# Pediatric Antiretroviral Agents: Regulatory Issues for Fixed-Dose Combination Products

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# Challenges to Pediatric ART

- Limited pediatric use information
- Limited pediatric formulations
  - Not all ART available in liquid formulations
  - Many capsules only available in adult doses
  - No FDC for small children
  - Poor palatability/tolerability for several critical medications
  - Difficulties of managing dosing and administration
- Limitations of existing pediatric formulations
- Lack of efficacy (resistance) or toxicity concerns due to under- or over-dosing

# General requirements for approval of ARV drugs

- Adequate preclinical and nonclinical data
- Mechanisms of resistance
- Pharmacokinetic and pharmacodynamic data
- Chemistry/manufacturing/controls
- Adequate and well-controlled clinical trials
- Demonstrate beneficial effect on CD4 counts, viral load and clinical course

# Requirements for approval of pediatric ARV drugs

- Includes new active ingredient, indication, dosage form, dosing regimen, or route of administration
- Data should be adequate to assess the safety and effectiveness of the drug or biological product
- Data should be adequate to support dosing and administration for each relevant pediatric subpopulation

# Approval for pediatric use

If indications for use are similar to those in adults:

- Efficacy can be extrapolated from adequate and well-controlled studies in adults if safety, and PK-PD data in children are available
- Extrapolation from one age group to another age group where appropriate may also be considered

# Data requirements

- Must include all aspects of general drug development (usually referenced)
- Plus must evaluate:
  - Differences in absorption, distribution, metabolism, elimination - PK profile for age
  - Differences in side effect profile
  - Differences in therapeutic effect - not different in HIV disease

# Rationale for developing Pediatric FDC products

- Combination therapy required for adequate viral suppression
- Combination therapy provides a mutational barrier to resistance
- Current standard of care includes:
  - 2 NRTIs + 1 NNRTI
  - 2 NRTIs + PI
  - 3 NRTIs

# Optimal Characteristics of Pediatric FDC products

- Full (3 drug) or partial (2 drug) regimens
- Preferred or alternate regimens in treatment naïve patients
- Clinical trials of proposed combination completed
- Favorable risk-benefit profile
- Easy administration and compatible dosing schedules and food requirements

# Categories of FDC Products

- Innovator FDC products developed from new chemical entities
  - e.g. Kaletra$^{R}$
- FDC products developed by combination of of individual marketed products
  - e.g. Combivir$^{R}$, Trizivir$^{R}$, Triomune$^{R}$
  - “Bioequivalent FDCs”

# Key Factors in the Development of FDCs

- Suitability of formulation
- Specifications for finished product, APIs, excipients, container, labeling, etc.
- Validated and controlled manufacturing procedures
- Stability under recommended storage conditions for duration of claimed shelf life
- Adequate and consistent bioavailability
- Validation of variations

## Regulatory Issues

- Rationale for development of the FDC
- Formulation issues
- Chemical & physical stability
- Analytical methodologies
- Compliance with Good Manufacturing Practice
- Bioequivalence testing
- Clinical safety and efficacy studies
- Post-Approval issues

# Rationale for development of FDC

- Appropriate and valid clinical justification for the FDC
- Pharmacokinetic characteristics of individual components
  - Food effects
  - Enzyme induction or inhibition
  - Drug-drug interaction
  - Safety/efficacy
  - Emergence of drug resistance
- Pharmacodymic properties of individual components
  - Synergistic/additive effects
  - Implications for toxicity
- Compatibility of components

# Formulation Issues

- Formulation must be based upon the chemical and physical properties of the individual APIs
  - Bioavailability of BCS Class I compounds (high solubility – high permeability) may not critically depend on the formulation
  - Bioavailability of BCS Class IV compounds (low solubility, low permeability) are highly dependent upon the formulation
  - Combination of multiple API's of markedly different properties can result in complex formulation development to target bioequivalence to individual marketed products
- All API's must be compatible with each other and with formulation excipients
- Excipients used must be described in internationally recognised compendia and must meet compendial standards for purity
- All APIs must meet acceptable standards for purity

# Chemical & Physical Stability

- All API's must be chemically and physically compatible with each other and with formulation excipients
  - Chemical stability – no significant change to degradation rates or introduction of new impurities over shelf-life
  - Physical stability – maintain desired solid form (or solution state) of respective API's over shelf-life
  - Some API's may have limitations with respect to exposure to air, light, humidity, or temperature
- Adequate controls must be in place for:
  - Polymorphic forms
  - Particle size (poorly soluble APIs)
  - Dissolution properties
  - Impurities
- The packaged FDC product must be chemically and physically stable over its claimed shelf-life (studied under a wide variety of use conditions)

# Analytical Methodology

- Validated analytical procedures must accurately monitor identity, strength, uniformity, quality, and purity of respective API's in the FDC product
  - Each API must be controlled through appropriate specifications
  - Complexity of FDC product leads to more complex test methods
- Uniformity of dosage must be demonstrated by assaying for each active component in the final product as well as during the manufacturing process
- Discriminating dissolution methods must be developed for each product and incorporated into the stability and quality control programme

# Compliance with Good Manufacturing Practice (GMP)

- Robust manufacturing process in accordance with GMP must be clearly defined to ensure routine production of a quality FDC product
- Effective system of quality assurance must be in place and be fully functioning
- Production and control procedures must be validated to ensure the identity, strength, quality and purity of the finished FDC product, e.g.
  - validation of uniform mixing
  - validation of variations

# Bioequivalence Studies

**Demonstration of bioequivalence may be sufficient if component drugs are already approved**

- Approved drugs must be very well characterised
- There must be extensive clinical experience of combined use
- There must be clear evidence of advantage for the combination

# Clinical Safety/Efficacy Studies

**Clinical studies of the FDC may be required if:**

- there is limited clinical experience with the component drugs
- the proposed benefit of the combination is unclear or unknown
- the safety of the combination is unknown (bridging toxicity studies may also be required)
- the combination includes a new molecular entity (non-clinical pharmacology/toxicology also required)

# Bioequivalence Testing

- Bioequivalence study
  - Appropriate design
  - Criteria for selection
  - Choice of comparator/reference products
- Pharmacokinetic parameters
  - Importance of AUC, $C_{max}$, $C_{min}$, $t_{1/2}$ for each API with respect to daily dosing regimen (QD, BID, TID)
- Effect of food on PK profile
- Characteristics of APIs (solubility, permeability) in relation to formulation (reduced particle size, stabilized amorphous systems, or solutions)
  - APIs typically dosed in an immediate release formulation, may show altered PK profiles if incorporated into a modified release formulation (altered bioavailability)
- *In vivo* interactions between API's or formulation excipients may alter PK profile

# Post-Approval Issues

- Importance of post-marketing surveillance and post-marketing studies to detect and evaluate new patient safety and efficacy data
  - Pharmacovigilance
  - Requirements for monitoring and reporting
- Specific FDC-related issues:
  - Allergy to a component in the FDC
  - Impact on emergence of drug resistant strains

Thank You