

Innovative regulatory thinking to advance pediatric product development:

**Prequalification's efforts to address immediate need as guidance to
aid long term development progresses**

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PQP
QUALITY MEDICINES FOR EVERYONE

Why prequalify medicines?

- Quality needs to be built into the product, it cannot be tested in.
- Provide quality products for UN procurement, but also other partners (GF, NGOs and country procurement).
- Lack of well established drug regulatory systems (50% have varying capacity and level of development, 30% minimal or limited regulation)
- Increasing demand for generics, several players, substandard products on the market
- Lack of quality assured medicines can have serious consequences – ineffective treatment, drug resistance, side effects etc

Therapeutic areas

- Therapeutic areas invited:
 - HIV/AIDS
 - Malaria
 - Tuberculosis
 - Reproductive Health
 - Influenza
 - Acute diarrhoea in children (zinc)
 - Neglected Tropical Diseases (NTDs)
- Potentially other categories of products, if there is the need

Key outputs

- **Published list of prequalified medicinal products (FPPs)**
 - Used principally by UN agencies, including UNAIDS and UNICEF, and any other agency or organization involved in bulk purchasing of medicines, to guide their procurement decisions
- **Published list of prequalified APIs**
 - Can be used by FPP manufacturers to assure the quality of APIs
 - Can be used by NMRAs who wish to verify the standard of APIs that have been used to manufacture nationally registered medicines
- **Published list of prequalified QC laboratories**
 - The list may be used by any organization to ensure that testing for quality monitoring is done to an acceptable standard

Scope of prequalification

- Limited to priority medicines (and APIs) as published in Invitations for Expression of Interest (EOI) on PQP website
- Medicines eligible for prequalification determined by WHO disease oriented programmes (“perceived medical need”)
- Mostly generics
- Only products are prequalified!

Pediatric products

- Although pediatric products are produced for the markets of SRAs, the rate of development and approval within these markets is insufficient to meet the urgent need for such products in developing countries.
- WHO disease oriented programmes identify pediatric strengths and sometimes specific pediatric dosage forms needed for treatment programmes

Pediatric products

- **The PQP attempts to fill the gap between need and availability by encouraging submission of pediatric products**
 - pediatric strengths of adult dosage forms
 - dosage forms developed specifically for pediatric use.
- **The issue becomes linking the “desired product” to the products currently available**
 - adult formulations
 - other types of pediatric formulations

Complications for development of multisource products

- **Pediatric products available on SRA markets are often liquids such as oral solutions and syrups**
 - **Products that are better suited to difficult shipping and storage situations are preferred for other markets**
- **A pharmaceutically equivalent comparator is frequently not available for the development of monocomponent or fixed dose combination (FDC) multisource products**

Pathways forward for multisource products

- **Flexibility in the design of comparative bioavailability studies**
 - multiple units of pediatric strength vs. single unit of adult strength
 - Consideration for differences in method of preparation/administration
- **FDC vs. monocomponent comparator products for combinations with constant ratio between age classes**

Pathways forward for multisource products

- **Application of Biopharmaceutics Classification System (BCS)-based biowaivers**
 - **Applicable to situations when pediatric strength for comparator exists**
 - **pharmaceutically equivalent comparator**
 - **PQP exploring additional opportunities**
 - **in cooperation with scientific community**
 - **pharmaceutically equivalence comparator does not exist**
 - **approach involves the introduction of a solubility criterion that accounts for differences in GI tract conditions**
 - **formulation comparisons relative to existing adult comparators**
 - **Reduce number of in vivo studies required and expedite availability of new multisource pediatric products**

Development of guidance to inform future work

- **WHO consolidated guideline**
 - As discussed earlier
- **Various EMA concept papers related to pediatric drugs**
- **US FDA information related to pediatrics in Science & Research section of website**
- **ICH E11 “Clinical Investigation of Medicinal Products in the Pediatric Population”**
 - 2000
 - Addendum currently under development

ICH E11: Perceived problem

- Pediatric drug development has been enhanced by advancements in several areas of general adult drug development since the current ICH E11 guideline was adopted in 2000.
- Considerable advances over last decade relevant to:
 - scientific and technical issues relevant to pediatric populations
 - regulatory requirements for pediatric study plans
 - infrastructures for undertaking complex trials in pediatric patient populations

ICH E11: Background

- EU and USA have now have permanent legislation in place that mandates plans for pediatric development as part of an overall product development strategy
- FDA and EMA to regularly share information related to the development of pediatric drug products
- More recently, the Japanese Ministry of Health Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA), and Health Canada (Health Products and Food Branch) have joined these discussions as observers.

Expert Working Group on Pediatric Drug Development

- Representatives of global regulatory authorities and world guidance bodies
 - EMA
 - FDA
 - MHLW/PMDA
 - Health Canada
 - WHO
 - EFTA
- members of regulated industry who represent the major trade associations
 - PhRMA, EFPIA, JPMA

ICH E11: Topics for addendum

- Formulation challenges in pediatric drug development
- Types of studies and methodology of clinical trials
- Age classification and pediatric subsets including neonates
- Timing of pediatric development milestone agreements with regulators and “commonality of content”
- Ethical considerations in pediatric studies
- Extrapolation of data
- Model-Informed Drug Discovery Development (MID3)

Conclusions

- PQP continues to attempt to bridge the gap between need and availability
- Development of ARV-specific guideline
 - WHO
- Development of general guidance on pediatric drug development
 - ICH E11 addendum

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