Innovative Approaches to Pediatric Drug Development and Pediatric Medical Counter Measures (MCM): A Role for Physiologically-Based PK?: Workshop Introduction

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Clinical Pharmacology Advisory Committee – March, 2012

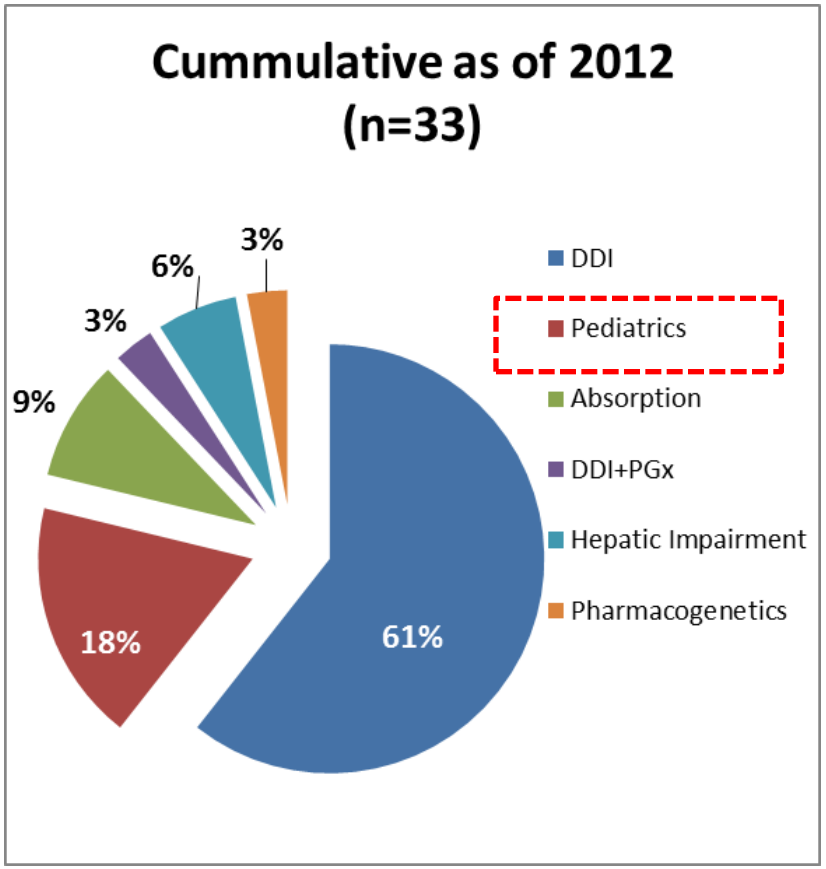
Focus was on pediatric drug development, and the problems that have been encountered over the past 10 years.

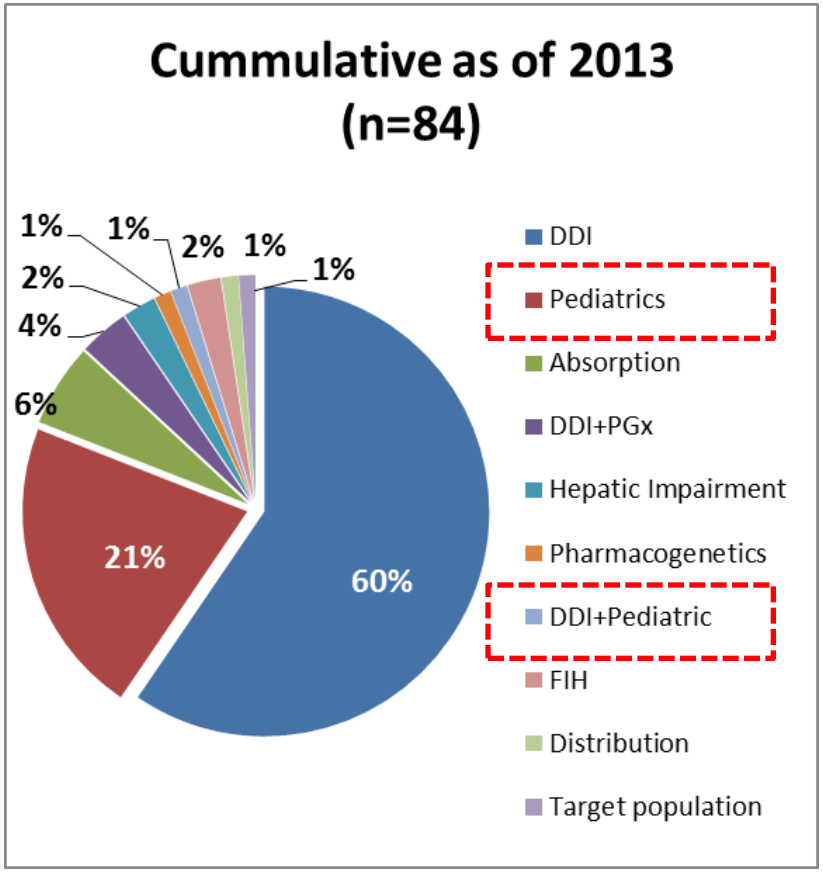
1. Should modeling and simulation methods be considered in **all** pediatric drug development programs?

(**VOTE**) **YES: 13** **NO: 0** **ABSTAIN: 0**

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm286697.htm

PBPK Being Utilized by Sponsors

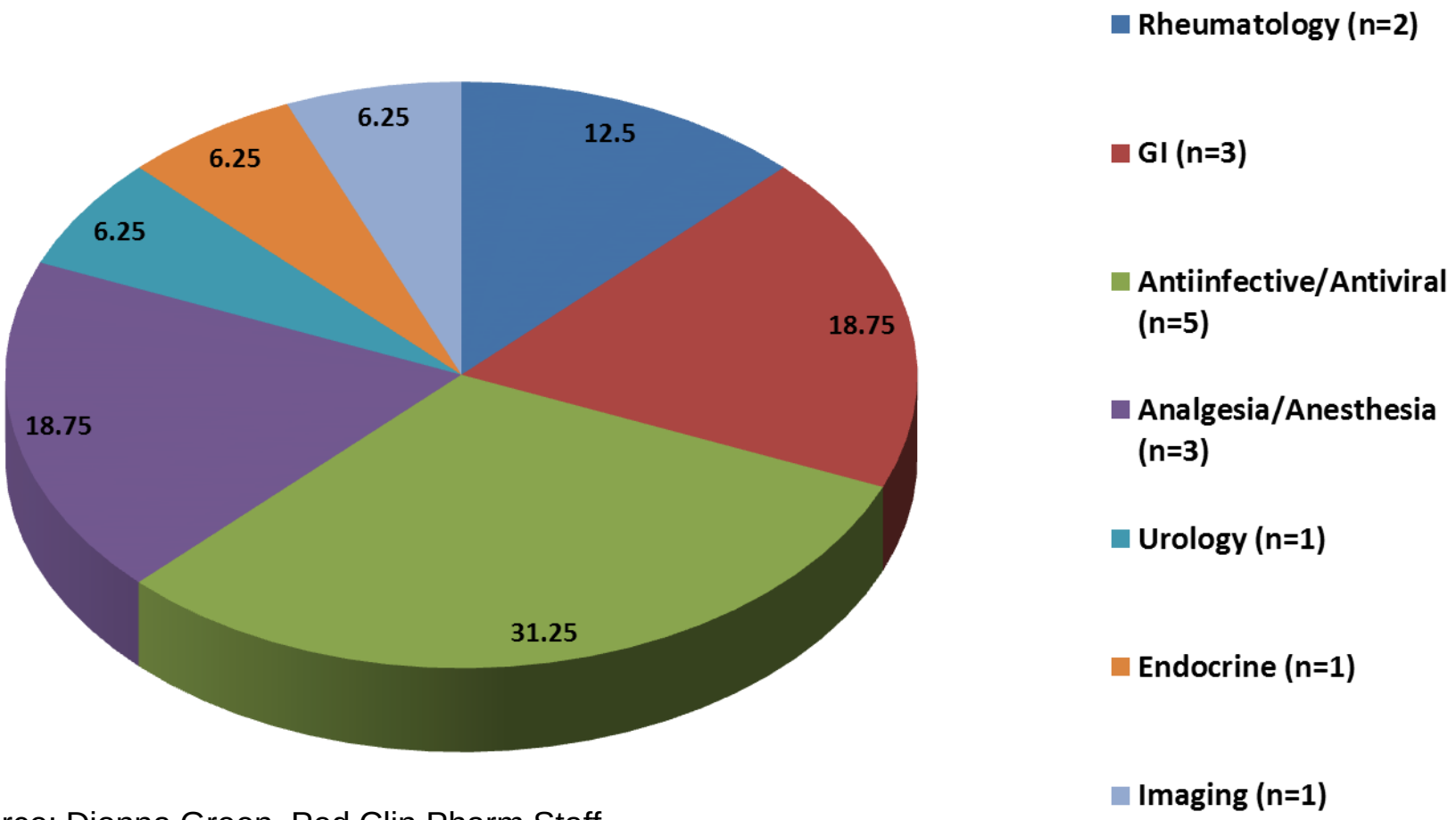




Huang et al, J Pharm Sci, 2013

Adapted from Zhao Ping PBPK Workshop 2014

36% (16/45) of partial extrapolation product reviews describe the use of M&S in development program



Source: Dionna Green, Ped Clin Pharm Staff

Types of Pediatric Studies Conducted Under BPCA and PREA

Breakdown of completed pediatric studies Sept. 27, 2007 – November 18, 2013

Type of Study	BPCA	BPCA + PREA	PREA	Total
Efficacy/Safety	45	31	201	277
PK/Safety	9	40	20	69
PK/PD	14	8	9	31
Safety	6	4	25	35
Other	2	10	45	57
Total	**76**	**93**	**300**	**469**

Total number of patients in completed FDAAA studies: 178,425

23,628 in BPCA studies; 32,839 in CDER PREA studies;

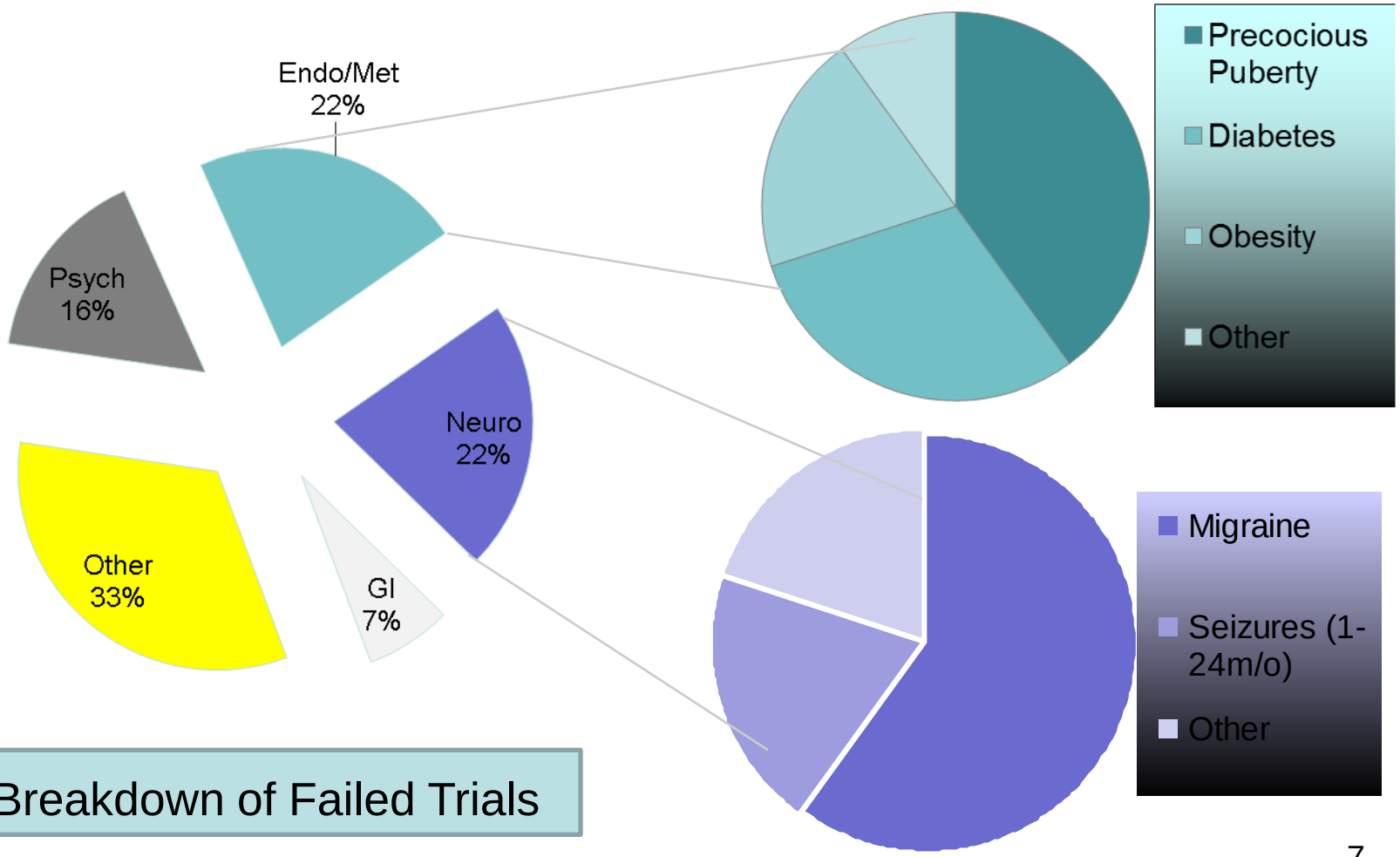
121,958 in CBER PREA studies (Vaccines and Blood Products)

New Pediatric Labeling Information

- **N = 500 Pediatric Labeling changes**
- **n = 453 with New Pediatric Studies; n = 47 with No New Pediatric Studies**
- **BPCA only = 157; BPCA + PREA = 66; PREA only = 228; Rule = 48; None = 1**

- Pediatric Labeling Changes as of September 30, 2013
- http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase

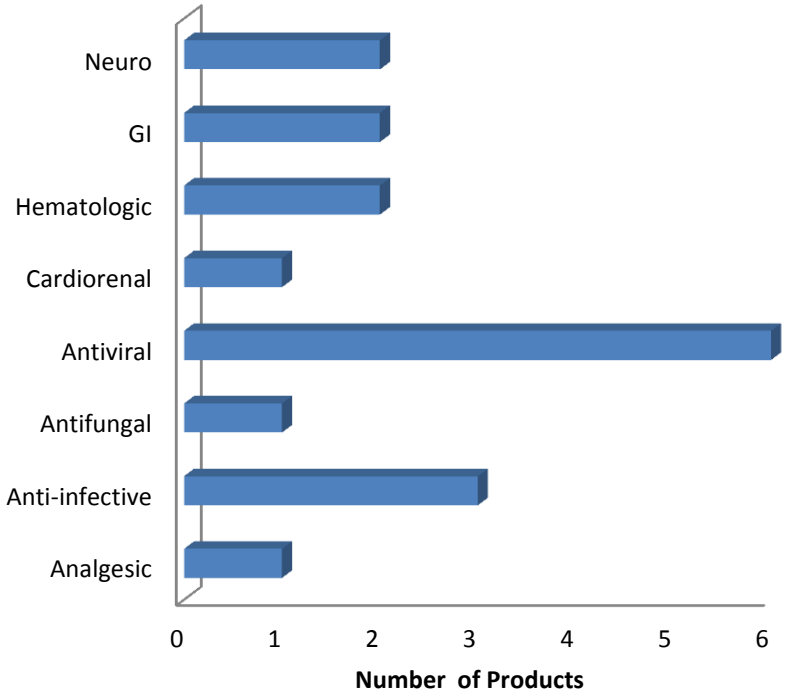
Challenge: Approximately 25% of pediatric trials fail to result in a labeled indication



Breakdown of Failed Trials

Source: Lily Mulugeta, Ped Clin Pharm Staff

Challenge: Lack of dosing information in neonates/infants



Medication	% exposed	US FDA labeling for premature infants
Ampicillin	74	None
Gentamicin	68	None
Cefotaxime	36	None
Caffeine citrate	19	None <29 weeks
Furosemide	19	None
Vancomycin	17	None
Beractant	14	Yes
Metoclopramide	11	None
Aminophylline	11	None
Dopamine	10	None

Only 18 out of 161 products studied under FDAAA have PK data in pts. <1yr. of age

Only 1 out of the top 10 products used in the NICU is labeled for use in premature infants

Source: Lily Mulugeta, Ped Clin Pharm Staff

Adapted from Laughon et al. *Expert Rev. Clin. Pharmacol*., 2011

Pediatric Trial Design Challenges

- Innovative trial designs for pediatric patients are rarely used;
  - The "**Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products"** December, 2012 Guidance for Industry provides a number of strategies and examples.
- Clinical trial simulation, as searched in FDA pediatric reviews, is not utilized.

Workshop Focus

- Focus on modeling and simulation in the most difficult pediatric populations;
  - Neonates and infants
  - Pediatric Medical Counter-Measures
- Identify those studies that would have to be performed to provide adequate support for the M&S approaches necessary to support pediatric drug development.
  - Selection and Validation of models
  - Understanding ontogeny
  - Understanding the place of in vitro and animal studies in providing pediatric M&S prior information