What we have learned from the Study of Drugs under the Pediatric Initiatives

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Overview

- Differences in Drug Exposure
- Examples of Labeling Improvement
- Significant Changes for Dosing or Risk
- Adverse Events
- Formulations, an Overview
- Exclusivity and New Pediatric Formulation and Extemporaneous Formulations
- Summary: What Have We Learned?

Differences in Drug Exposure:

- Bioavailability
- Clearance

  -A measure of body's efficiency in eliminating drug – obtained after IV dose, and represents loss of drug from all routes of drug elimination such as renal and non-renal (e.g. hepatic, biliary).

  -- Highly influenced by maturation and development of involved organs, drug transporters, and metabolic enzyme systems.

  - Clearance obtained after oral dose (apparent oral clearance) is influenced by fraction of dose absorbed.

General Examples of Changes in Pediatric Labeling: Lower Apparent Oral Clearance

Pharmacologic Findings	Drug Name	Findings By Age, Gender and/or Weight
Lower drug clearance (or apparent oral clearance)	Fluvoxamine	**Lower apparent oral clearance in pts. 6-11yrs.old; (females 8-11 yrs. old may benefit from lower doses)**
	Famotidine	**Lower oral clearance in younger patients based on I.V. dose. (0-3 month old patients had 50% less apparent oral clearance than older children and adults)**
	Lamivudine	**Substantially reduced oral clearance in patients less than 3 months old and particularly in 1 week old neonates**
	Methyl phenidate	**Approximately 40 % reduced apparent oral clearance in children (6-12 yrs. old) compared to adolescents**

General Examples of Changes in Pediatric Labeling: Apparent Oral Clearance Increases with Body Weight

Drug clearance (or apparent oral clearance) increases with body-weight (up to adult values)	Atovaquone/ proguanil	**Atovaquone and proguanil apparent oral clearance values are lower for patients who weigh 11 to 20 kg compared to patients who weigh more than 40 kg.**
	Fluoxetine	**Differences in fluoxetine exposure between younger patients and adolescents are explained by differences in body-weight**
	Leflunomide	**Lower clearance of M1 metabolite in patients whose body-weight is equal to or less than 40 kg**

General Examples of Changes in Pediatric Labeling: Higher Apparent Oral Clearance

Higher apparent oral clearance	Gabapentin	**Higher oral clearance in children less than 5 years old**
	Benazepril	**Higher oral clearance in hypertensive children (6-12 yrs. old) and adolescents compared to adults. Terminal elimination half-life in children was one-third of that of adults.**

General Examples of Changes in Pediatric Labeling: Apparent Oral Clearance and distribution Volume Increase with Increasing BSA

Apparent oral clearance and distribution volume increase with increasing BSA	Sotalol	**Exposure is similar following corrections for dose and BSA, except smallest patients (Body Surface Area less than 0.33 m^2), who have greater exposure and response. Additional monitoring and dose-adjustment are needed for these patients.**

General Examples of Changes in Pediatric Labeling: Other Examples

Other	Remifentanil	Clearance and distribution volume were higher and larger, respectively, in younger patients compared to adolescents and older patients. High variability in pharmacokinetics in neonatal patients, individual dose titration is recommended.
	Nelfinavir	High variability in pharmacokinetics confounded by variable food effect and food intake in pediatrics; dose not established in < 2 yrs. old.

Examples of Labeling Improvements

Growth and Development

- **Fluoxetine - Prozac**
  - effectiveness established in Major Depressive Disorder 8-17 yrs. & Obsessive Compulsive Disorder 7-17 yrs.
  - In 19 week clinical trial pediatric patients treated with fluoxetine gained an average of 1.1cm less in height (p=0.004) and 1.1 Kg less in weight (p=0.008) than those treated with placebo
  - height and weight should be monitored periodically in pediatric patients treated with fluoxetine

Growth and Development

Gabapentin – Neurontin (Seizures)

- oral clearance normalized per body weight increased in children < 5 years
- higher doses of gabapentin required in children < 5 years
- Safety and effectiveness established down to 3 years

Growth and Development

- **Atomoxetine –Strattera (ADHD)**
  - **18 mo treatment**
    - **gained average 6.5 kg while mean weight percentile decreased slightly from 68-60**
  - **Among pts treated at least 6 months**
    - **mean weight gain was lower for poor metabolizer (PM) patients as compared with extensive metabolizer (EM) patients**
    - **+ 0.7 kg for PM vs + 3.0 kg for EM**
    - **no difference in height PM vs EM**

Product Labeling with Significant Changes for Dosing or Risk

Progress: Product Labeling with Significant Changes for Dosing or Risk

Betamethasone (Diprolene AF): Corticosteroid responsive dermatoses; NOT RECOMMENDED in pediatric patients <12 years of age; HPA axis suppression; local adverse reactions, including signs of skin atrophy in 10% of patients 3 mo-12 years of age

Betamethasone (Diprosone Cream, Ointment, Lotion):

NOT RECOMMENDED in patients <12 years of age; HPA axis suppression; local adverse reactions included signs of skin atrophy (telangectasia, bruising, shininess) in cream and ointment but not lotion

Betamethasone (Lotrisone): NOT RECOMMENDED in patients <17 years of age; HPA axis suppression

Progress: Product Labeling with Significant Changes for Dosing or Risk

Gabapentin (Neurontin): - adjunctive Rx in partial seizures - higher doses required in children less than 5 years of age in order to control seizures; new adverse events (e.g. hostility and aggression) identified in children less than 12 years

Propofol (Diprivan): -induction and/or maintenance of anesthesia - increased mortality when used for pediatric ICU sedation over standard sedative agents (9% vs. 4%); causality not determined; serious bradycardia when propofol is concomitantly administered with fentanyl

Sevoflurane (Ultane): induction and maintenance of general anesthesia - rare cases of seizures reported in children without a previous seizure history

Progress: Product Labeling with Significant Changes for Dosing or Risk

Midazolam (Versed): Sedation/anxiolysis/amnesia- higher risk of serious life-threatening situations in children with congenital heart disease and pulmonary hypertension and identified need to begin therapy at lower end of dosing range in this subpopulation to prevent respiratory compromise

Etodolac (Lodine): JRA sign/symptom relief (6yr-16yr)

-higher dose (per kg basis) needed in younger children approximately 2 times the lower dose recommended in adults for effective treatment

Fluvoxamine (Luvox): Rx of OCD - higher doses in adolescents than previously recommended**; girls ages 8-11 years may require lower doses.**

Progress: Product Labeling with Significant Changes for Dosing or Risk

Ribavirin/Intron A – Rebetron: indicated for the treatment of chronic hepatitis C-increased incidence of suicidal ideation or attempts among pediatric patients as compared with adults (2.4% vs. 1%); decreased rate of linear growth and weight gain during therapy, with general reversal in the post treatment period

Pimecrolimus – Elidel:indicated for short-term and intermittent long-term therapy in mild to moderate atopic dermatitis in non-immunocompromised patients 2years of age and older; (NOT RECOMMENDED in patients <2 years of age for safety concerns including infections, pyrexia, and diarrhea)

Progress: Identification of a Safety and Effectiveness Issue

- Buspirone – Buspar
  - Safety and effectiveness were NOT established in patients 6-17 years of age for treatment of General Anxiety Disorder at doses recommended for adults;
  - AUC and Cmax of buspirone and active metabolite were equal to or higher in children and adolescents as compared with adult PK parameters

Progress: Product Labeling with Significant Changes for Dosing or Risk

Famotidine (Pepcid): gastroesophageal reflux

- Lower dose recommended in patients <3 months of age;
- Pediatric patients 0-3 months of age had clearance values 2 to 4-fold less than those in older patients and adults;
- In a clinical study of 35 pediatric patients <1 year of age, agitation was observed in 5 patients on Famotidine and resolved upon discontinuation of the drug.

Progress: Product Labeling with Significant Changes for Dosing or Risk

Isotretinoin (Accutane):

- severe recalcitrant nodular acne
- Identified an increased incidence of back pain, arthralgia and myalgia in pediatric patients;
- New general precautions subsection regarding pediatric patients with disorders of bone metabolism;
- Adolescents who participate in sports with a repetitive impact may be at increased risk for bone related injuries;
- Decreases in lumbar spine bone mineral density (BMD) and decreases in total hip BMD seen in open-label study

BPCA Section 17: Adverse Event Reporting

- BPCA mandates review of all adult and pediatric AE reports for one-year period after pediatric exclusivity granted
- Report to Pediatric Advisory Committee for review
- Have reported on 54 drugs to date

Adverse Events Related to Growth and Development

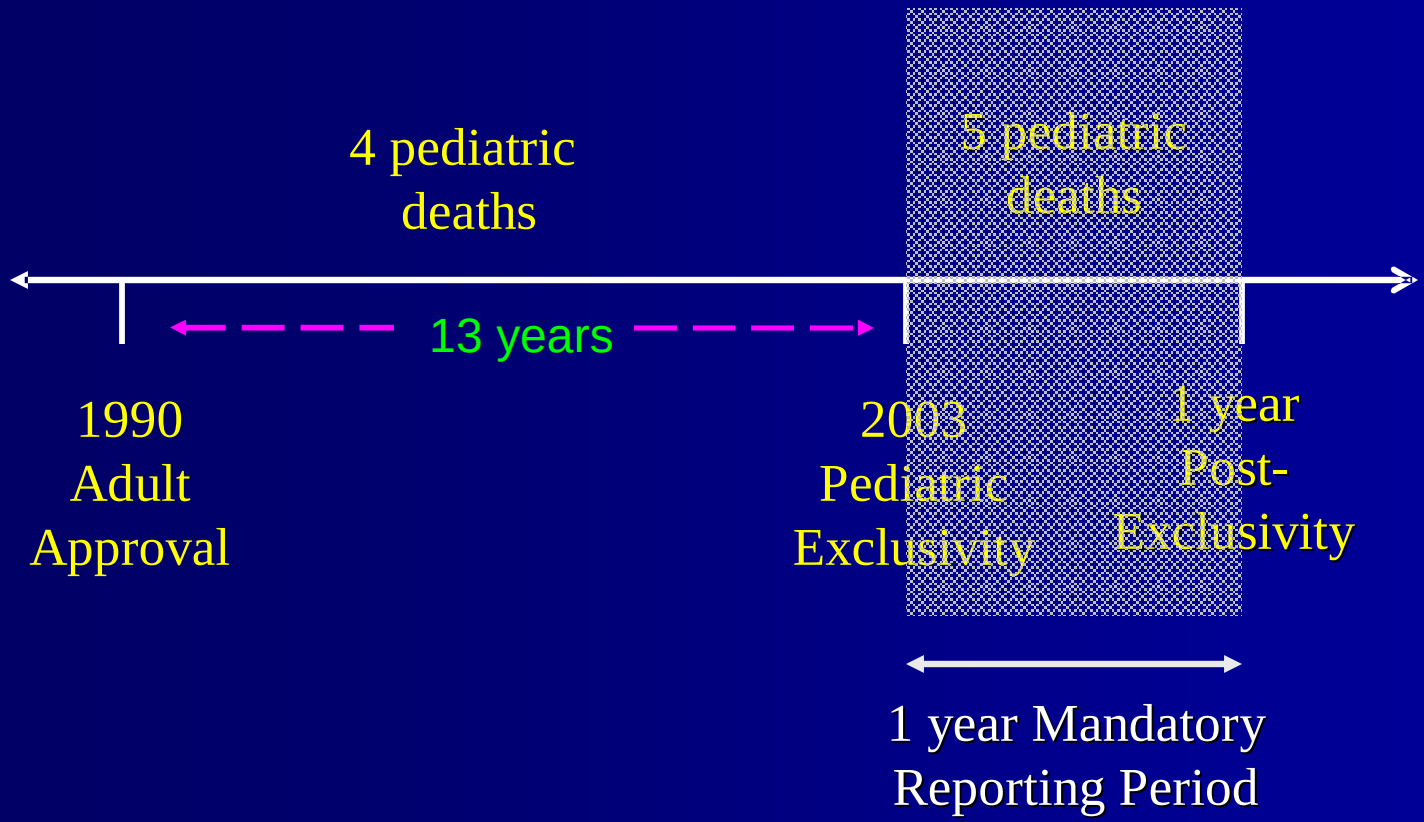
- Neurodevelopment
  - Suicidal ideation: SSRIs and Ribavirin/Intron A
  - Hostility/aggression: Gabapentin and ADHD drugs
- Growth
  - Suppression of linear growth: fluoxetine and systemic corticosteroids
- HPA axis suppression
  - Increased incidence in younger patients: betamethasone (dermatologic)

Duragesic® (Fentanyl Transdermal System)
Pediatric Deaths

- Accidental exposure
- Misuse or abuse
- Examples of off-label use:
  - Post-tonsillectomy and adenoidectomy pain
  - Infectious mononucleosis and sore throat pain
  - Chronic headaches and infectious mononucleosis
  - Acute migraine

Duragesic® (Fentanyl Transdermal System)

Spontaneous Reports of Pediatric Deaths



Formulations - an Overview

Sulfanilamide

- Elixir of Sulfanilamide introduced in September 1937
- Compounded with a solvent, diethylene glycol (chemically related to antifreeze)
- Caused 107 deaths including many children
- President Roosevelt signed the Food, Drug and Cosmetic Act on June 25, 1938
- Firms had to prove to FDA that any new drug was safe before it could be marketed

Age Appropriate Non-Parenteral Formulations

Capsules

Tablets

- Fixed concentration not amenable to mg/kg dosing
- Developmental issues with administration

Age Appropriate Non-Parenteral Formulations

Oral Solutions

- Safety Issues
  - Excipients
  - Accidental Overdose
  - Medication Errors

Sulfanilamide

Age Appropriate Non-Parenteral Formulations

Chewable Tablets

Sublingual Tablets

- Addresses developmental administration issues
- Commercially available formulations
  - Chewable tablets
  - Sublingual tablets
  - Wafers
  - Effervescent tablets
- Disadvantage
  - Fixed dose concentration

Age Appropriate Non-Parenteral Formulations

Lollipop

Transdermal Patches

- New delivery methods
- Unique pediatric safety issues
  - Accidental overdose
  - Location of patch on young children
  - Potential for variable dose delivery
    - Occlusive dressing
    - Heat
    - Adherence

Exclusivity: Summary of Important Findings from On-Patent Drugs

- **New Pediatric Formulations N=12**

  Medications for sedation and analgesia, HIV, malaria, nasal congestion, seizures, hepatitis C, asthma, esophagitis (GERD), allergic rhinitis, influenza

- **Information on preparation of oral formulation N=8**

  (Cardiovascular drugs)

(May 2006)

New Product pediatric Formulations

- Midazolam-Versed (Roche) 9/18/98 (10/15/98)*
- Abacavir-Ziagen (Glaxo) 12/14/98 (12/17/98)*
- Atovaquone/Proguanil- Malarone (Glaxo) 7/14/98 (12/2/03)*
- Ibuprofen/pseudoephedrine Motrin suspension-(McNeil) (8/1/00)*
- Gabapentin-Neurontin (Parke–Davis) 2/2/00 (10/12/00)*
- Oseltamivir-Tamiflu (Roche) 3/22/04 (12/14/00;6/24/04)*
- Ribavirin-Rebetol–Schering 5/9/01 (12/28/01;7/29/03)
- Ibuprofen/Pseudoephedrine Advil Suspension-Whitehall) 9/19/01 (4/18/02)*
- Montelukast-Singulair (Merck) 12/10/01 (7/26/02)*
- Nizatidine-Axid (Reliant Pharms) (5/25/04)*
- Desloratidine-Clarinex (Schering) 2/18/08 (9/1/04)*
- Emtricitabine-Emtriva (Gilead Sciences) (9/28/05)*

* Exclusivity granted (labeled)

Pediatric Extemporaneous formulations

- Sotalol-Betapace (Berlex) 1/6/00 (10/1/01)*
- Linosipril-Prinivil (Merck) 11/19/01 (5/29/03)*
- Enalapril-Vasotec (Merck) 2/22/00 (2/13/01)*
- Linisipril-Zestril (Astra Zeneca) 11/9/01 (7/1/03)*
- Fosinopril-Monopril (Bristol-Myers) 1/27/03 (5/27/03)*
- Benazepril-Lotensin (Novartis) 7/2/03 (3/23 04)*
- Losartan-Cozar (Merck) 3/20/02 (3/1104)*
- Amlodipine-Norvasc (Pfizer) 11/27/01/(1/8/04)*

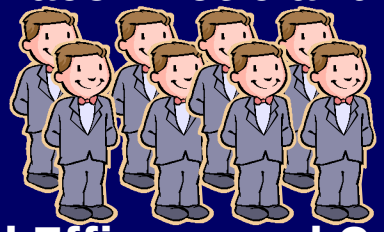
* exclusivity granted (labeled)

Summary: What Have We Learned?

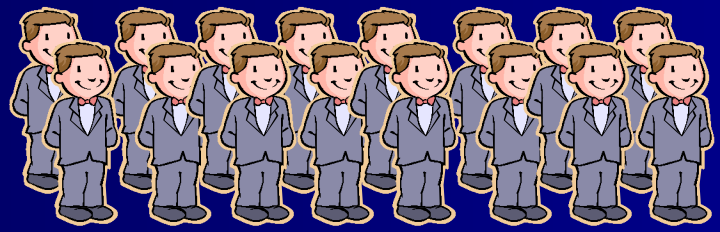
- New legislation is having a positive impact on development of therapies for children
- Physiologically, children are even more dynamic and variable than anticipated
- Endpoint definition and assessment tool validation of critical importance

Back up Slides

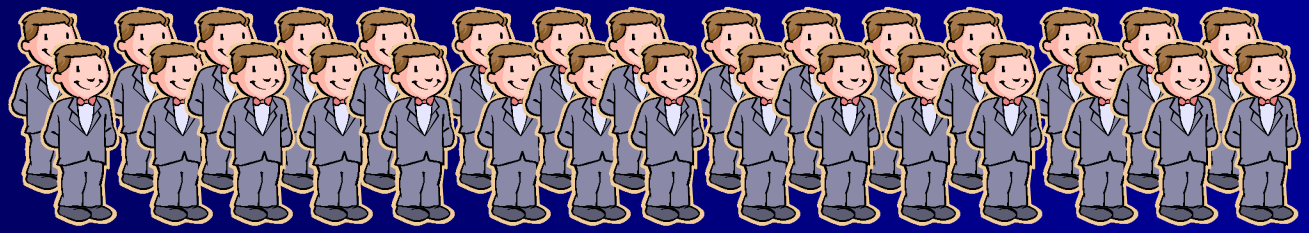
Phase 1 Trials (Pharmacokinetic and Initial Safety Data)



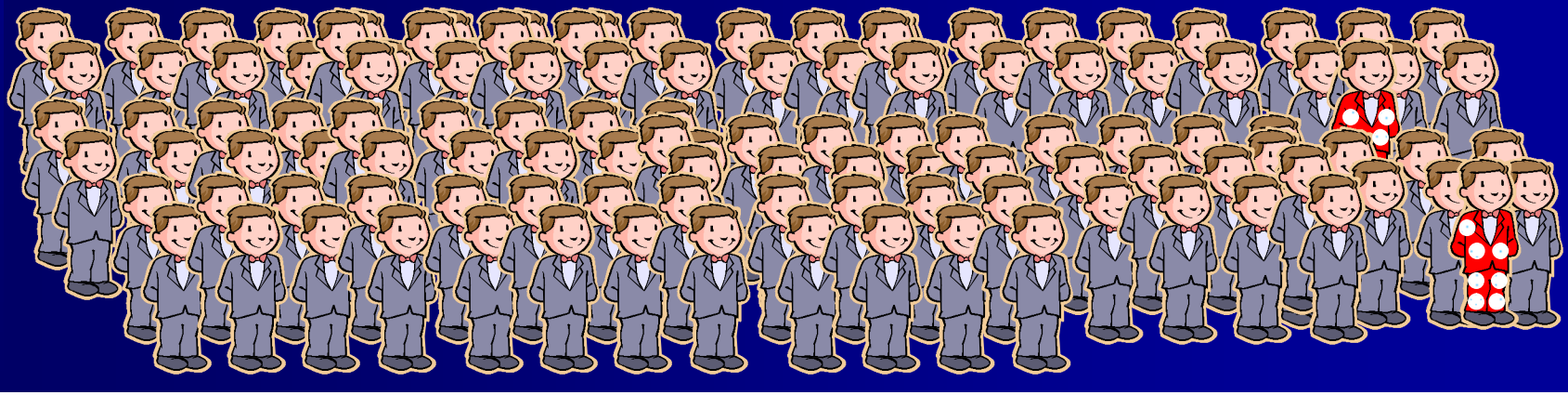
Phase 2 Trials (Initial Efficacy and Continuing Safety Data)



Phase 3 Trials (Pivotal Efficacy and Continuing Safety Data)



Phase 4 Trials (Postmarketing Efficacy and Safety Data)



Adverse Events Reporting

- Significant pediatric safety signals have been seen from adverse event reviews
- Example:
  - Neonatal withdrawal and SSRI/SNRI use during pregnancy
- Report your AEs to Medwatch