Challenges and Strategies to Facilitate Formulation Development of Pediatric Drug Products

Session 5: Safety Qualification of Excipients

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* **Disclaimer:** Opinions expressed do not necessarily reflect those of the FDA or its policy
Excipients: Not always inert, Use must be justified

- **FDA 2005**: New excipients - inactive ingredients intentionally added
  - Not intended to exert therapeutic effects at intended dose; may improve product delivery (e.g., enhance absorption or control release of drug)
  - Not fully qualified by existing safety data with respect to currently proposed level of exposure, duration of exposure, or route of administration
  - May not be inert

- **EU 2003**: Excipients are generally considered to be ‘inert’
  - Desirable that excipients should have little or no pharmacological action, however, some have a recognized action or effect in certain circumstances

- **EU 2013**: Need comprehensive development rationale considering relative benefits and risks of possible alternatives
  - Avoid excipients with a potential cause for concern (pending more research)
  - Justify added value of a novel excipient
Risk: Exposure and Toxicity

Excipient Functionality & Exposure

Characterizing Toxicity/Hazard in a dynamic system of physiological development

Dose/Exposure x Response Relationship

6/6/2016 Pediatric Excipients Workshop - Session 5
Risk : Benefit Assessments

Exposure Characterization

Hazard Identification

Dose/Exposure - Response Analysis

Risk:Benefit Assessment
Understanding risk in the context of benefits

Risk Management
Minimize / mitigate risk to patients

What do we know? What don’t we know? What do we need to know, given particular clinical scenarios

Heightened Safety Monitoring
Risk: Benefit Assessments – All agree on the Need

Risk Considerations

- Target age group?
- Pharmaceutical form and use?
- Excipient function?
- Route of administration?
- Excipient proportion in medicinal product?
- Daily intake?
- Composition?

EU Guideline: Guideline on pharmaceutical development of medicines for paediatric use 2013

**HOWEREVER**

Not Everyone Agrees on the “How” or the “What”

be consulted in order to assess the safety profile of each excipient in a paediatric formulation resulting in an overall conclusion as to whether or not additional data are needed

- Performing risk-benefit assessments on proposed new excipients in drug products to establish permissible & safe limits
- Existing human data can substitute for certain nonclinical safety data
Juvenile toxicology studies: Performed ‘for cause’

- Toxicology studies may be necessary if the use of an existing excipient in a paediatric medicine can not be justified based on information sources (EU 2013)
- Consider all relevant information first
- Avoid routine, “box-ticking” conduct of standard juvenile animal tox studies

**Consider relevance / value to inform clinical practice**

- If warranted, a juvenile toxicology study with the active drug can be used to assess the safety of excipients at the same time
- Interspecies extrapolation further confounded by translational complexities across postnatal development stages
Safety Qualification of Excipients in Paediatrics

- Limited availability of and access to safety data, esp for paediatric use

**Gaps in Current Paradigms**

- Extrapolation uncertainties in exposure & effect

- Lack of standardization with regard to what is adequate / necessary to sufficiently characterize risk:benefit for excipient use in (various) pediatric patients and disease states

**NEED**

Risk: Benefit Assessment Framework
- Knowledge-based, standardized approach
Session 5: Case Scenarios & Questions to Inform Development of a Risk Assessment Framework

Two Breakout discussion groups:

**GROUP 1**
New/Novel Excipients
- “Inactive” vs biologically active agents (e.g. SNAC)
- European vs. US approaches

**GROUP 2**
Established / Standard Excipients
- Clarify what is known (experience) as it relates to the proposed setting
- Identify information gaps
- Identify alternative sources of information & the appropriateness thereof

incomplete information (e.g., a new use, dose, duration, route, disease severity, age group, etc.)
Breakout session discussion
How to justify excipient use (novel, established) in paediatrics? What are the hurdles?

Risk assessment & Information needs
• Can a **common template or approach** (framework) be developed for implementing risk assessments for individual excipients?
• **What minimum information** is required? What additional data is required?
• What circumstances and factors should be considered regarding the justification for **juvenile tox studies**?
• Should toxicology studies with the final formulation be conducted? If so, **when & which studies**?
• **What alternative options** are available if no additional information is available?
• **What clinical trial design factors** can be incorporated to provide information on the safety of excipients?
• Where are the **knowledge gaps** and how would you **prioritize studies needed** to approach the evaluation of excipients for paediatrics?

Information sharing platform
• Where to find the existing information?
• Platform to share information? (eg, STEP database)
• extending the FDA inactive ingredient database to paediatrics

Proposed Framework – Your opinion matters!!
• Would the proposed framework help address the issues of use of excipients in paediatrics?
  • What are the **pros and cons** of the presented framework?
  • What **additional elements** would you consider in the framework?
• Can we evaluate data on excipients & present in a format which will satisfy regulators?