

Pediatrics Pharmacokinetics and Pharmacodynamics in Drug Development

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Disclaimer: The opinions expressed are those of the author, and should not be interpreted as the position of the US FDA.

Objectives

- Review the origins of the PK/PD orientation in pediatric clinical pharmacology;
- Address the questions that would naturally arise in designing a pediatric PK/PD study in drug development; and
- Explore the current challenges in regulatory science for pediatrics for PK/PD.

The Father of Pediatric Clinical Pharmacology: Dr. Sumner Yaffe



- Stanford, Director of the Clinical Research Center for Premature Infants
- Developed Pediatric Clin Pharm programs at Buffalo (1963) and Philadelphia Children's Hospitals
- At Buffalo, collaborated with Dr.'s Gary Levy and Bill Jusko, and incorporated pharmacokinetics into pediatric clinical pharmacology studies.**
- Long time supporter of the Pediatric Pharmacy Advocacy Group (PPAG), and the Yaffe Award is given annually
- Director of the Center for Research for Mothers and Children at the National Institute of Child Health and Human Development, National Institutes of Health**

Created the Pediatric Pharmacology Research Units (PPRU's) as a trial of integrated pediatric research sites

Dr. Gary Levy



- Joined SUNY-B faculty in **1960**;
- Most-highly noted for leading the developing quantitative relationships between drug concentrations and response or PK/PD with a strong focus on discerning pharmacologic (PK of PD) mechanisms.
- the **quantitative aspects of pharmacodynamics did not begin until the 1960s when Gary and his students published their seminal articles** that described the mathematical relationships between drug concentrations and pharmacological effects.

<https://pharmacy.buffalo.edu/news-events/events/annual-events/levy-lecture.html>

Yaffe's influence through the 1970's, 1980's and 1990's: Pediatric Clinical Pharmacology embraced PK/PD

Clinical Implications of Salicylate-Induced Liver Damage

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Clinical Implications of Perinatal Pharmacology*

S. J. Yaffe

RIBOFLAVIN ABSORPTION AND EXCRETION IN THE NEONATE

**William J. Jusko, Ph.D., Narinder Khanna, M.D., Gerhard Levy, Pharm.D.,
Leo Stern, M.D., and Sumner J. Yaffe, M.D.**

Pharmacokinetics of Methicillin in Patients with Cystic Fibrosis

**Sumner J. Yaffe, Louise M. Gerbracht, Louis L.
Mosovich, Mary E. Mattar, Michele Danish, and
William J. Jusko**

*From the Departments of Pediatrics and Pharmaceutics,
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Fillmore Hospital, Buffalo, New York*

Pediatric Dosing Remains a Critical Part of Successful Pediatric Trials

- Of 189 products studied under pediatric exclusivity (1998-2012), pediatric labeling for that indication was not established for 78 (42% FAILED!)
 - *Pediatrics* 2014;134:e512–e518
- Failures were on the basis of dosing, differences in disease process, trial design, placebo response, etc
 - *Clinical Pharmacology and Therapeutics* 2015; doi: 10.1002/cpt.142
- Current assessment of pediatric failure rate is 25-30% for efficacy studies.

Questions

- Do we need to conduct a PK study?
- What type of study do we need to conduct?
- How can I break out the age groups?
- What number of pediatric patients must be studied?
- What are the pediatric PD endpoints that are accepted?
- Should I conduct a PK/PD clinical trial simulation prior submitting the Pediatric Study Plan; prior to submitting the pediatric protocol?

Do I need to conduct a PK study?

- How will the drug concentration information be used?
 - Are they obtained for safety only?
- Age groups of interest do matter;
 - What, if any, age groups are waived from pediatric studies?
 - Have pediatric studies been conducted with the drug in another disease state?

Pediatric Dermatologic Products and PK

Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products

Therapeutic Innovation
& Regulatory Science
1-8
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tirs.sagepub.com

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Edward Dennis Bashaw, Pharm. D¹, Doanh C. Tran, Ph.D¹,
Chinmay G. Shukla, Ph.D¹, and Xiaomei Liu, Pharm. D¹

- In adults, there are “maximal use PK trials”;
- A waiver of pediatric studies or a reduced sampling strategy is possible (review issue).

Pediatric Maximal Use Trial Example

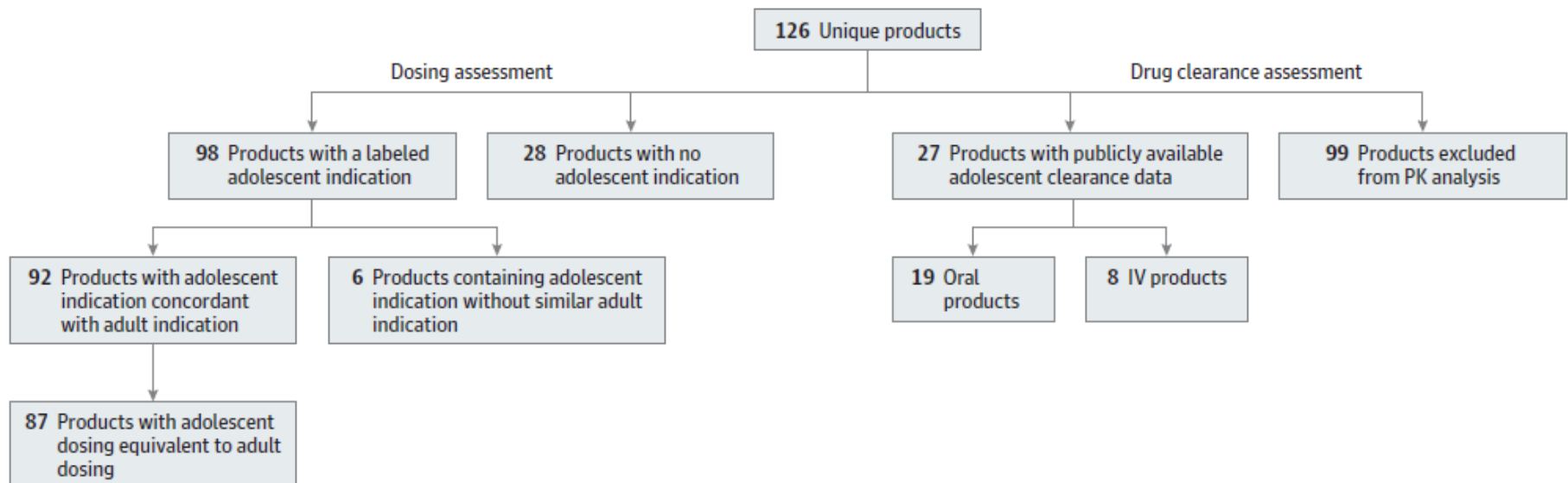
- Naftifine 2% cream (Naftin)
 - <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM533639.pdf>
 - 27 pediatric patients, 2 to <12 years of age
- (C_{max}) and area under the plasma concentration-time curve (Day 14)
 - For 6 - <12 years old, 3.31 ng/mL and 52.4 ng*h/mL
 - For 2 to < 6 years, 3.98 ng/mL and 54.8 ng*h/mL

Adolescent PK Studies

Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007

Jeremiah D. Momper, PharmD, PhD; Yeruk Mulugeta, PharmD; Dionna J. Green, MD; Alyson Karesh, MD; Kevin M. Krudys, PhD; Hari C. Sachs, MD; Lynn P. Yao, MD; Gilbert J. Burckart, PharmD

JAMA Pediatr. 2013;167(10):926-932. doi:10.1001/jamapediatrics.2013.465



Adolescent Dosing Matches Adult Dosing

- Of these 92 products, 87 (94.5%) have equivalent dosing for adult and adolescent patients.
- For 18 of these 92 products, a minimum weight or body surface area (BSA) threshold is recommended for adolescents to receive the adult dose.
- Therefore a PK study in adolescents does not always have to be performed (review issue).

What type of study do we need to conduct?

- Pediatric extrapolation plays a critical role in determining what type of PK/PD that you need to conduct in pediatric patients;
- The Pediatric Study Planning and Extrapolation Algorithm will assist you;
- Look carefully at what has worked (resulted in labeling for the indication) in prior pediatric studies in your therapeutic area, NOT at what has been done before and failed.



General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Gilbert J. Burckart at 301-796-2065.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2014
Clinical Pharmacology

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Pediatric Study Planning & Extrapolation Algorithm

Is it reasonable to assume that children, when compared to adults, have a similar: (1) disease progression and (2) response to intervention?

No to either

Yes to both

Is it reasonable to assume similar exposure-response in pediatrics and adults?

No

Yes

Is the drug (or active metabolite) concentration measurable^{c,d} and predictive of clinical response?

No

Yes

Is there a PD measurement that can be used to predict efficacy in children?

No

Yes

“Full extrapolation”^f

Conduct:

- (1) Adequate PK study to select dose(s) to achieve similar exposure as adults.^e
- (2) Safety trials^a at the identified dose(s).

“No extrapolation”^f

Conduct:

- (1) Adequate dose-ranging studies in children to establish dosing.^e
- (2) Safety^a and efficacy^b trials at the identified dose(s) in children.

“Partial extrapolation”^f

“Partial extrapolation”^f

Conduct:

- (1) Adequate dose-ranging study in children to select dose(s) that achieve the target PD effect.^e
- (2) Safety trials^a at the identified dose(s).

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.

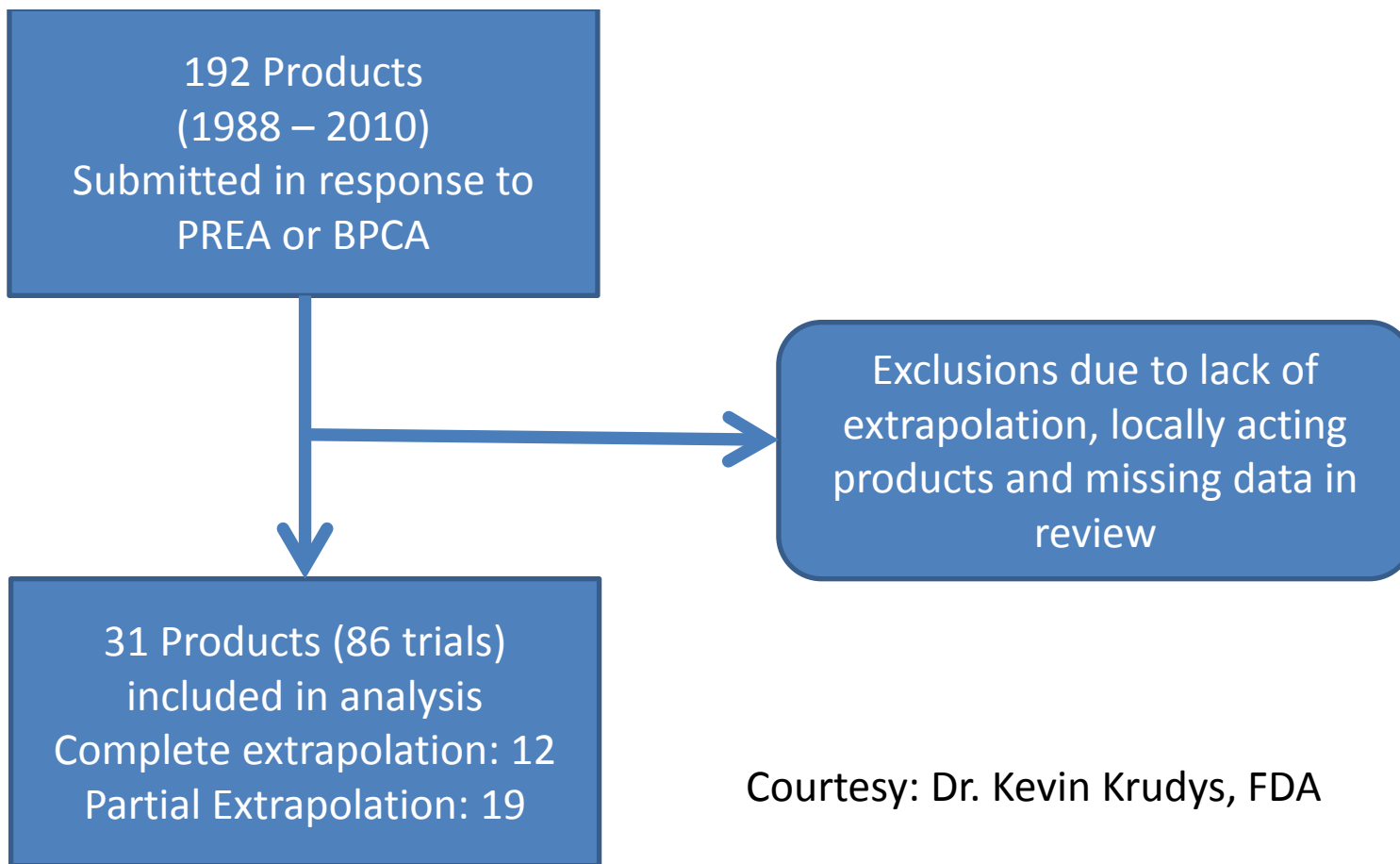
Use of the Algorithm

- Footnote “e” applies to all pathways: When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or clinical trial simulation is appropriate.
- Is it reasonable to assume similar exposure-response in pediatrics and adults?
 - Traditionally this assessment has NOT been performed by comparing ER relationships;
 - A well-designed Exposure-Response study can serve as an efficacy study in pediatric patients.

Exposure-Matching for Full Pediatric Extrapolation

- When efficacy in pediatric patients can be fully extrapolated from adult studies, then only pediatric dosing and safety studies are required;
- BUT, the ability to match the drug concentrations in adults has to be demonstrated!
- Our prior study revealed that (1) a priori standards for matching exposure are not established, and (2) “matching” is inconsistent.

Exposure Matching for Extrapolation of Efficacy in Pediatric Drug Development



Courtesy: Dr. Kevin Krudys, FDA

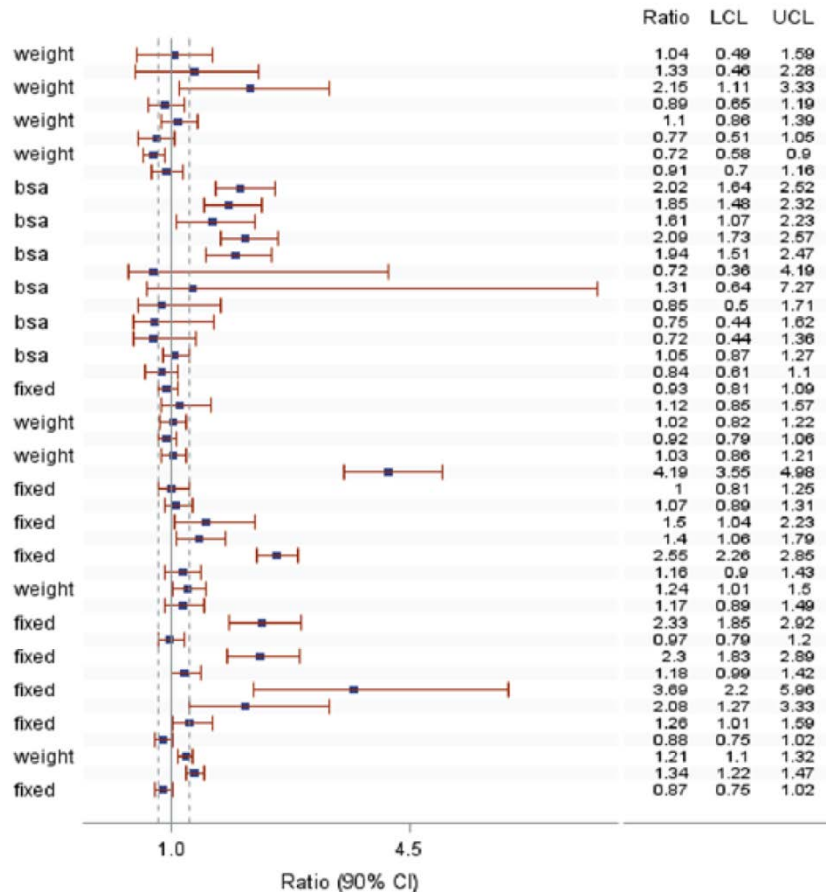
Results - Data

- Antivirals (55%), antihistamines (13%), histamine H2-receptor blockers (6%) and anti-infectives (6%)
- 25 products were studied in more than one age group
- 80% of trials used an intensive PK sampling strategy

Courtesy: Dr. Kevin Krudys, FDA

Results – Exposure Agreement (Cmax)

Cmax Ratio (Pediatrics/Adult)-Products approved with same dose



- Pediatric Cmax were generally higher than adult Cmax
- Range of Cmax ratios (pediatric/adult) was 0.63 to 4.19
- AUC comparisons were similar

Courtesy: Dr. Kevin Krudys, FDA



Results – Exposure Matching Criteria

- Adult data were obtained from separate studies in healthy volunteers or patients with condition
- 7 of 86 trials had a predefined acceptance boundary used to match adult exposures
 - Specific target values
 - Acceptable percentage of adult exposure
- Key exposure metric for matching was predefined for antiviral and anti-infective products

Courtesy: Dr. Kevin Krudys, FDA

Approaches For Matching Systemic Exposures

FDA Guidance	Proposed Approach 1	Proposed Approach 2
Renal Impairment	Modeling of relationship between renal function and PK parameters	Provide analysis of study data to show relevant PK measurements are similar
Bioavailability and bioequivalence studies	90% CI of 80% to 125% for AUC and Cmax	
Drug Interactions	Specific no-effect boundaries or clinical equivalence intervals	No-effect boundary of 90% CI of 80% to 125% for AUC and Cmax
Hepatic Impairment	No-effect boundary based on concentration-response	90% CI of 80% to 125% for AUC and Cmax

Courtesy: Dr. Kevin Krudys, FDA

How can I break out the age groups?

- There is nothing magical about the age groups that are listed as an example in the Guidance;
- “The distinct age groups to be studied should be chosen based upon what is known about the development of the drug-metabolizing enzymes and excretory mechanisms, and safety considerations.”

Example of age groups to be studied for the drug or biologic product
≥1 month to <6 months
6 months to <24 months
2 years to <6 years
6 years to <12 years
12 years to <17 years

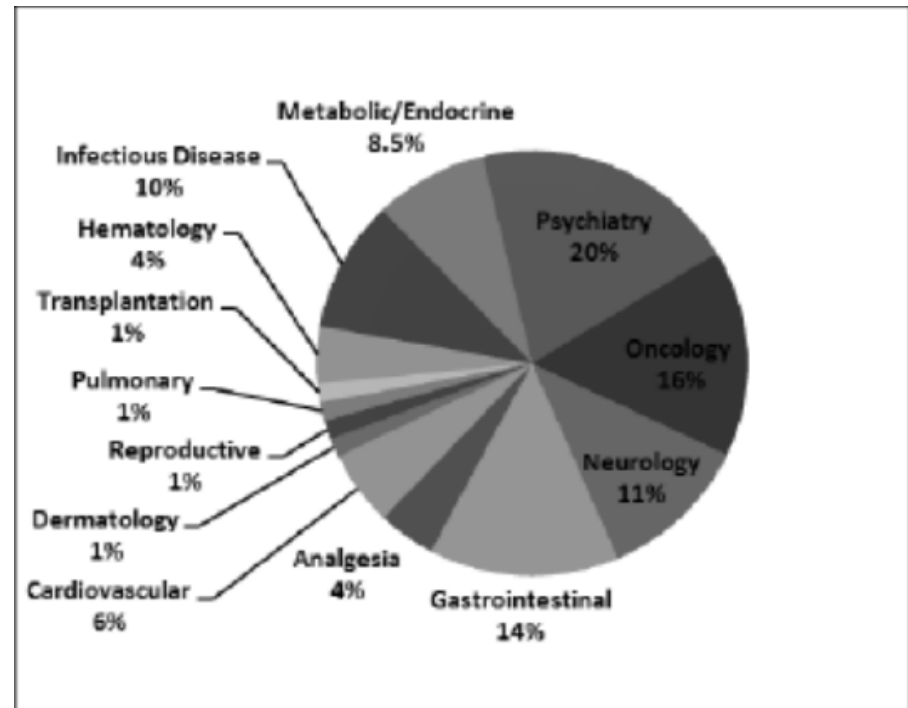
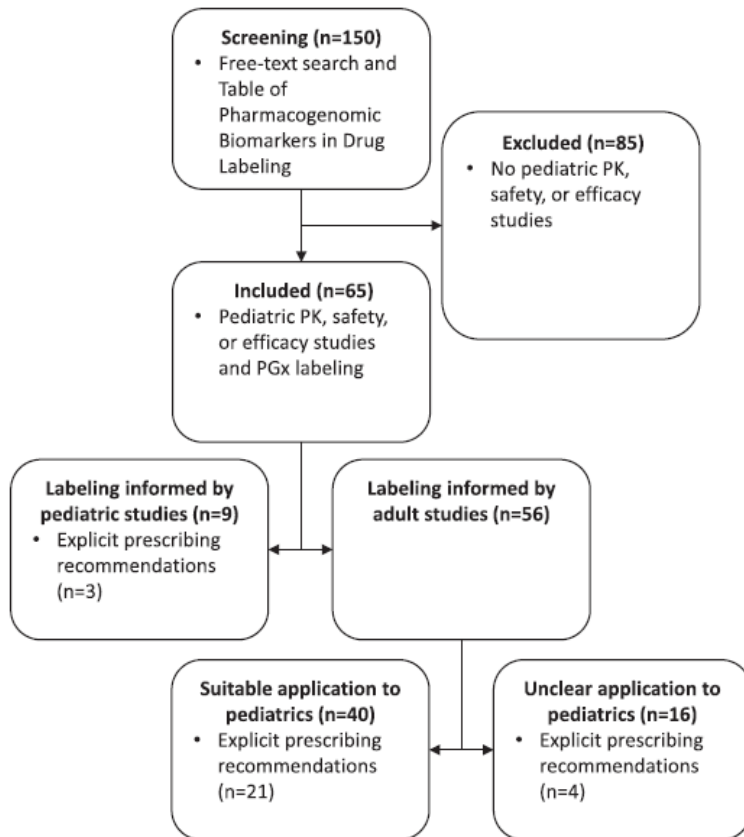
Reasons for Selecting an Age Group

- If polymorphic enzymes, transporters, or receptors are involved, ontogeny may dictate the selection of the age groups for a PK/PD study;
- Disease expression can vary within the pediatric age group, requiring focusing patient recruitment on certain age groups.

Pharmacogenomic Information in FDA-Approved Drug Labels: Application to Pediatric Patients

DJ Green¹, P Mummaneni², IW Kim³, JM Oh³, M Pacanowski² and GJ Burckart¹

Clinical Pharmacology and Therapeutics 2016;
99:622-632; doi:10.1002/cpt.330



Genomic Information on PK/PD In Adults Is Not Always Suitable For Application in Pediatrics

Table 3 Suitability of applying adult-derived PGx data in 56 drug labels to pediatric patients

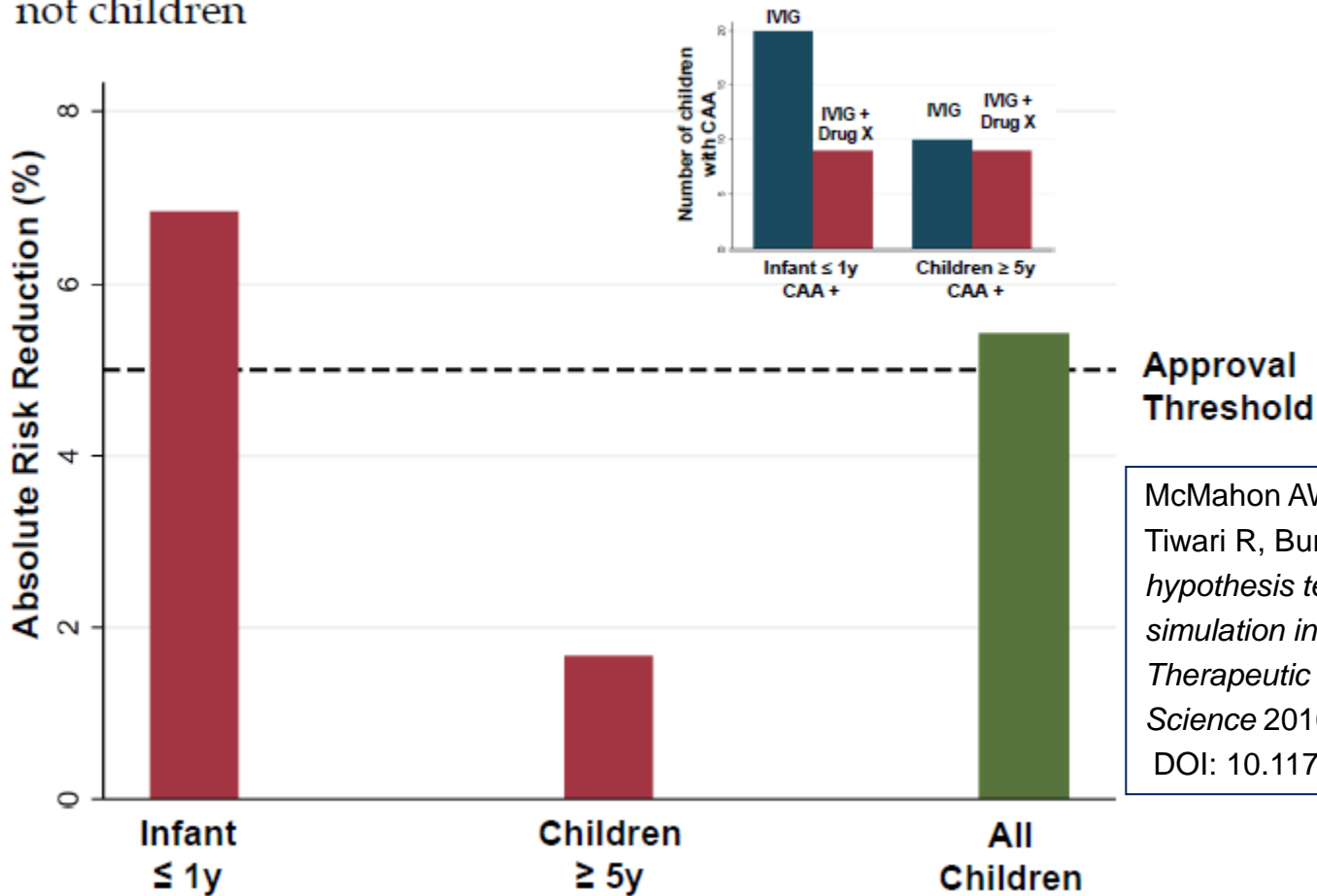
Drug name	Pediatric age group studied in PK, safety, and/or efficacy studies	PGx biomarker in labeling	Biomarker classification	Suitability of extrapolating PGx data from adults to pediatrics	Comment
Abacavir	3 months & older	HLA-B*5701	Immunologic	Suitable	^a
Anastrozole	2 years & older	Estrogen receptor	Target/Pathway	Unclear	Diseases studied in adults (breast cancer) and pediatrics (McCune Albright Syndrome & gynecomastia) were different. PGx biomarker (estrogen receptor) only relevant to the adult disease.
Aripiprazole	6 years & older	CYP2D6	Metabol/Transport	Suitable	^b

- The application of PGx information from adults to pediatrics was deemed suitable for 71.4% (n = 40) of the drugs and unclear for 28.6% (n = 16).

Clinical Trial Simulation Prediction of Outcome of Pediatric Trials



Hypothesis 2: Drug X + IVIG decreases risk of CAA in infants but not children

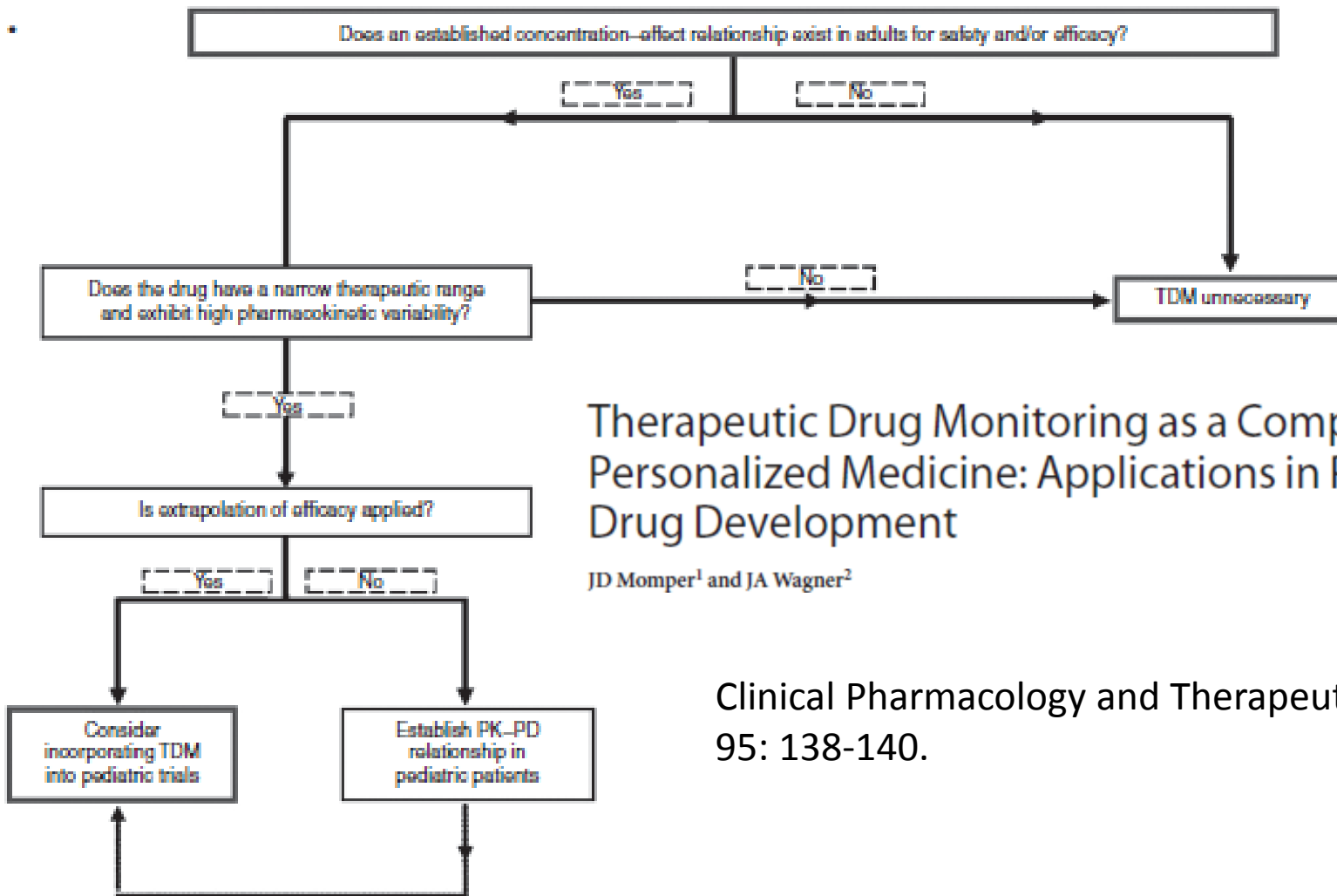


McMahon AW, Watt K, Wang J, Green D, Tiwari R, Burckart GJ. *Stratification, hypothesis testing, and clinical trial simulation in pediatric drug development. Therapeutic Innovation and Regulatory Science* 2016; DOI: 10.1177/2168479016651661

What number of pediatric patients must be studied?

- Considerable variability in PK has been noted in the pediatric population;
 - The extreme example is the neonatal population;
- The Guidance states that: **“Justification should be provided for the sample size selected. For example, one approach would be to prospectively target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for the drug in each pediatric subgroup with at least 80% power.”** (J Clin Pharmacol 2012; 52: 1601-1606).

Therapeutic Drug Monitoring and Pediatric Drug Development



Therapeutic Drug Monitoring as a Component of Personalized Medicine: Applications in Pediatric Drug Development

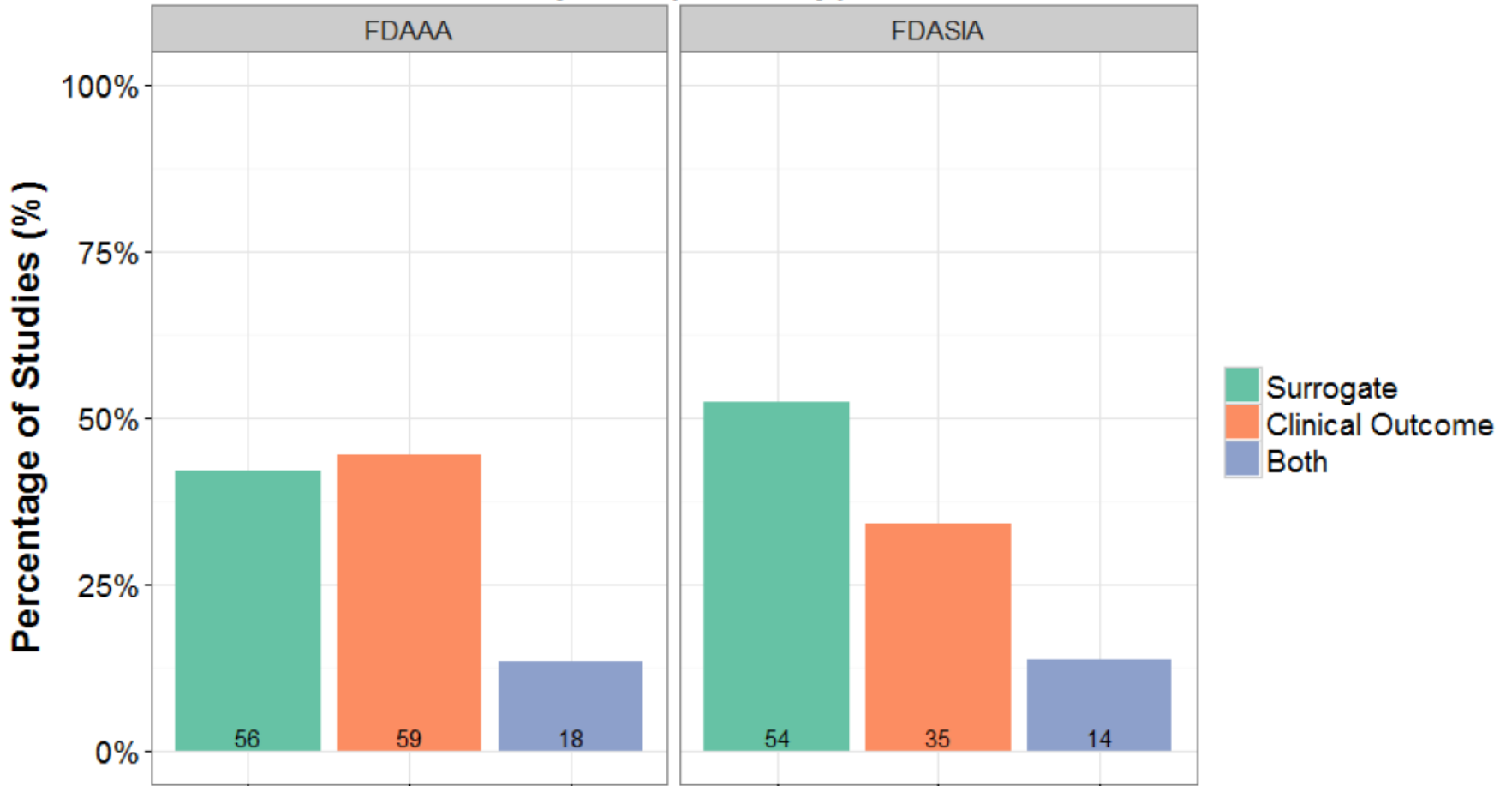
JD Momper¹ and JA Wagner²

Clinical Pharmacology and Therapeutics 2014; 95: 138-140.

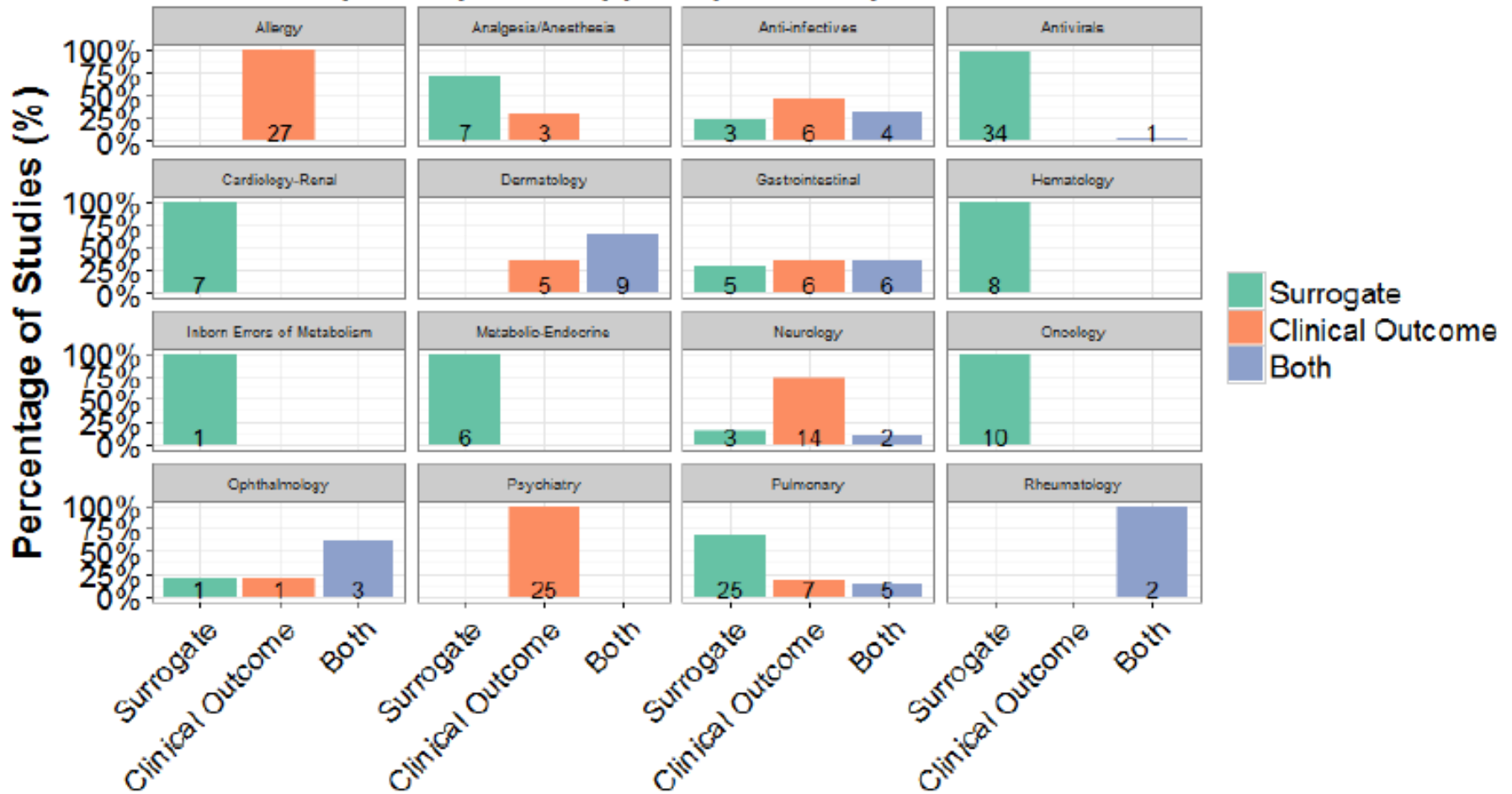
What are the pediatric PD endpoints that are accepted?

- Most PD endpoints in pediatric clinical trials are surrogate endpoints;
- A **surrogate endpoint** of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives.
 - Changes induced by therapy on the **surrogate endpoint** are expected to reflect changes in a clinically meaningful endpoint;

Study Endpoint Type



Study Endpoint Type by Therapeutic Area



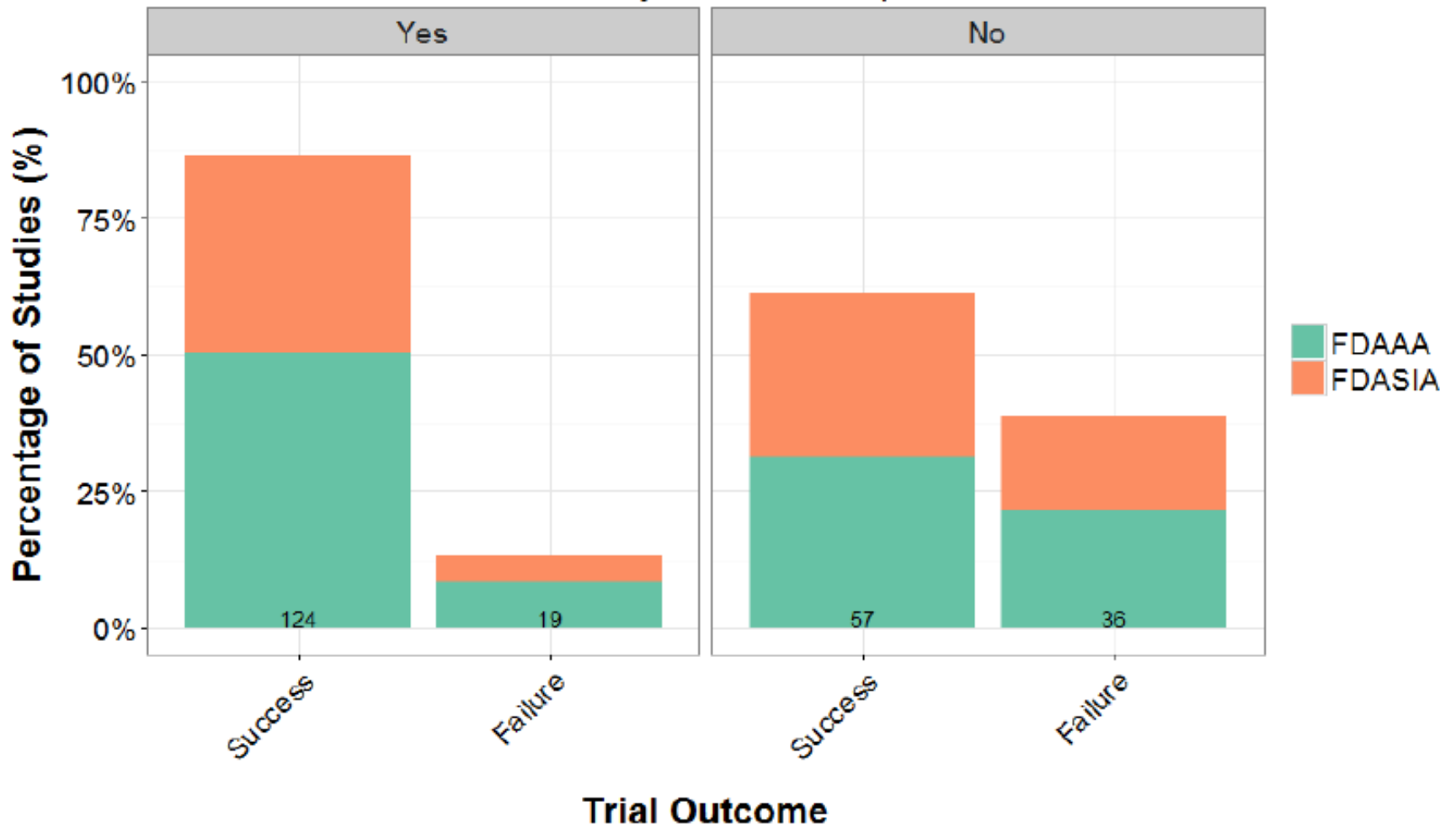
PD Endpoint Selection

- Endpoints are NOT always the same for pediatrics as in the corresponding adult studies;
- Using a different PD marker for your pediatric trial affects the chances of having a failed trial;
- Patient reported outcomes may require a validated pediatric tool;

Examples – Failed Trials where the Pediatric & Adult Endpoint are Not the Same

Indication	Ped Age Grp	Ped Endpoint	Time of Measurement	Adult Endpoint	Time of Measurement
PAH	1 - 17 yrs	Percent change in VO2 peak	16 wks	6-minute walk	12 wks
Chronic HBV	2 – 17 yrs	HBV DNA <1000 copies/mL & ALT normalization	48 wks	Histological improvement (biopsy)	48 wks
Bronchospasm	0 - 5 yrs	Daily asthma SS; Ped Asthma Caregiver Assessment	4 wks	FEV1	12 wks
Ppx or Tx of thrombosis (pts w/ HIT)	0 - 16 yrs	aPTT & ACT	2 hrs following every infusion	Death & amputation & new thrombosis	Time to event
Anticoagulation (PTCA or PCI or at risk of HIT)	0 – 16 yrs	ACT	30 days	Death, MI, urgent revascularization, vessel closure	Time to event
PONV	2 – 16 yrs	Complete control (no nausea, vomiting, or rescue meds)	Within 2 hrs following extubation	Complete control (no nausea, vomiting, or rescue meds)	Within 24 hrs after surgery
Ulcerative colitis	5 – 17 yrs	Treatment success defined by PUCAI	6 wks	Treatment success defined by PGA	6 wks

Trial Outcome by Same Endpoint Used



Should I conduct a pediatric PK/PD clinical trial simulation?

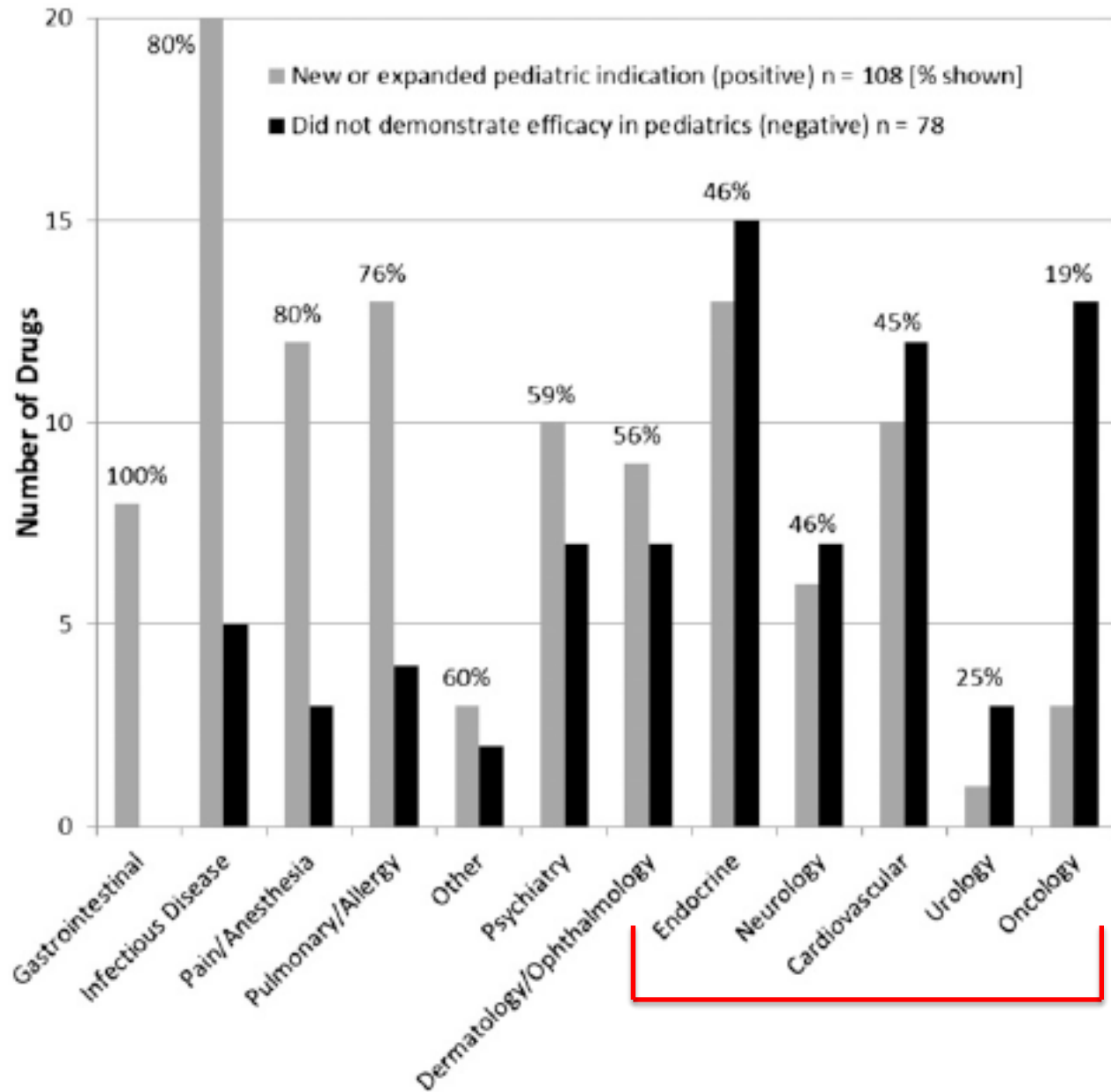
- 1990's – Dr. Carl Peck, Director of CDER, was one of the drivers of incorporating CTS into the drug development process;
- Dr. Peck started with PK/PD, but then moved to CTS that encompassed all aspects of trial design;
- CTS has become an integral part of drug development for adults.

Conducting a Pediatric CTS

- CTS prior to the Pediatric Study Plan may be too early for many programs;
 - Too many assumptions would need to be made.
- In therapeutic areas where a number of pediatric failed trials have occurred, pediatric trail simulation may be essential to incorporate new information;
 - Prior reports have identified problem therapeutic areas.

Failed Pediatric Trials occur in Multiple Therapeutic Areas

Pediatrics 2014;
134:e512–e518



Ethical Considerations for Pediatric PK Studies

- Designing a pediatric PK requires special ethical considerations, discussed in the Guidance.
- In general, studies cannot be conducted in “normal children”, only in patients, and the pediatric patients should benefit from the study.
- “Clinical pharmacology studies generally do not provide a direct clinical benefit to individual pediatric subjects, and must therefore present no more than minimal risk (21 CFR 50.51) or a minor increase over minimal risk (21 CFR 50.53)”.

Ethical Considerations - Options

- The options for pediatric patients include:
 - Incorporating the PK study into a clinical trial offering benefit to the pediatric patient;
 - Designing the pediatric PK study with an option for an open label continuation on the drug therapy;
 - An adaptive design where several doses are used prior to a pre-designed evaluation, with continuation on the most effective dose.

Pediatric Challenges Relating to PK/PD

- Pediatric dosing is not yet a science;
 - Inconsistent use of allometric scaling, PopPK, PBPK
 - Selection of dose(s) to be taken into pediatric clinical studies
 - Exposure matching doesn't "match"
- Application of M&S to reduce numbers of patients for pediatric studies;

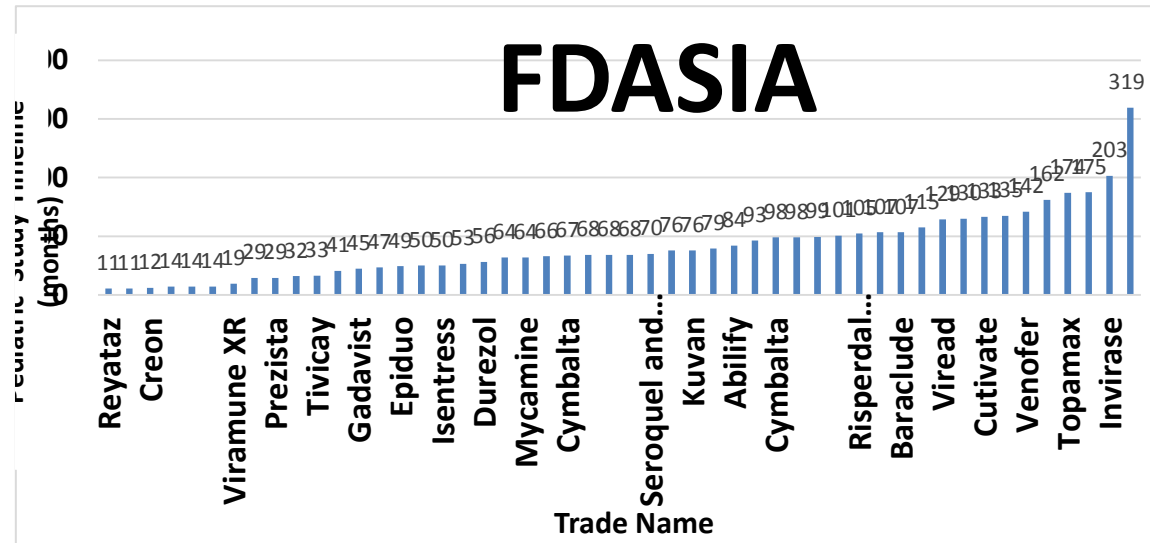
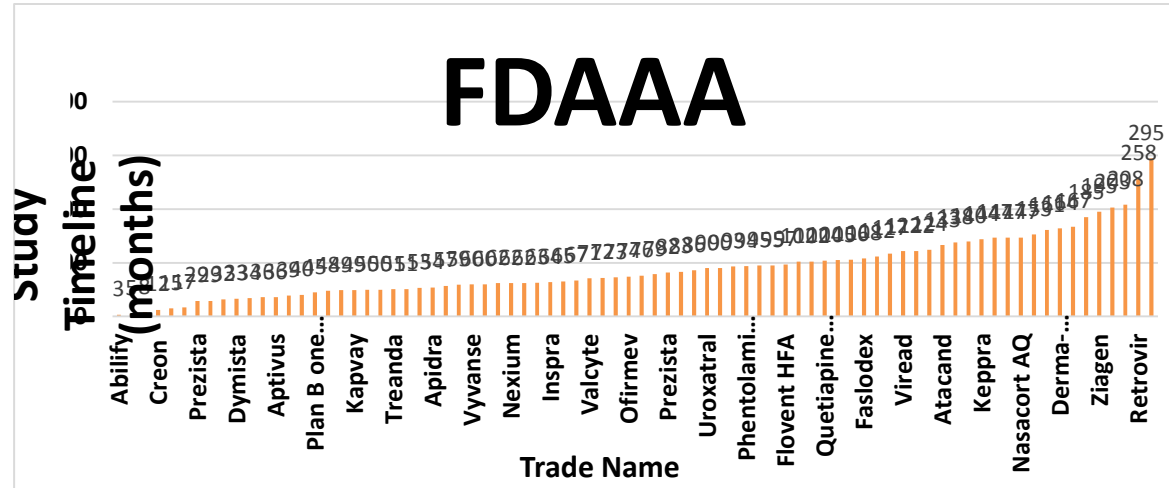
ICH E11 Addendum Adds Some Challenges for Modeling and Simulation

- The usefulness of M&S in pediatric drug development includes, but is not limited to:
 - clinical trial simulation
 - dose selection
 - choice and optimization of study design
 - endpoint selection
 - extrapolation
- Risk assessment is a critical part of M&S.

Pediatric Challenges

Drug development times (adult approval to pediatric labeling) are not decreasing!

Better and earlier PK/PD studies may enable earlier initiation of pediatric clinical trials!



Summary

- Pediatric PK/PD studies have made significant progress in the past 20 years;
- A number of failed pediatric trials are still on the basis of dosing and PK/PD studies, so we should learn from these prior trials;
- The future of pediatric drug development looks very bright in light of an improved understanding of pediatric PK/PD and the application of modeling and simulation to pediatric study design.

