Pediatric Drug Development Experience with Dose Selection

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The comments and concepts presented are those of the speaker and should not necessarily be interpreted as the position of the US FDA

Development of Pediatric Regulations

- 1997- Food & Drug Administration Modernization Act
  - initial BPCA pediatric incentive program
- 1998 - Pediatric Rule- mandated pediatric studies under particular circumstances
- 1998 - Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
- 2002 Best Pharmaceuticals for Children Act
  - renewal of pediatric incentive program
  - study of off patent drugs
  - public dissemination of pediatric information
  - Still required 5 year renewal

Current Era of Pediatric Drug Development

- 2002 Pediatric Rule Enjoined
- 2003 Pediatric Research Equity Act
- 2007 FDA Amendment Act (FDAAA)
  - 5 yr renewal of BPCA and PREA
  - Pediatric labeling requirement
  - Pediatric Review Committee
- 2012 FDA Safety and Innovation Act (FDASIA) – Title V
  - Neonatal studies

Numbers of Pediatric Products Submitted to the FDA

- January, 2002 – September, 2007
  - Number of products = 87
- September, 2007 – July, 2012
  - BPCA =27, PREA = 105, both = 30
  - Total 162 products
- July, 2012 to present
  - BPCA = 26, PREA = 93, both = 4
  - Total 123 products
- TOTAL = 372 products

Summary of Approaches to Extrapolation
(Assessment of 166 products between 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)

Adapted from Dunne J et al. Pediatrics 2011;128;e1242.

Pediatric Imperative

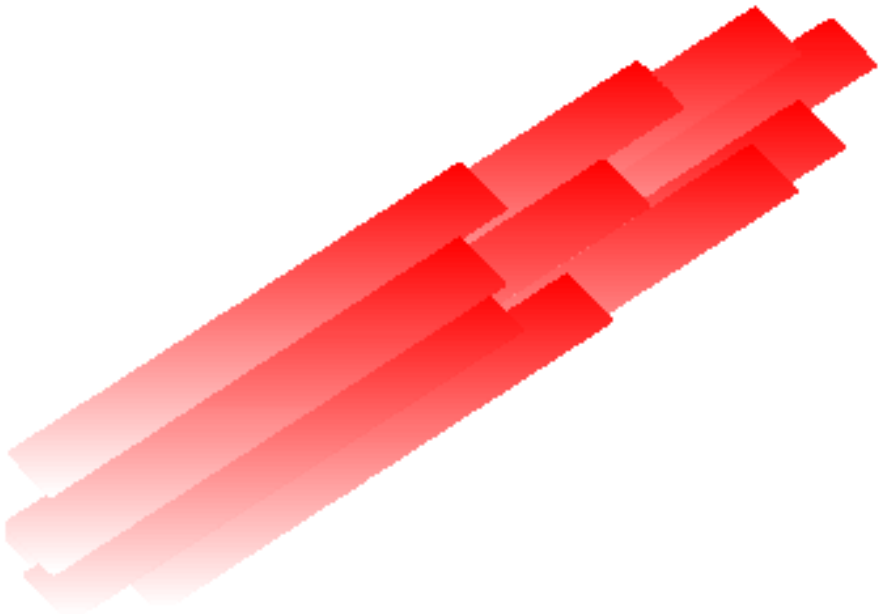
- Therefore over 1,000 pediatric studies have been submitted to the FDA to date;
- Ethical considerations require that there be a benefit to the pediatric patient to enroll that patient in a research study;
- If that study fails, there is little benefit.

Regulatory Requirements

- The standards for approval for pediatric patients are no different than those of adults.
  - 1998 Evidence of Clinical Effectiveness Guidance provides the standards;
  - The Guidance provides some flexibility for interpretation by the Agency.
- The sponsor is required to identify an “effective” dose, not the optimal dose.

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
Clinical 6

1998 Guidance

- Establish effectiveness using “substantial evidence”
- Describes the circumstances under which a single study is sufficient.

That single study could be a well designed exposure-response study.

Establishment of Pediatric Dosing

1. Best examples of poor dose selection come from failed attempts to establish a pediatric indication;
2. Endpoints for the drug effect is a critical part of designing pediatric drug dosing and effectiveness trials;
3. Understanding the pediatric disease process is a critical part of developing a dosing strategy.

1. FDA reviews of Pediatric Failed Studies

Impact of Pediatric Exclusivity on Drug Labeling and Demonstrations of Efficacy

WHAT'S KNOWN ON THIS SUBJECT: Most therapeutic products used in children have not been studied in that population. There is a need for special incentives and market protection (pediatric exclusivity) to compensate drug sponsors for studying these

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Pediatrics 2014;134:e512–e518

Failed Pediatric Drug Development Trials

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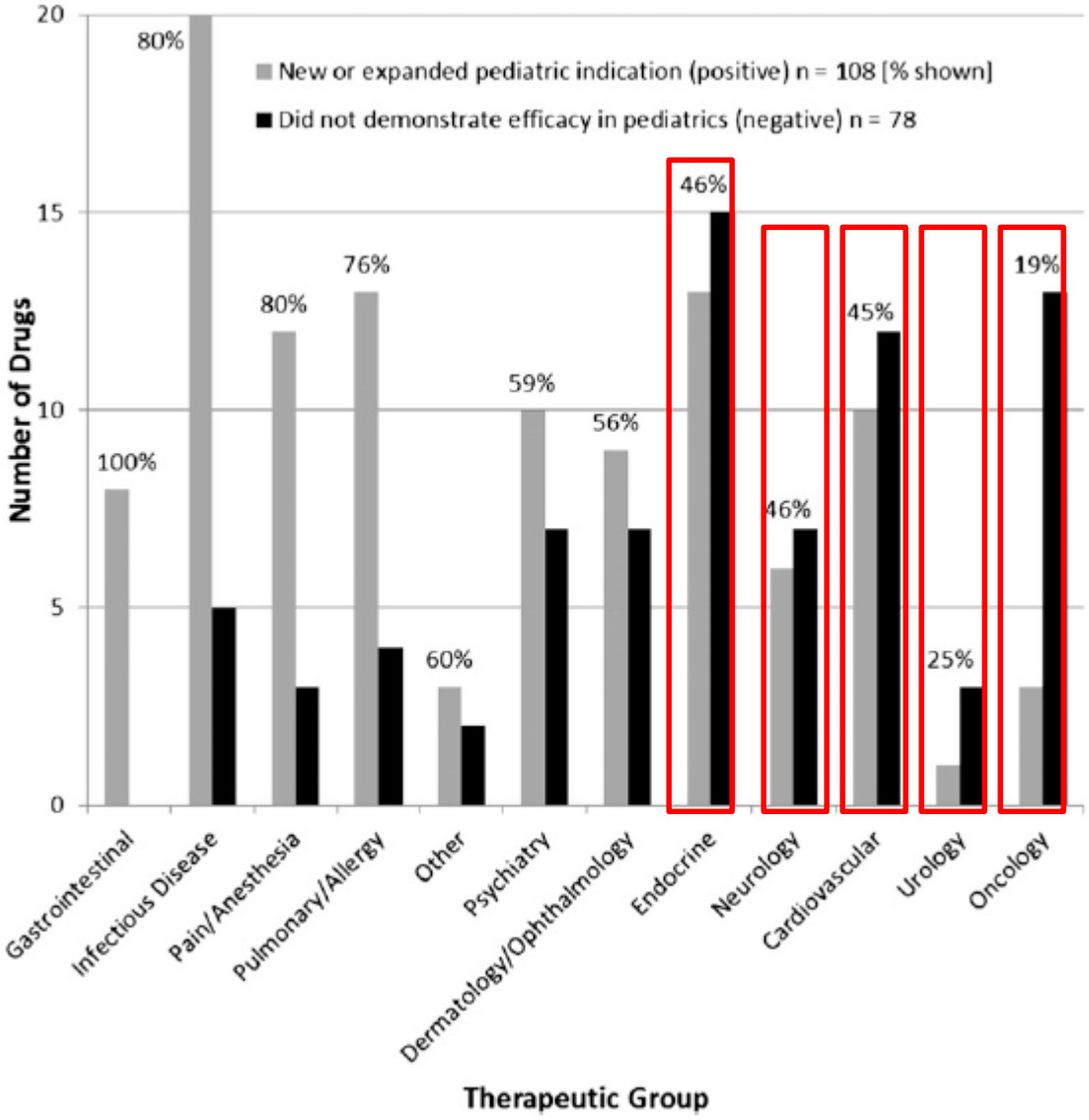
Clinical Pharmacology and Therapeutics 2015 (Sep); 98:245-251

Failed Studies Under BPCA

- 1998-2012 – 189 products studied;
- Efficacy was not established for 78 drugs;
- 43% failed to get a new or expanded pediatric indication;
- Failures were associated with some specific therapeutic areas.

Pediatrics 2014;134:e512–e518



Drugs granted PE by therapeutic group and positive trial rate 1998 to 2012

% = success rate

Wharton GT et al. Impact of Pediatric Exclusivity on Drug Labeling and Demonstrations Of Efficacy. *Pediatrics* 2014; 134:e512-518

Review of Failed Pediatric Trials

- 44 products failed in pediatric programs between 2007-2014
- Reasons for failure are not always clear;
- Primary contributing factors were:
  - **Drug dosing;**
  - Understanding the pediatric vs. the adult disease process;
  - Placebo response;
  - Study design.

CPT 2015 (Sep); 98:245-251

Determining the Correct Pediatric Dose

- Contributing factor in 25% of failed trials;
- Issue 1: Not testing a range of doses
  - albuterol, anastrazole, clopidogrel, docetaxel, fulvestrant
- Issue 2: Limiting pediatric drug exposure to that which has been shown to be efficacious in adults for a clinically distinct disease
  - alfuzosin, bendamustine, bicalutamide, clopidogrel, docetaxel, eszopiclone, tamsulosin

Testing a Range of Pediatric Doses

- Hypertension in Pediatric Patients
  - Benjamin DK Jr, et al. Pediatric Antihypertensive Trial Failures Analysis of End Points and Dose Range. *Hypertension* 2008;51:834-840.
  - Reviewed 6 agents; 3 successful and 3 failed drugs
  - In the **failed** amlodipine, fosinopril and irbesartan trials, dosing ranges were also small, at 2-, 6- and 9-fold, respectively.
  - The **successful** enalapril, lisinopril, and losartan trials had considerably higher dosing ranges, at 32-fold, 32-fold, and 20-fold, respectively.
  - Fixed rather than body weight dosing (amlodipine) was also identified as a problem.

Limiting Drug Exposure in Pediatric Patients to That Observed in Adults

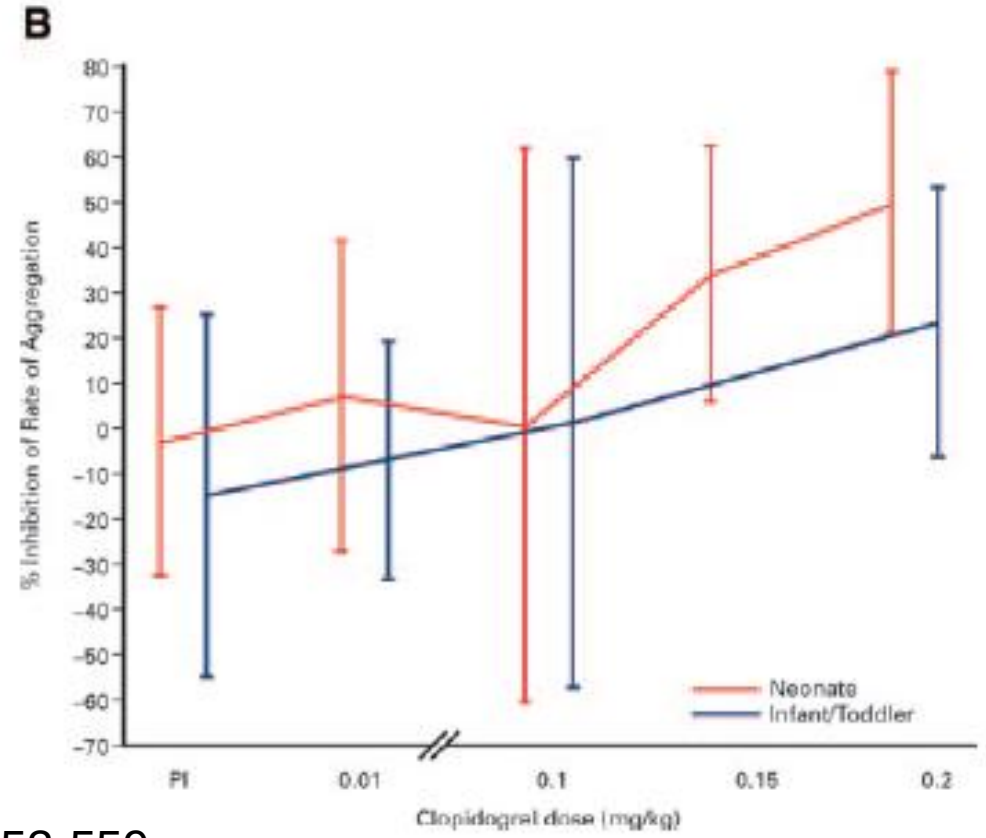
- Neurogenic Bladder
  - Momper JD et al. Drug Development for Pediatric Neurogenic Bladder Dysfunction: Dosing, Endpoints, and Study Design. The Journal of Clinical Pharmacology 2014; 54(11) 1239–1246.
  - Four agents reviewed, all with limiting exposure to that observed in adults with OAB or BPH; 3 of the 4 agents failed.
  - A publication in adults with NBD suggested that doubling the recommended dose for OAB was effective.
- Pediatric Oncology
  - New area where pediatric dosing will be difficult;
  - Recent discussion: will the adult exposure targeting melanoma be effective in pediatric glioblastoma?

2. Pediatric Endpoints and Dose Selection

- Use of an unvalidated endpoint in a pediatric trial may lead to poor dose selection and trial failure;
  - Clopidogrel pediatric development program
- Especially critical when the endpoint is specific to pediatric patients and is not shared with adult studies;
  - 3X the failure rate when the pediatric and adult endpoints are different

Results of the Platelet Inhibition in Children On Clopidogrel (PICOLO) Study

"The upcoming Clopidogrel to Lower Arterial thrombotic Risk In NEonates and infants Trial (CLARINET) is a multicenter, randomized, controlled trial that will assess efficacy and safety of the presently established dose of clopidogrel **0.2 mg/kg/day** in neonates and infants……"



Li JS et al. Circulation 2008;117;553-559

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CLARINET failed to demonstrate efficacy of clopidogrel with the 0.2 mg/kg dosage

Event	Placebo (N=439)	Clopdigrel 0.2 mg/kg/day (N= 467)
Primary Outcome	90 (20.5%)	89 (19.1%)
Death	60 (13.7%)	51 (10.9%)
Shunt Thrombosis	21 (4.8%)	26 (5.6%)
Cardiac Procedure <120 days considered as thrombotic in nature	9 (2.1%)	12 (2.6%)
Relative Risk Reduction, % (95% C.I)	11.1 (-19.2 to 33.6)	
Log Rank Test, p-value	0.4340	

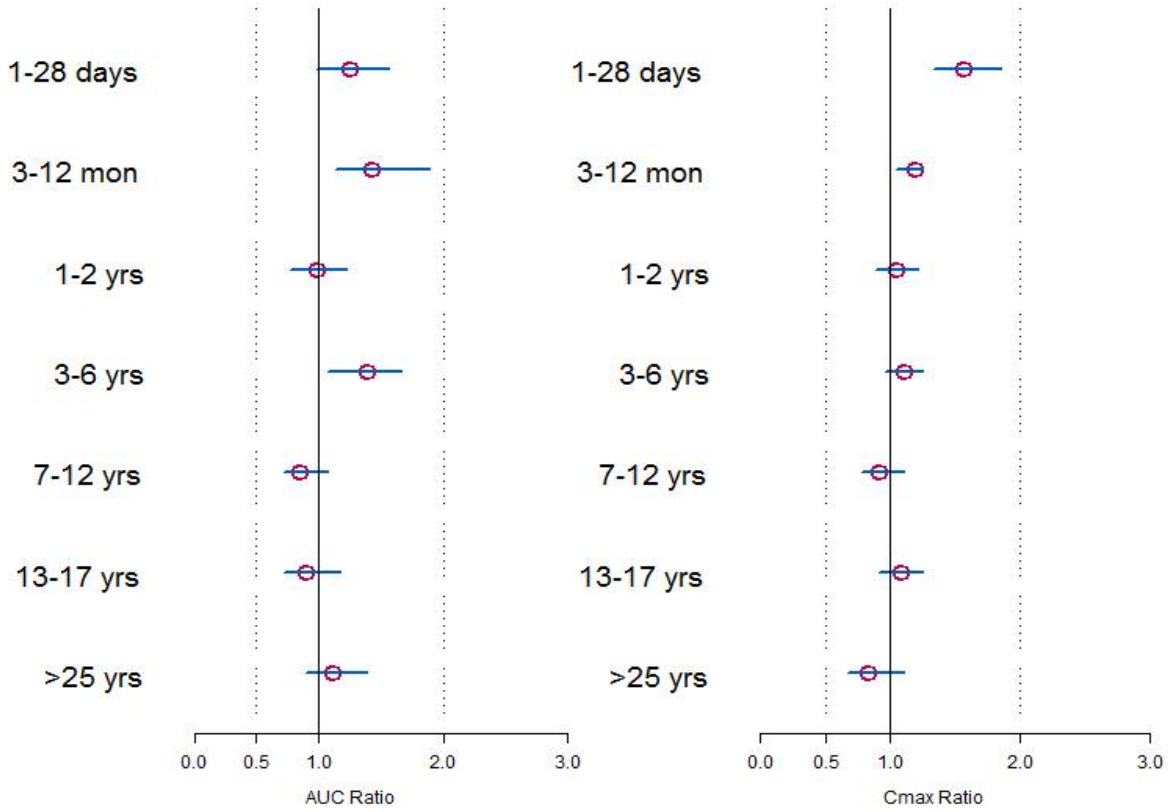
3. Understanding the Pediatric Disease Process as Part of Dose Selection

- Gastroesophageal Reflux Disease (GERD) in Infants
  - Symptomatic GERD in infants is primarily related to motility and abnormal transient lower esophageal sphincter relaxation, while sGERD in older children and adults is acid-mediated.
  - Multiple acid-suppressing agents had been tested in neonates and infants;
  - Based on this information and the advice of the FDA Gastrointestinal Drugs Advisory Committee (November 5, 2010), the FDA no longer requires trials in sGERD in infants for acid-suppressing drugs.

Techniques Used to Select A Pediatric Dose

- Allometric Scaling
  - Edginton AN et al. The Integration of Allometry and Virtual Populations to Predict Clearance and Clearance Variability in Pediatric Populations over the Age of 6 Years. *Clin Pharmacokinet* (2013) 52:693–703.
- Population PK
  - "limited confidence in the extrapolation of PopPK modeling for the purposes of neonatal PK prediction"; Wang J et al. *J Clin Pharmaco*l 2015, 55(10) 1175–1183
- Physiologically-based PK
  - Predictions in neonates for renally-eliminated drugs may be possible (Dr. Jian Wang, FDA, observations)

Linezolid PBPK Across Pediatric Age Groups



Comparison between the linezolid predicted and observed value of the ratio of the area under the plasma concentration-time curve (AUC) (Left); and the ratio of the maximum concentration (C_{max}) (Right). Results are presented as mean ratios (red solid circles) in each age group with a 95% CI (horizontal lines).

Source: Jian Wang, Ph.D., US FDA

Summary

- Pediatric dosing remains a significant problem, especially as we move to studies in the youngest pediatric patients;
- When pediatric diseases are or may be different from the adult disease, testing a range of doses and not relying on adult exposures appears to be a prudent strategy;
- A better understanding of pediatric endpoints and diseases will facilitate better pediatric dosing strategies.