Development of Pediatric ARV Drugs – FDA Perspective

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Rationale for FDA pediatric initiatives

- Lack of pediatric use information poses significant risks for children
- Lack of appropriate formulations may deny access and expose children to "homemade" formulations
- Prevent adverse events or overdose
- Prevent under treatment

Development of pediatric formulations- Key issues

- Stability of formulation (temperature, reliable drug release)
- Acceptable palatability
- Ability to achieve target exposure associated with efficacy in adults
- Convenience

Approaches to pediatric formulations

- Approved formulations- Liquids predominate; one oral powder
- Must be open to other approaches and extemporaneous formulations
  - Delavirdine - disperse tablet in water; example where bona fide formulation not achieved after sufficient developmental effort

Extra problems - use of adult formulations in children

- If splitting tablets- ensure that procedure can be performed reliably by target population
- If crushing tablets or opening capsules- may need PK data to support that route
- If using adult FDC- must ensure each component provided in recommended dose for age range being treated

U.S. legislation affecting pediatric drug development

- Best Pharmaceuticals for Children Act
  - Extends 6 months patent protection to companies that perform requested pediatric studies (voluntary)
- Pediatric Research Equity Act (2003)
  - Any drug that may provide benefit to children must be studied in children (mandatory)

Evaluating pediatric formulations – new drugs

- Pharmacokinetic evaluation
  - Determine how to achieve target exposure found to be safe and effective
  - Should include all age groups (enough patients sampled to identify variability)
  - Initial dose estimate- consider developmental changes in absorption, metabolism, excretion
- Monitor tolerability and safety
- Assess activity in pediatric age groups

Evaluating pediatric formulations – "generics"

Evaluate bioequivalence

- Single product - compare generic to reference drug (innovator)
  - For FDC product - compare generic FDC to individual reference drugs taken together
  - Preferred study design is randomized, single-dose, 2-way cross-over
- Monitor tolerability and safety

Evaluating pediatric formulations – "generics"

- Considerations
  - Bioequivalence studies need not be done in children
  - If comparing 2 oral solutions no BE study required, if comparing formulations other than solutions BE study required
  - Evaluating solid or suspension formulations – dissolution testing required (assurance of reproducible drug release)

Application of pediatric initiatives to FDC development

- Fixed dose combination products
  - Want to encourage development of FDCs appropriate for pediatric patients
  - Some FDCs may not be appropriate for all ages (dose, proportion of component drugs)
  - Need to consider on a case-by-case basis