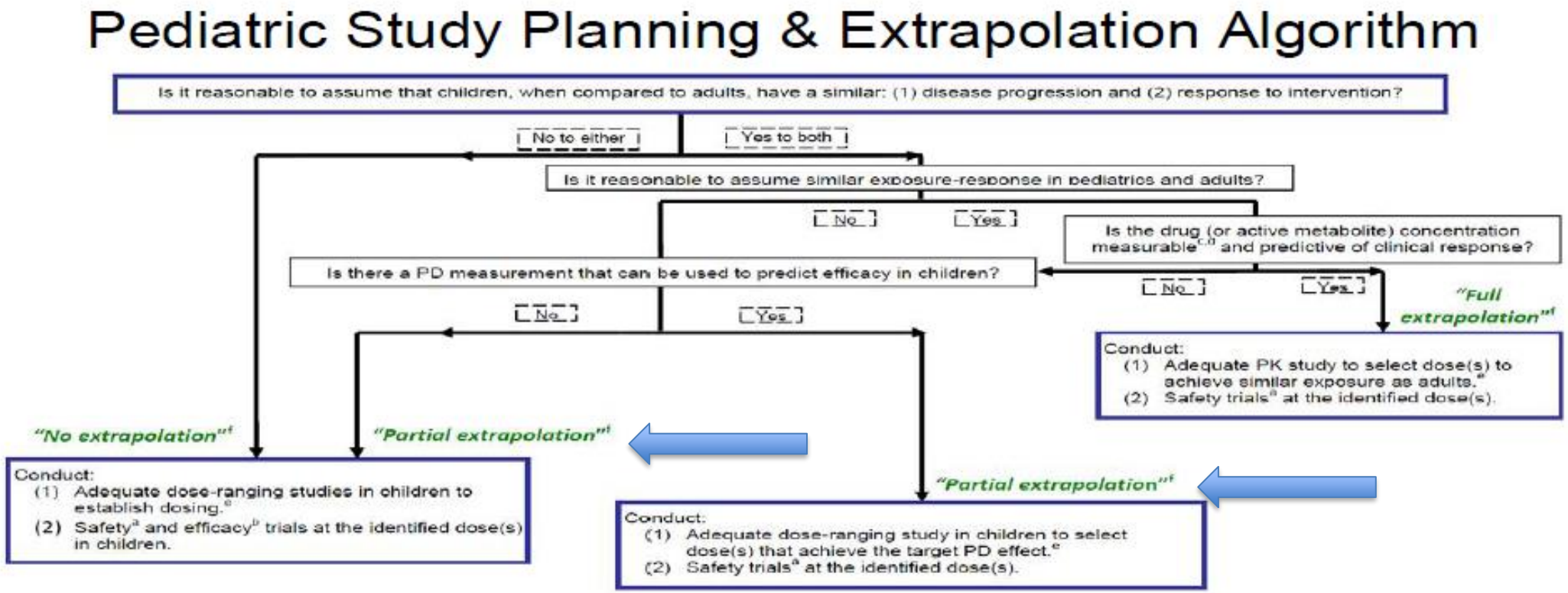
A Systematic Analysis and Historic Perspectives of Triptan Trials in Adolescents

Haihao Sun, MD, PhD; Eric Bastings, MD; Jean Temeck, MD; P. Brian Smith, MD, MPH, MHS; Angela Men, MD; Veneeta Tandon, PhD; Dianne Murphy, MD; William Rodriguez, MD, PhD

JAMA Pediatrics 2013; 167:243-249

Rizatriptan failed in pediatric migraine in a 1999 trial, but demonstrated effectiveness in a 2011 trial with a different trial design.

Partial Extrapolation in the 2014 Pediatric Clinical Pharmacology Guidance



Footnotes:

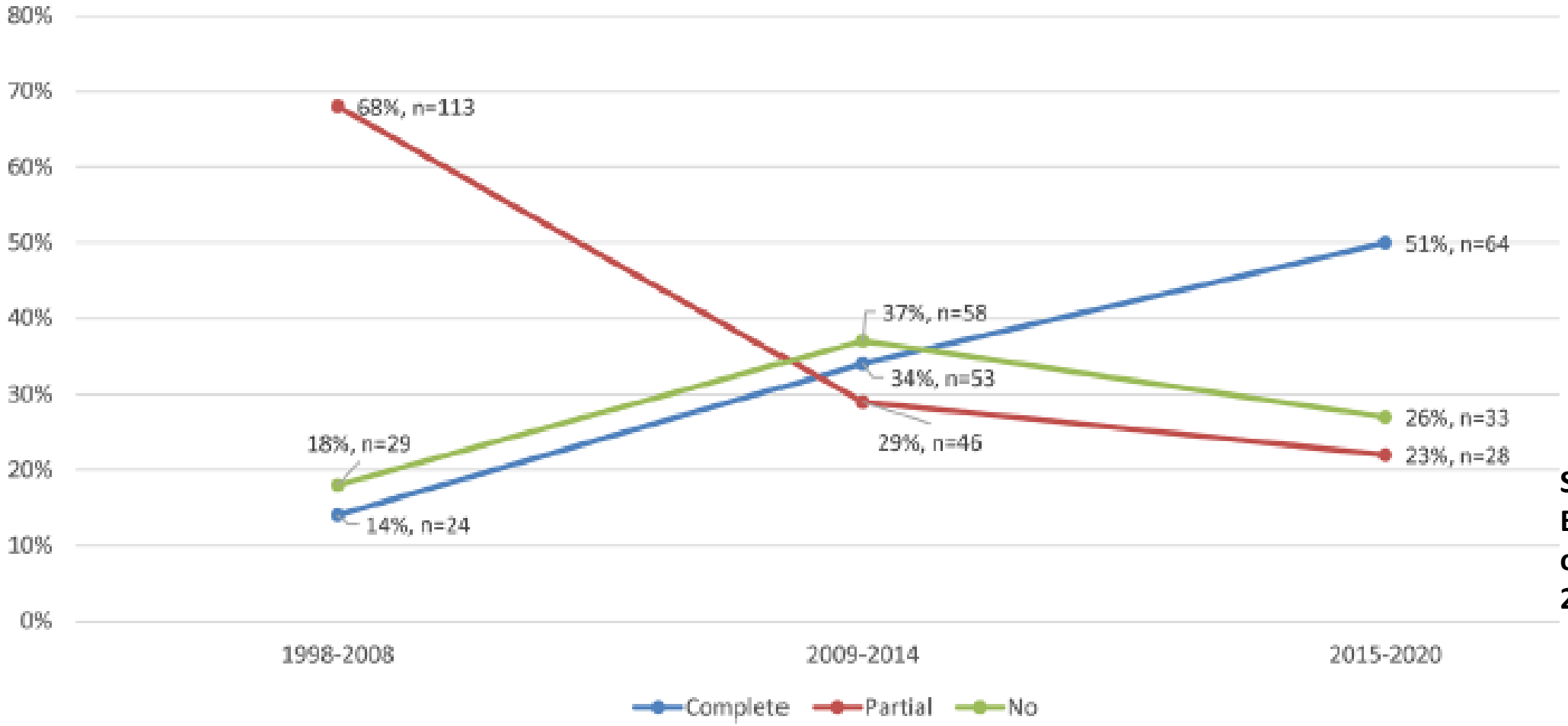
a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

Information on pediatric products assessed in extrapolation evaluation

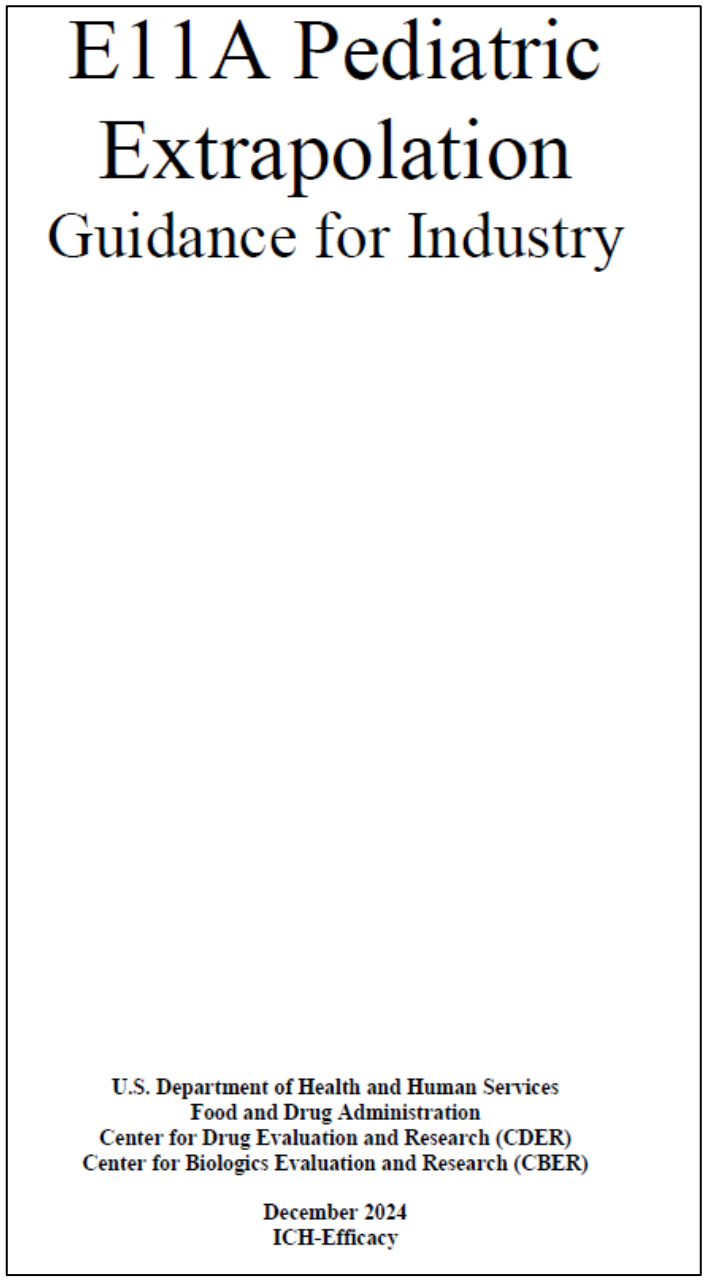
(2015-2020) Samuels S et al. J Clin Pharmacol 2022; doi: 10.1002/jcph.2160

Pediatric Labeling Date	Trade Name	Generic Name or Proper Name	Indications	Age	Extrapolation Category
12/19/2019	CONJUPRI	levamlodipine maleate	Treatment of hypertension	6 to 17 y	Partial
10/1/ 2019	ENTRESTO	Sacubitril/ Valsartan	Treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction	1 to < 18 y	Partial

Transition from Partial Extrapolation to the Current Continuum In Pediatric Extrapolation



Samuels S……. Burckart GJ. Journal of Clinical Pharmacology 2023; 63:307-313.



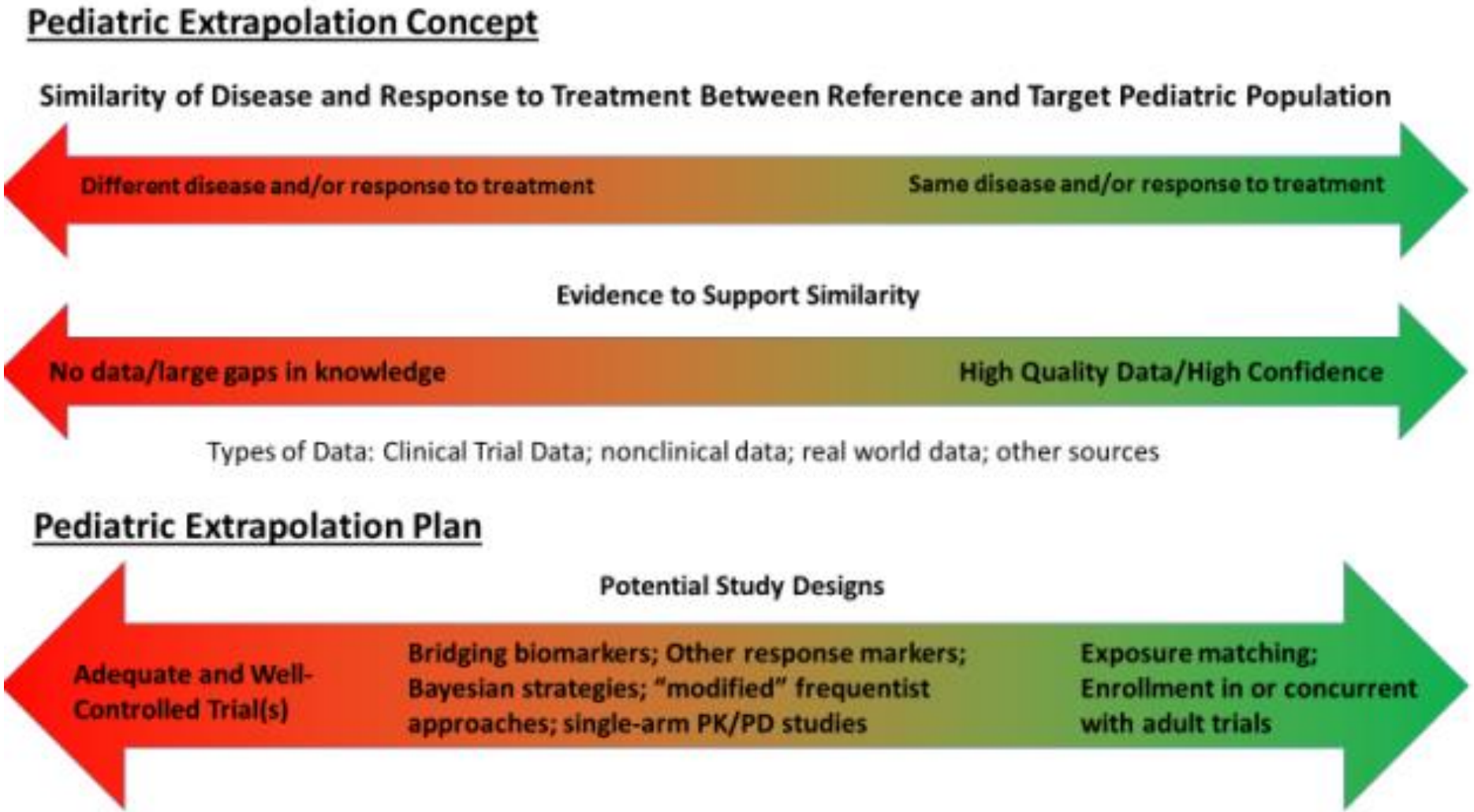
Culmination of years of effort on the parts of the FDA, EMA and PMDA in conjunction with industry;

Includes pediatric extrapolation of efficacy and safety;

Focus on a **Pediatric Extrapolation Plan;** asks many of the right questions that need to be addressed;

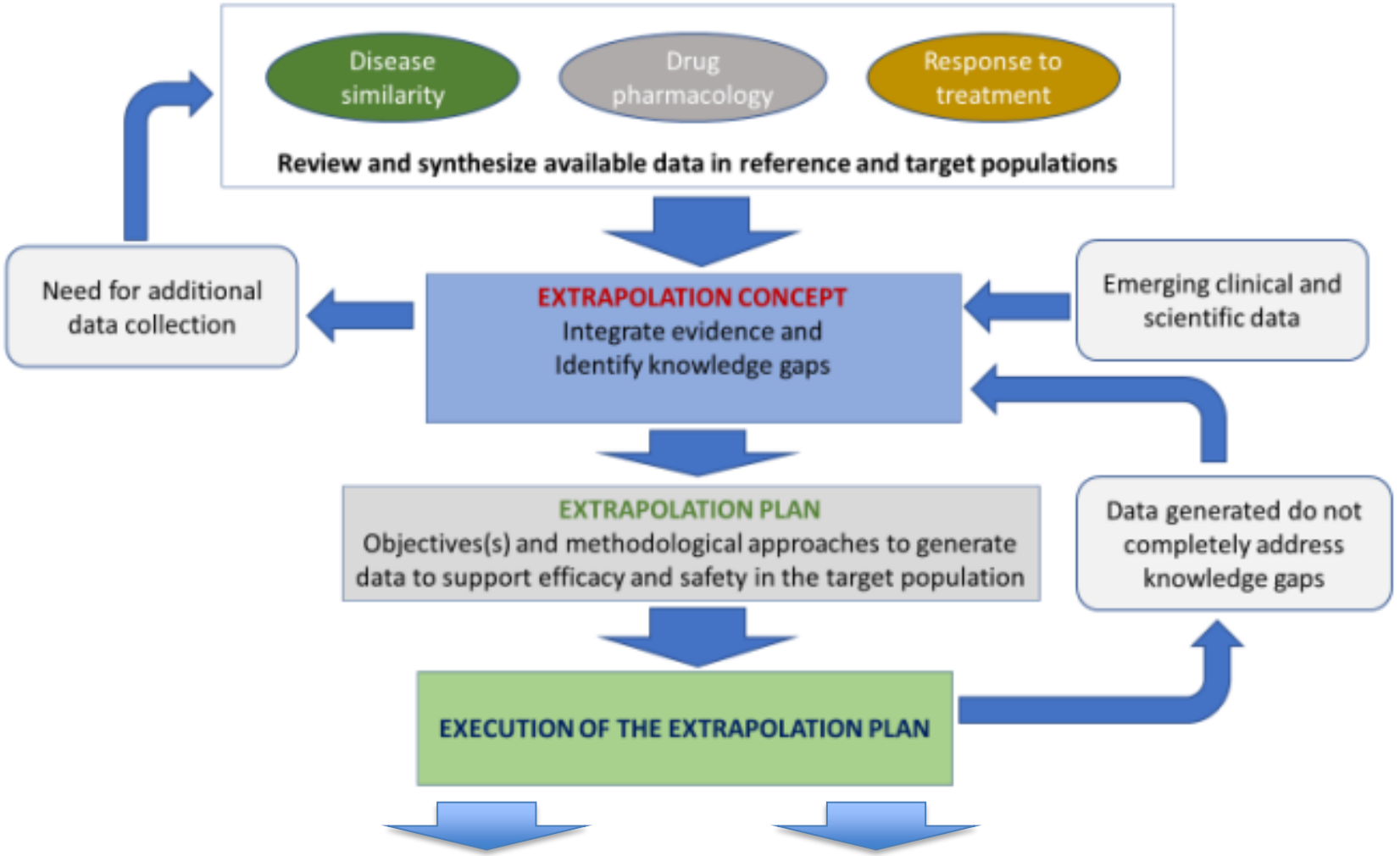
Extrapolation of safety is new, so needs particular attention.

Pediatric Extrapolation Continuum



ICH guideline E11A on pediatric extrapolation Step 2b

Pediatric Extrapolation Framework

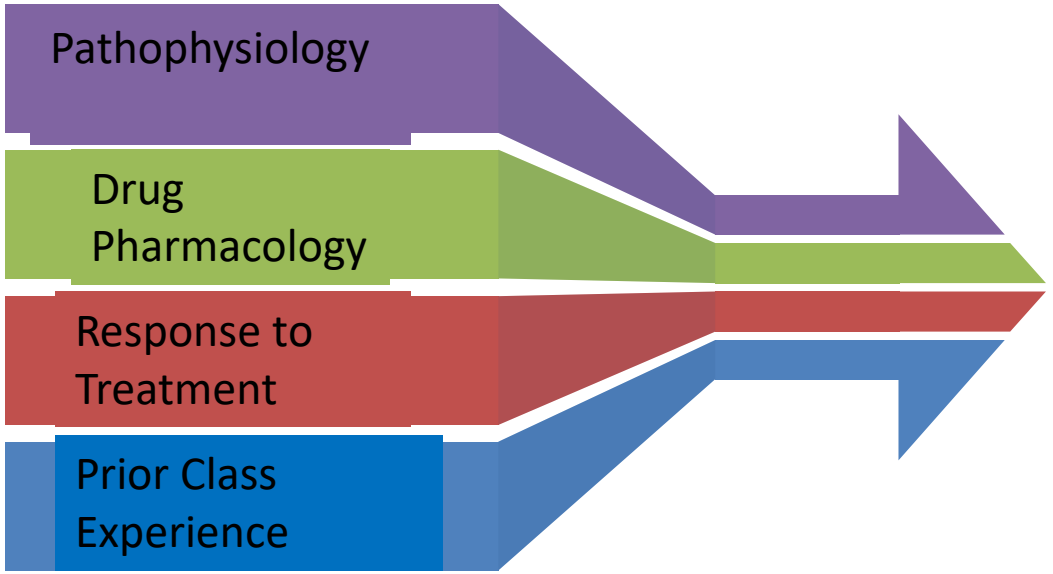


See: US Food and Drug Administration; E11A Pediatric Extrapolation: Guidance for Industry December 2024

Pediatric Extrapolation Concept

Disease definition

- What are the manifestations or diagnostic criteria that define the disease?
- How similar are the manifestations between the reference and target populations?
- How are the manifestations measured?
- Are there similar measurements used to define manifestations of the disease in the reference and target populations?
- Are there subtypes (e.g., based on severity, genetics, molecular markers, etc.) of the disease that occur in the reference or target populations?
- What are the similarities and differences in the subtypes of the disease in the reference and target population?
- Are there other factors to consider (e.g., prognostic, predictive, genetic/epigenetic, psychosocial, etc.) that are needed to define the disease?



Prediction of Disease Similarity

Pediatric Benefit/Risk Assessment

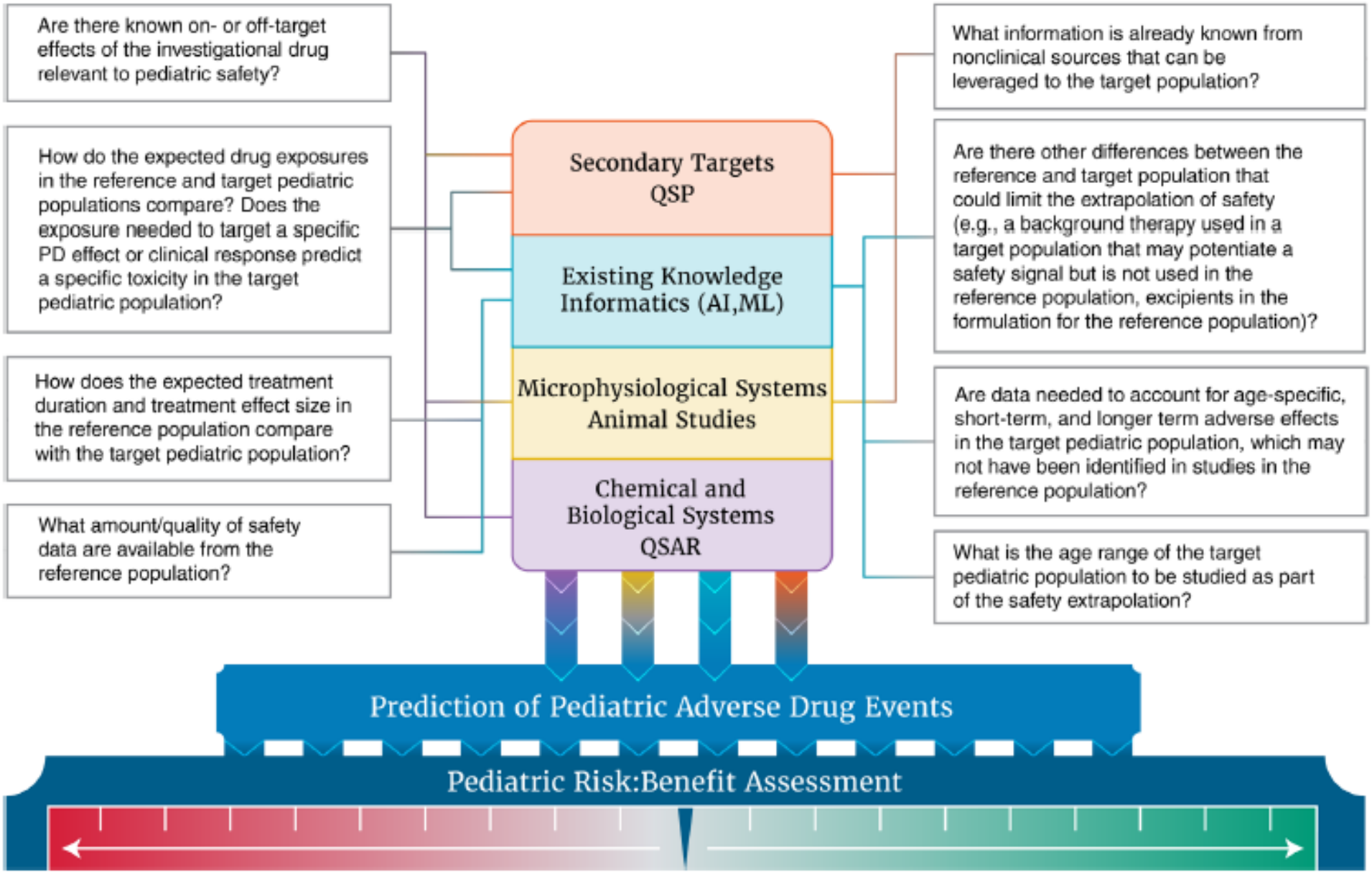
Course of disease

- What are the similarities and differences of the clinical course of the disease between the reference and target populations?

Are there differences in the course of the disease based on factors such as the age of onset of the disease?

- Are there similar endpoints and/or biomarkers available that help to measure progression of disease in both the reference and target populations?
- Are the short-term or long-term outcomes of the disease similar for the reference and target populations and can these outcomes be measured similarly?
- What are the available treatments being used for both the reference and target populations?
- What effect do these treatments have (e.g., timing of treatment relative to onset of disease and age of the patient, frequency of treatment, length of treatment) on the course of the disease in the reference and target populations?

Safety Related Questions in E11A



From: Burckart GJ et al. Pediatric Developmental Safety Assessment: Are We Ready for the Next Thalidomide? *Clinical Pharmacology and Therapeutics* 2025; doi:10.1002/cpt.70148

Special Considerations for Adult-Pediatric Comparisons

1. Placebo responses may differ in adult and pediatric patients

Pediatric and Adult Placebo Response Rates in Placebo-Controlled Clinical Trials Submitted to the US Food and Drug Administration 2012–2020

The Journal of Clinical Pharmacology
2022, 0(0) 1–13
© 2022, The American College of Clinical Pharmacology
DOI: 10.1002/jcph.2035

Kyunghun Park, PharmD[1], Ngan K. Tran, PharmD, MS HCDA[2], Jeremiah D. Momper, PharmD, PhD[3], Dionna J. Green, MD, FCP[4], and Gilbert J. Burckart, PharmD, FCP[1]

2. Exposure-response analysis has little precedent in some pediatric diseases

Exposure–Response Assessment in Pediatric Drug Development Studies Submitted to the US Food and Drug Administration

Yifei Zhang[1], Yaning Wang[2], Mona Khurana[3], Hari Cheryl Sachs[3], Hao Zhu[2], Gilbert J. Burckart[2], John Alexander[1], Lynne P. Yao[3] and Jian Wang[1,*]

Clinical Pharmacology and Therapeutics 2020 Jul;108(1):90-8.

Special Considerations for Adult-Pediatric Comparisons -2

3. The incidence of important adverse effect may be significantly different in pediatric patients.

updates

A Comparison of Pediatric and Adult Safety Studies for Antipsychotic and Antidepressant Drugs Submitted to the United States Food and Drug Administration

Xiaomei I. Liu, PharmD[1], Paul Schuette, PhD[2], Gilbert J. Burckart, PharmD[3], Dionna J. Green, MD[4], Julie La, PharmD[5], Janelle M. Burnham, MD[3], Natella Rakhmanina, MD, PhD[1], Adelaide Robb, MD[1], Shiew Mei Huang, PhD[3], and John N. van den Anker, MD, PhD[1]

The Journal of Pediatrics 2019;208:236-42.

4. Using the same endpoint in pediatric trials as was used in adult trials significantly succeeds more often.

Primary Endpoints in Pediatric Efficacy Trials Submitted to the US FDA

The Journal of Clinical Pharmacology
2018, 0(0) 1–6
© 2018, The American College of Clinical Pharmacology
DOI: 10.1002/jcph.1109

Dionna J. Green, MD[1], Janelle M. Burnham, MD[1], Paul Schuette, PhD[2], Xiaomei I. Liu, PharmD[3], Brian M. Maas, PharmD[4], Lynne Yao, MD[5], Susan K. McCune, MD[6], Joseph Chen, PharmD[7], John N. van den Anker, MD, PhD, FCP[4], and Gilbert J. Burckart, PharmD, FCP[1]

Special Considerations for Adult-Pediatric Comparisons -3

5. Using all three enrichment strategies (practical, prognostic, predictive) more often results in a successful pediatric trial.

Enrichment Strategies in Pediatric Drug Development: An Analysis of Trials Submitted to the US Food and Drug Administration

Dionna J. Green[1], Xiaomei I. Liu[1], Tianyi Hua[2], Janelle M. Burnham[1], Robert Schuck[1], Michael Pacanowski[1], Lynne Yao[3], Susan K. McCune[4], Gilbert J. Burckart[1] and Issam Zineh[1]

Clinical Pharmacology and Therapeutics 2017;
doi: 10.1002/cpt.971

Summary

- Pediatric extrapolation significantly contributes to pediatric drug development today;
- The pediatric extrapolation of efficacy and safety requires a well-developed plan that addresses all of the questions posed by the E11A guidance;
- Knowledge of the prior programs that have demonstrated differences in adult and pediatric drug development is extremely valuable in planning your pediatric drug development program.