A ‘Layperson’s Guide’ to Pediatric Formulation Development

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I Active Ingredient-- Molecules

- Mechanism of action
- Adsorption, Distribution, Metabolism, Excretion
- Physical/chemical properties
- Dose range (BCS)

II Pediatric Patients

- Pediatric patients across age classifications
  - Preterm
  - New born (0 to 27 days)
  - Infants and toddlers (28 days to 23 months)
  - Preschool (2-6 years)
  - School age (6-11 years)
  - Adolescents (12 to 16-18 years)
- Physiological changes
- Developmental changes
- Excipient sensitivities
- Taste Preferences
- Care giver considerations

II Factors for PK Differences Between Pediatric and Adult Populations

Physiology	Age related changes
Gastric Emptying Time	Preterm gastric emptying is slow and linear, approaches adult within first 6 to 8 months of age.
Gastric pH	At birth pH is neutral, falls to 1-3 within first 24 h after birth, returns to neutrality by day 10 and slowly declines to adult values. By age 3 gastric acid /kg body weight like adult.
Intestinal transit	Transit time prolonged in neonate, reduced in older infants. Immature secretion and activity of bile and pancreatic fluids in neonate and infants over first few months, immaturity of the intestinal mucosa, immaturity of transport systems. Reduced first pass metabolism,
Renal blood flow	At birth 5 to 6% of cardiac output, 15 to 25% by one year of age, reaches adult values after two years. Renal clearance reaches adult levels after 2 years of age.
Percutaneous adsorption	Permeability rates 100 to 1000 fold greater before 30 weeks gestation, full term neonate have 3 to 4 fold greater permeability than adults.

E. Fernandez, R. Perez, A. Hernandez, P. Tejada, M. Arteta and J. Ramos. Pharmaceutics **3**(2011) 53-72.

III Formulations Options

- Route of administration
- Dosing Flexibility
- Safety
- Age appropriateness
- Organoleptics
  - Taste
  - Smell
  - Mouth feel
- Stability
- All aspects of the Target Product Profile

III Oral Pediatric Options

Matrix: Route of adminstration/dosage form vs Age

Route Dosage Form	Preterm infants	Term infants (0-28 d)	Infants and Toddlers (1m-2y)	PreSchool (2-5y)	School age (6-11)	Adolescents (12-16/18y)
Peroral						
Solution/Drops	2	4	5	5	4	4
Emulsion/Suspension	2	3	4	5	4	4
Effererescent DF	2	4	5	5	4	4
Powders/ Multiparticulates	1	2	2	4	4	5
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5
Orodisersible DF	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5

Rating system 1-5 (5 reflecting best applicability)

European Medicines Agency Reflection Paper: Formulations of Choice for the Paediatric Population 2006

III Excipient References

- Issues in the formulations of drugs for oral use in children. Role of excipients. Drugs **4**(6) (2002) 371-379.
- Benzyl Alcohol
  - N. Engl. J. Med. **307**(2) (1982) 1384-1388.
  - Lancet **1** (1982) 1250-1251.
- Propylene glycol
  - J. Pediatrics **77**(5) (1970) 877-878.
  - Ped. **72** (1983) 353-355.
- Sodium benzoate
  - Handbook of Food, Drug and Cosmetic Excipients (1992) 351-357.
- Parabens and Potassium Sorbate
  - J. Pharm Sci **72** (1983) 1039-1041.

III Organoleptics

- Preclinical tools
  - E-tongue, e-nose
    - Abs ACS meeting 28 Mar-1 April (2004).
    - J. Pharm. Sciences 90(12) (2001) 2042-2048.
    - Food Technology 55(10) (2001) 44-50.
    - Chem. Pharm. Bull. 52(8) (2004) 132-140.
  - Rodent models
    - Chem Senses 25 (2000) 361-368.
- Clinical tools
  - Sensory panels
    - Chem. Senses 29(5) (2004) 431-439
    - Sensory Evaluation Techniques CRC Press 1999
  - Sensory Panels for children
    - Clin. Thera. 30(11) (2008) 2120-2132.

IV Manufacturing Processes

- Towards Quality by design
  - Robust
  - Well characterized
  - Reproducible
  - Stable
    - Physical
    - Chemical
- Manufacturing Scale
- Critical Product Quality Attributes

V Assurance of Supply

- Adequate shelf life
  - Especially for low volume products
- Assurance of integrity of product from production to patient
  - Supply chain
  - Stability
  - Quality

Ongoing Efforts for Pediatrics

- US PFI/ EU PFI working to standardize taste evaluation tools for children
- EU PFI seeking to fully define ‘age appropriateness’.
- EU and US PFI working to develop an excipients database for pediatrics

Pediatric Formulation—Future Efforts

- Molecule, Patients, Formulation, Manufacture, Supply
- More Pediatric Formulations Motivates Science
  - Novel delivery systems
    - Micro tabs, films, granules
  - Devices to aid compliance
    - Dosing syringes, pacifiers etc
  - Formulations to enable accurate and convenient dosing flexibility

Clinical and Regulatory Challenges

- Clinical
  - Population and designs
- Regulatory
  - EMA and FDA

Clinical Challenges

Conduct

- HIV paediatric studies are difficult to conduct in US and EU as there are very few patients
- Changing landscape in the prevention of mother to child transmission (PMTCT)
- Studies in infants
  - Early infant diagnosis (EID) in some settings struggle with numerous barriers that include accessing HIV exposed infants, differing treatment guidelines (e.g., some don't recommend testing until 6 weeks of age)

Design

- Studies are getting larger (20+ children/age cohort)
- Studies are longer (at least 48 wks w/3-5 years follow-up)
- Efficacy as an endpoint

Some Abbreviations

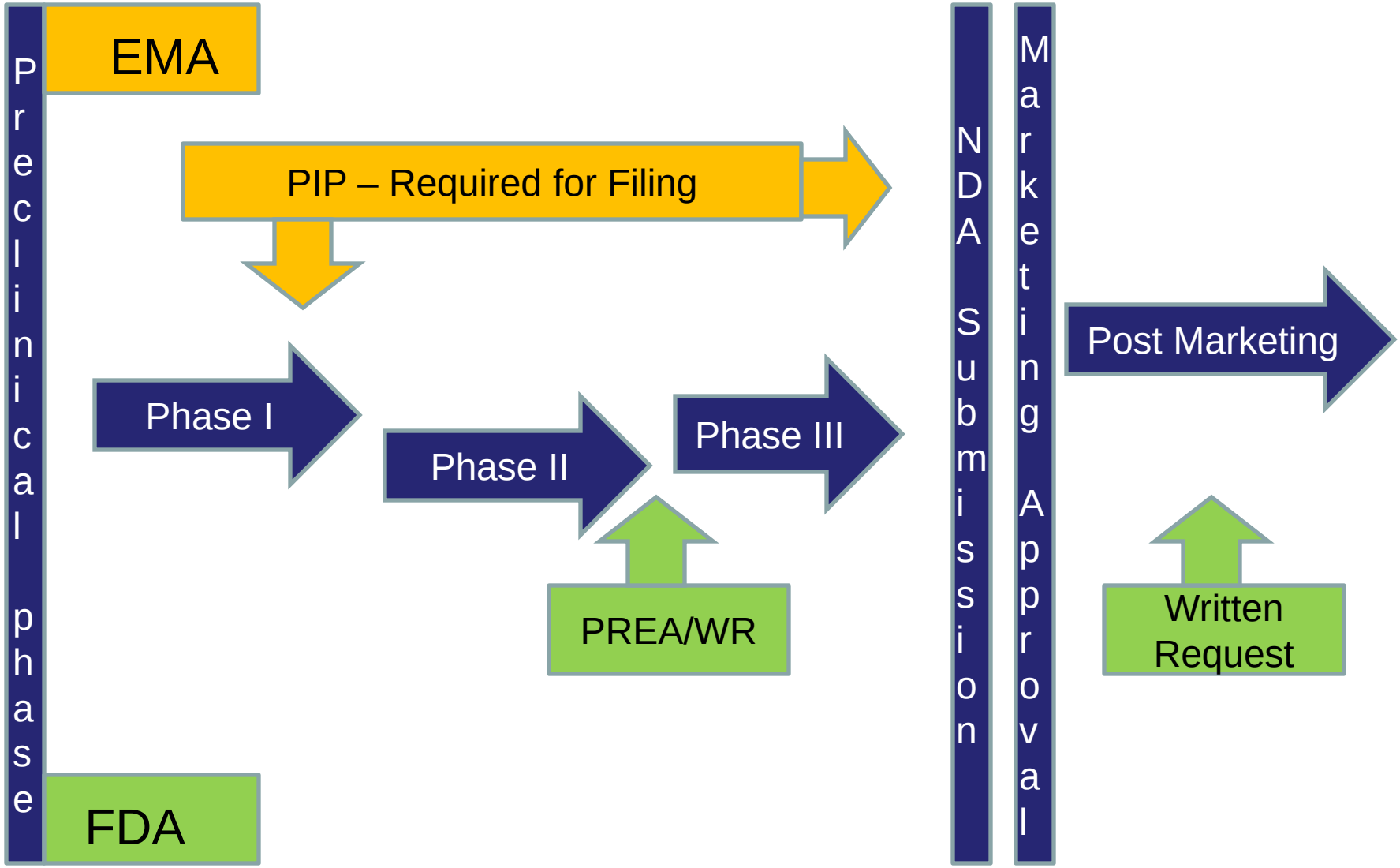
US

- Pediatric Research Equity Act (PREA)
- Best Pharmaceutical for Children Act (BPCA)
- Pediatric Review Committee (PeRC)
- Written Request (WR)

EU

- Paediatric Committee (PDCO)
- Paediatric Investigation Plan (PIP)

Schematic of Topline Regulatory Process



Regulatory Challenges

- EU Paediatric Investigation Plan (PIP) Development
  - Large undertaking at an early time in development
  - Spans background rationale to overall development of the product

- Differences between EU and FDA
  - Different age cohorts
  - Different PK requirements/endpoints

Successes

Abbott

- Development of heat stable formulation of ritonavir that could be sprinkled over food or added to liquid is underway

Gilead

- Recent approval of tenofovir pediatric powder (micro encapsulation for taste masking)

ViiV/GSK

- Recent FDA approval of fosamprenavir oral suspension down to 4 weeks of age
- Partnership with Matrix/CHAI in development of a dispersible formulation of ABC/3TC

Merck

- Recent FDA approvals for raltegravir in pediatrics and a chewable formulation