Experience in FDA Submissions with Matching Pediatric Drug Exposure to Adult Drug Exposure

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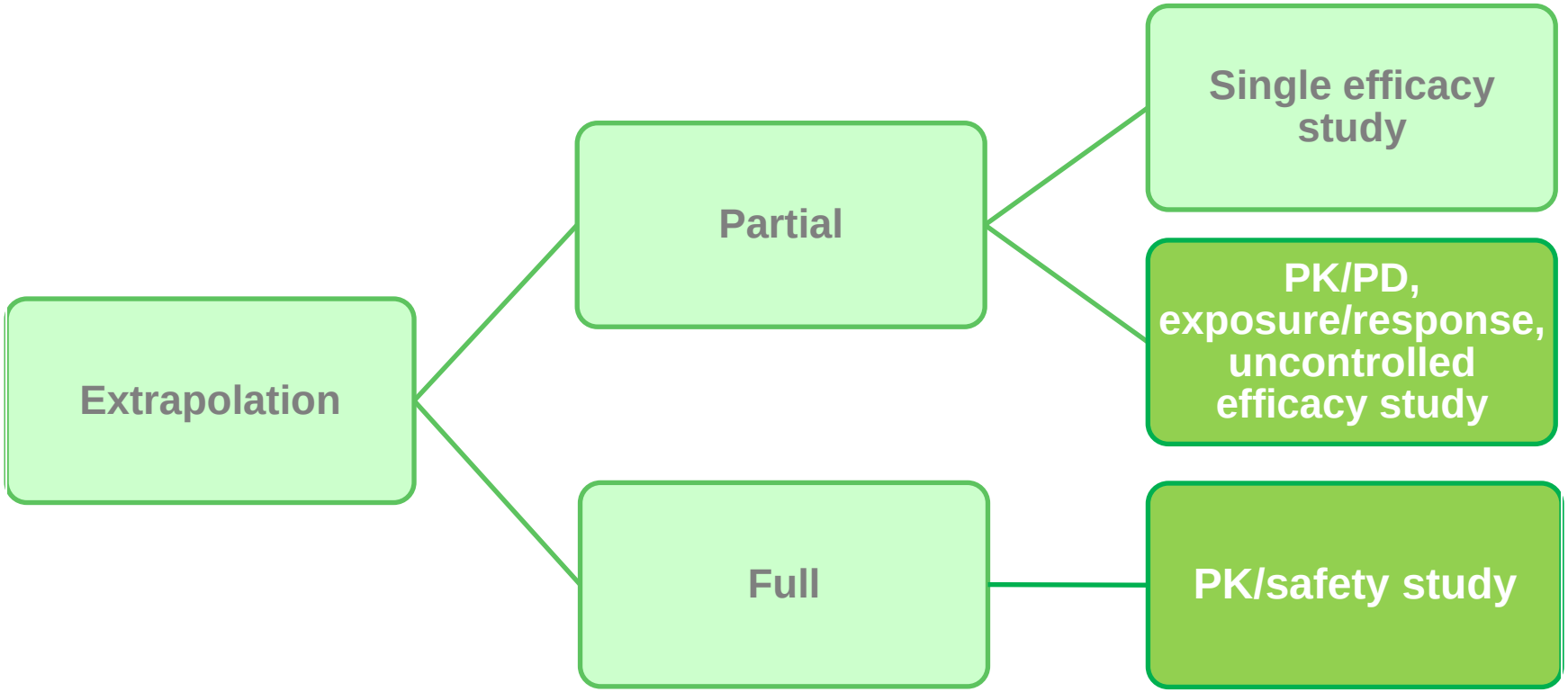
Extrapolation of Efficacy in Pediatric Drug Development

Level of extrapolation	Products studied in response to BPCA *	Products studied under FDAAA/FDASIA +
	1998-2008	2007-2014
Full/Complete	14.5%	11.3%
Partial (PK/PD, ER, uncontrolled efficacy, single efficacy study)	68%	72.6%
No Extrapolation	17.5%	16.1%
	n=166	*n=113*

Source: * Dunne et al. Extrapolation of adult data and other data in pediatric drug development programs. *Pediatrics* 2011

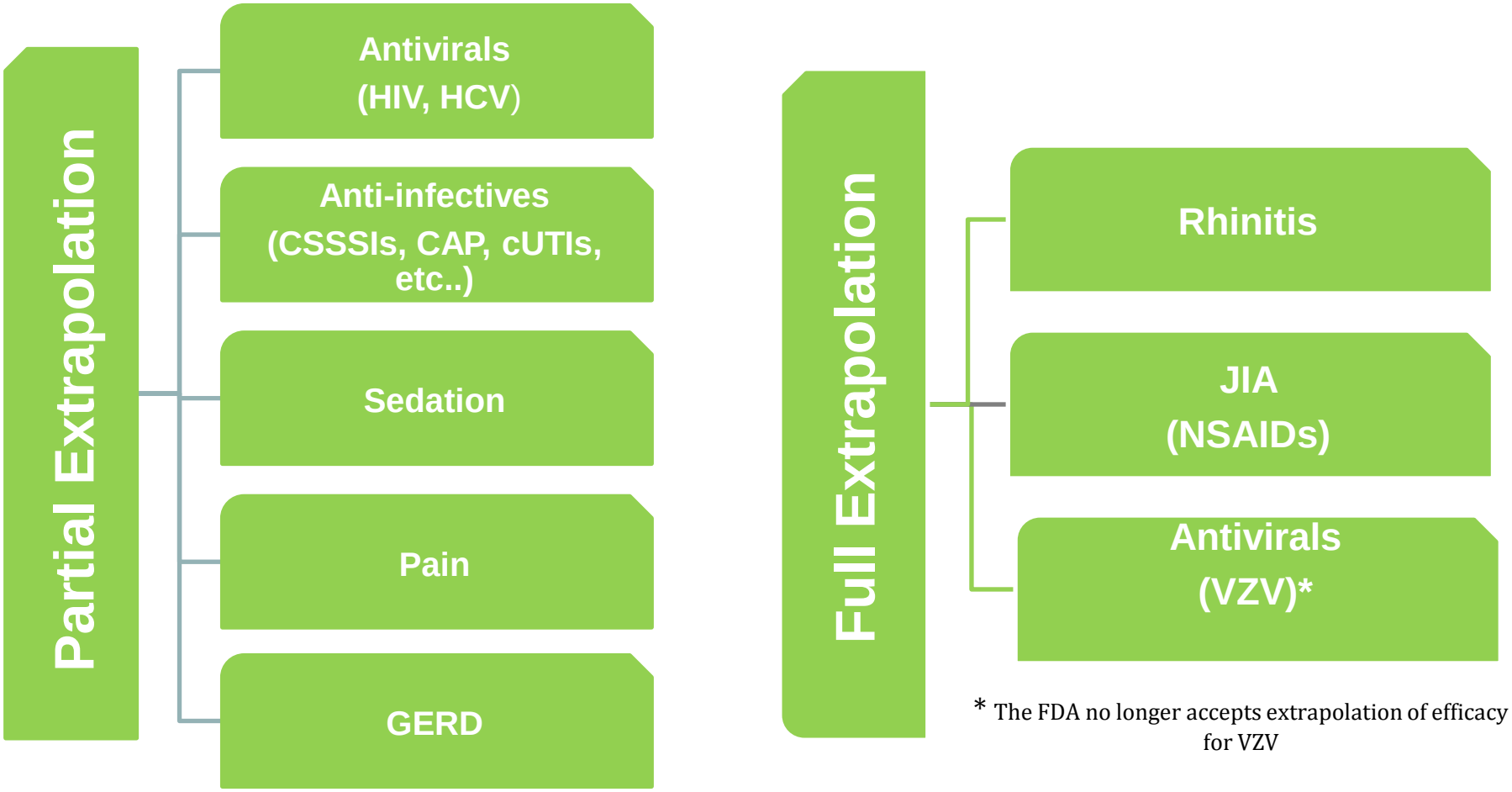
+ : FDA Office of Pediatric Therapeutics Descriptor of Pediatric Studies under FDAAA and FDASAI; Excludes CBER products including vaccines

Extrapolation of Efficacy : Exposure Matching



Source: * Dunne et al. Extrapolation of adult data and other data in pediatric drug development programs. *Pediatrics* 2011

Extrapolation of Efficacy : Exposure Matching



* The FDA no longer accepts extrapolation of efficacy for VZV

Source: * Dunne et al. Extrapolation of adult data and other data in pediatric drug development programs. *Pediatrics* 2011

Key Question: What constitutes exposure matching (achieving similar exposure as adults)?

Exposure matching: Review of FDA Submissions

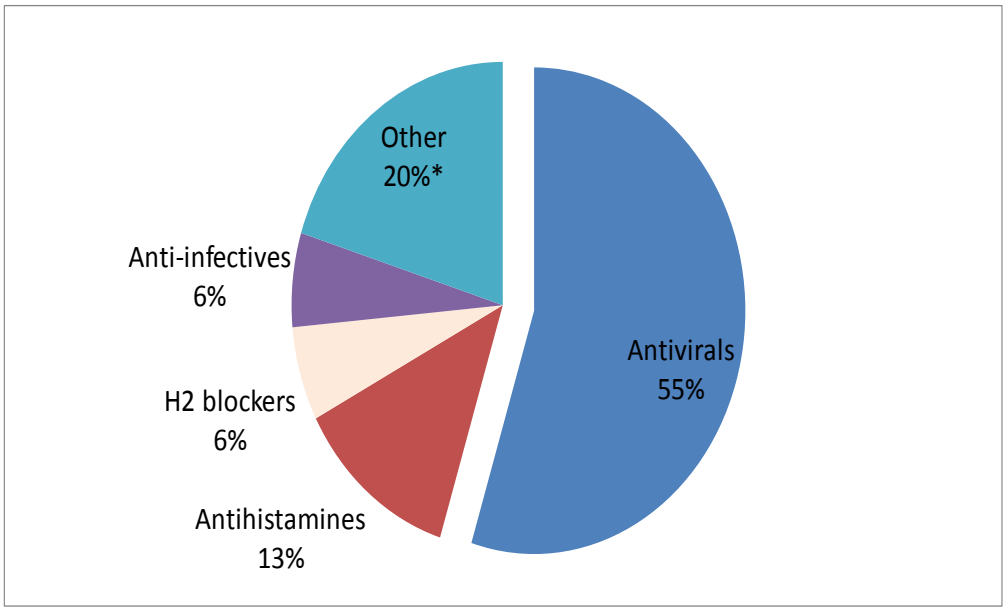
- Retrospective review of pediatric trials submitted under PREA or BPCA 1998-2012
- Included trials with full or partial extrapolation relying on exposure matching
- Data retrieved from FDA clinical pharmacology reviews*
- Excluded locally acting products; focus on systemic drugs
- Data on trial design, key exposure metric, justification for target exposure, acceptance criteria
- Excluded trials without mean pediatric and adult PK values + variability reported in FDA review

*Source: http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm

Characteristics of studies

- A total of 31 products (86 trials) included from February 1998 to August 2012 with full or partial extrapolation relying on exposure matching
  - 12 (38.7%): Full extrapolation
  - 19 (61.3%): Partial extrapolation

Majority of products were antivirals, studied in more than 1 pediatric age group



Age groups	Trials (%)
Birth to less than1 month	12.5
1 to less than 6 mons	28.1
6 mons to less than 2 yrs	25
2 – 6 yrs	53
6 – 12 yrs	46.9
12 – 17 yrs	37.5

*Other drug classes include: analgesics, sedatives, proton pump inhibitors, and drugs in other drug classes.

The majority of the products were antivirals and antihistamines. The majority (78.1%) were studied in more than one pediatric age group.

Trial Design

- 7/86 trials (8.1%) had a pre-defined target exposure or an acceptance boundary to match adult exposures (e.g. 80-125%)
- Majority (80.3%) used intensive sampling (NCA)
  - 8 (9.3%) sparse sampling (Pop PK)
  - 9 (10.4%) both NCA and Pop PK
- Dosing: BW based (44.8%), BSA (24.1%), fixed dose (31.1%)
- Sample size varied across trials and between age groups
- Multiple trials evaluated more than 1 dose level in the target pediatric age group

Assessment of Similarity

- Assessment of pediatric and adult systemic exposures based on cross-study comparison; Adult data either healthy volunteers or patients with condition
- Key exposure metric consistently defined post-hoc for antivirals and anti-infectives
- Assessment of similarity was primarily based on comparison of mean exposure values
- Acceptable boundaries for exposure similarity not explicitly stated post-hoc

Assessment of Similarity

- 48 (55.8%) approved at the studied dose
  - Mean Cmax (Ped/adult) ratio: 0.63-4.19
  - Mean AUC (Ped/adult) ratio: 0.36-3.60
- 18 (20.9%) approved at a modified dose
  - To "match" adult exposures
  - Few to provide fixed dose recommendations for specific weight bands
- 20 (23.3%) did not result in an indication in all or part of the studied population
  - 13 had insufficient evaluation of efficacy or qualitative evaluation of efficacy not supportive
  - 7 trials, dosing could not be established or sample size was too small

Case Example 1: Tipranavir

- Multiple dose, open-label, randomized study safety and PK study
- Age stratification: 2 to <6 yrs (n=24), 6 to <12 yrs (n=16) and 12 to 18 years (n=12)
- 2 dose levels evaluated 290mg/m^2 and 375mg/m^2
- Target concentration or exposure metric not predefined
- Sparse PK sampling performed at wk. 2

Source: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049872.htm

Case Example 1: Tipranavir

Pharmacokinetic Parameter	Adult HIV+ Females	Adult HIV+ Males	All Pediatric Patients
	(n = 14)[a]	(n = 106)[a]	(n = 51)
Cp0,12h (μM)	41.6 ± 24.3	35.6 ± 16.7	29.36 – 42.17[b] 39.02 – 65.32[c]
Cmax (μM)	94.8 ± 22.8	77.6 ± 16.6	77.51 – 120.73[b] 125.58 – 147.39[c]

[a] adult patients receiving TPV/r 500/200 mg; [b] 290/115m2 dose group; [c] 375/150mg/m2 dose group

- Low dose (290mg/m2) "reasonably matched" adult exposures at approved 500mg dose.
- 14 mg/kg ultimately approved:
  - Dose predicted to provide similar exposures to the high dose (375 mg/m2 dose)
  - Supported by ER in adults and need to maximize benefit
  - Simulations used to predict distribution of min concs under various BW dosing regimens

Case Example 2: Nelfinavir; Unapproved in infants

- Studies evaluated BID and TID dosing of nelfinavir in pediatric patients birth-13 yrs
- Doses 10-35mg/kg TID and 14-75mg/kg BID evaluated
- Formulation: tablet, crushed tablet mixed with liquid, or oral powder mixed with liquids or food
- Predefined target exposure: AUC_{24} 43.6-52.8 mμg*hr/mL
- Method for assessing/quantifying similarity in exposure not pre-specified

Source: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm161894.htm

Case Example 2: Unapproved in infants

Age Category	AUC24 (Mean +/- SD)	Dosing (mg/kg)
Adults (n=10)	52.8+/-15.7	1250mg BID
(n=11)	43.6+/-17.8	750mg TID
2-9 months (n=4)	33.8+/-8.9	39+/- 4 TID
(n=12)	37.2+/-19.2	66+/- 8 BID
0-6 weeks (n=10)	44.1+/- 27.4	37+/-7 BID
(n=10)	45.8+/- 32.1	29+/-12 BID

- None of the doses studied in infants < 2 yrs reliably achieved target nelfinavir exposure
- Additional studies not required by the FDA
- Resulted in lack of approval and dosing recommendation for nelfinavir in infants < 2yrs

Source: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm161894.htm

Summary

- Exposure matching is an important part of pediatric dose development when exposure is a surrogate for efficacy
- Variable methods for assessing similarity of systemic exposures in reviewed sample
- Target exposure range and acceptance criteria not consistently pre-defined
- No specific trend by therapeutic area or indication

Points for discussion

- Need for a consistent approach to assessing similarity of exposures in the context of the drug, indication, age group, and formulation?
- Need for a priori determination of similarity?
  - Target exposure range and acceptance criteria
  - Basis for target criteria based on therapeutic range of the drug and risk benefit of the product for a given indication
  - Simulations of doses when planning pediatric trials
  - Need for adaptive approach to achieve target exposure versus using modeling and simulation post-hoc for dose optimization?
- Need for statistical equivalence approach for assessing exposure similarity?
  - e.g. X% CI for ratio of mean exposure metric in pediatric vs adult within a predefined limit based on defined target criteria;
  - e.g. X% of population at different age/weight groups within a predefined exposure range

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Questions?

Back-up slides