Challenges and Strategies to Facilitate Formulation Development of Pediatric Drug Products

Session 5: Safety Qualification of Excipients

Session Chairs: Darren Fegley (FDA)
Lorrene Buckley (Eli Lilly & Co)
Jacqueline Carleer (FAGG-AFMPS)
Gerri Baer (FDA)

Anthony Nunn
Honorary Fellow
Dept Women's & Children's Health
University of Liverpool

Darren Fegley*
Pharmacologist
USFDA/CDER/OND/DPP

Gerri Baer*
Lead Medical Officer
USFDA/OC/OPT

Smita Salunke
Sr Scientific Manager
EuPFI
UCL School of Pharmacy

Lorrene Buckley
Sr Research Fellow
Toxicology & Pathology
Lilly Research Laboratories

Brian Aylward
Irish HPRA
PDCO, Member
Chair, Formulations WG

Karen Thompson
Sr Principal Scientist, Oral Formulation Science & Technology
Merck Research Laboratories

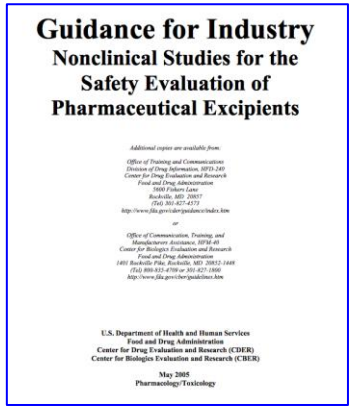
Jacqueline Carleer
Belgian FAM
PDCO, Alternate Member
Chair, Nonclinical WG

Mark Turner
SL / Consultant
Dept Women's & Children's Health
University of Liverpool

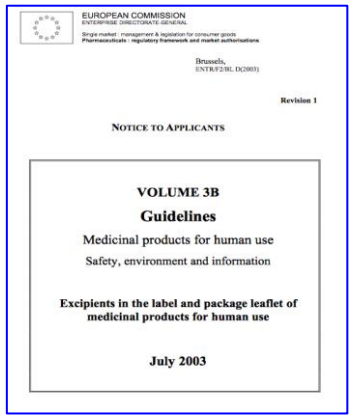
*** Disclaimer: Opinions expressed do not necessarily reflect those of the FDA or its policy**

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



USFDA Guidance: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients 2005

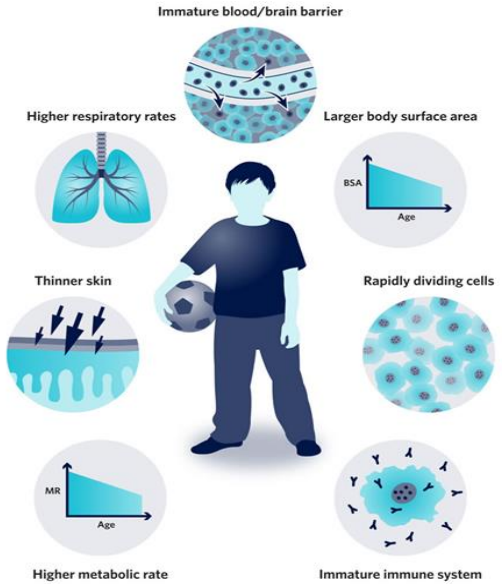


EU Guideline: Excipients in the label and package leaflet of medicinal products for human use 2003

EU Guideline on pharmaceutical development of medicines for paediatric use 2013

Risk: Exposure and Toxicity

Excipient Functionality & Exposure



Characterizing Toxicity/Hazard in a dynamic system of physiological development

Dose/Exposure x Response Relationship

Risk : Benefit Assessments

Exposure Characterization

Hazard Identification

Dose/Exposure - Response Analysis

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

Risk:Benefit Assessment
Understanding risk in the context of benefits

Risk Management
Minimize / mitigate risk to patients

Heightened Safety Monitoring

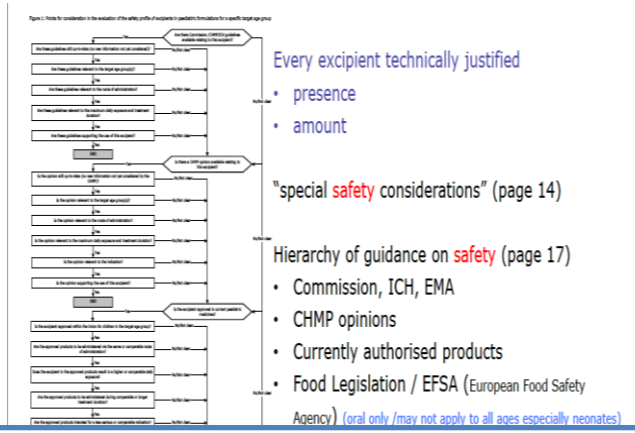
Risk:Benefit Assessments – All agree on the Need


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 August 2013
EMA/CHMP/QWP/805880/2012 Rev. 2
Committee for Medicinal Products for Human Use (CHMP)
Paediatric Committee (PDCO)

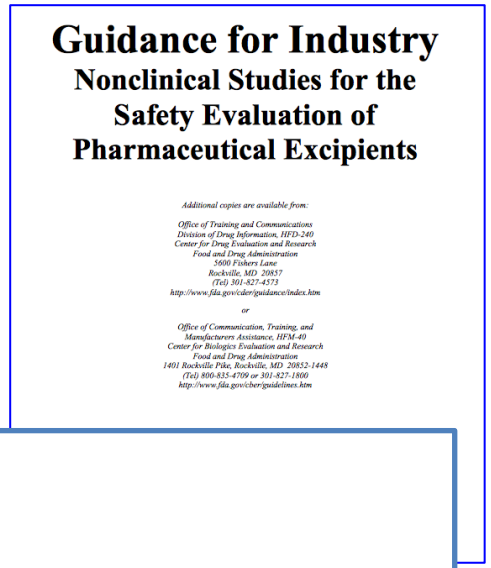
Guideline on pharmaceutical development of medicines for paediatric use

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


Every excipient technically justified
- presence
- amount

"special safety considerations" (page 14)

Hierarchy of guidance on safety (page 17)
- Commission, ICH, EMA
- CHMP opinions
- Currently authorised products
- Food Legislation / EFSA (European Food Safety Agency) (oral only /may not apply to all ages especially neonates)


Guidance for Industry
Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients

Additional copies are available from:

Office of Training and Communications
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training, and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800
http://www.fda.gov/cber/guidelines.htm

Risk Considerations

Lin

-
-

- Excipient function?
- Route of administration
- Excipient proportion in medicinal product?
- Daily intake?
- Composition?

HOWEVER

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***

- ients 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

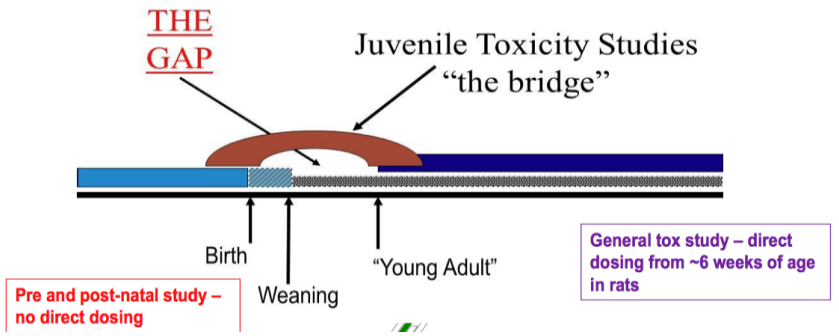


Image source: http://users.unimi.it/gazzalab/wordpress/wp content/uploads/2014/11/FINAL_PreclinicalFormulation_05NOV204-ALL-Monzani-Colombo.pdf

Consider relevance / value to inform clinical practice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children

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Review

Safety of Excipients in Pediatric Formulations—A Call for Toxicity Studies in Juvenile Animals?

Georg Schmitt

F. Hoffmann-La Roche Ltd., Roche Pharmaceutical Research and Early Development,

- 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

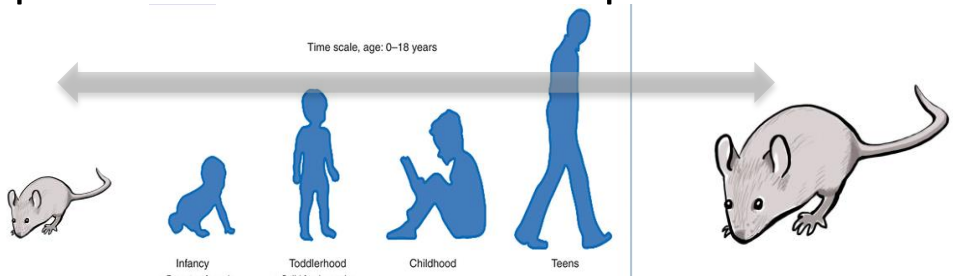
- Limited availability of and access to safety data, esp for paediatric use

Gaps in Current Paradigms

STEP database
Safety & Toxicity of Excipients For Paediatrics

FDA IID => Paediatrics??

- Extrapolation uncertainties in exposure & effect



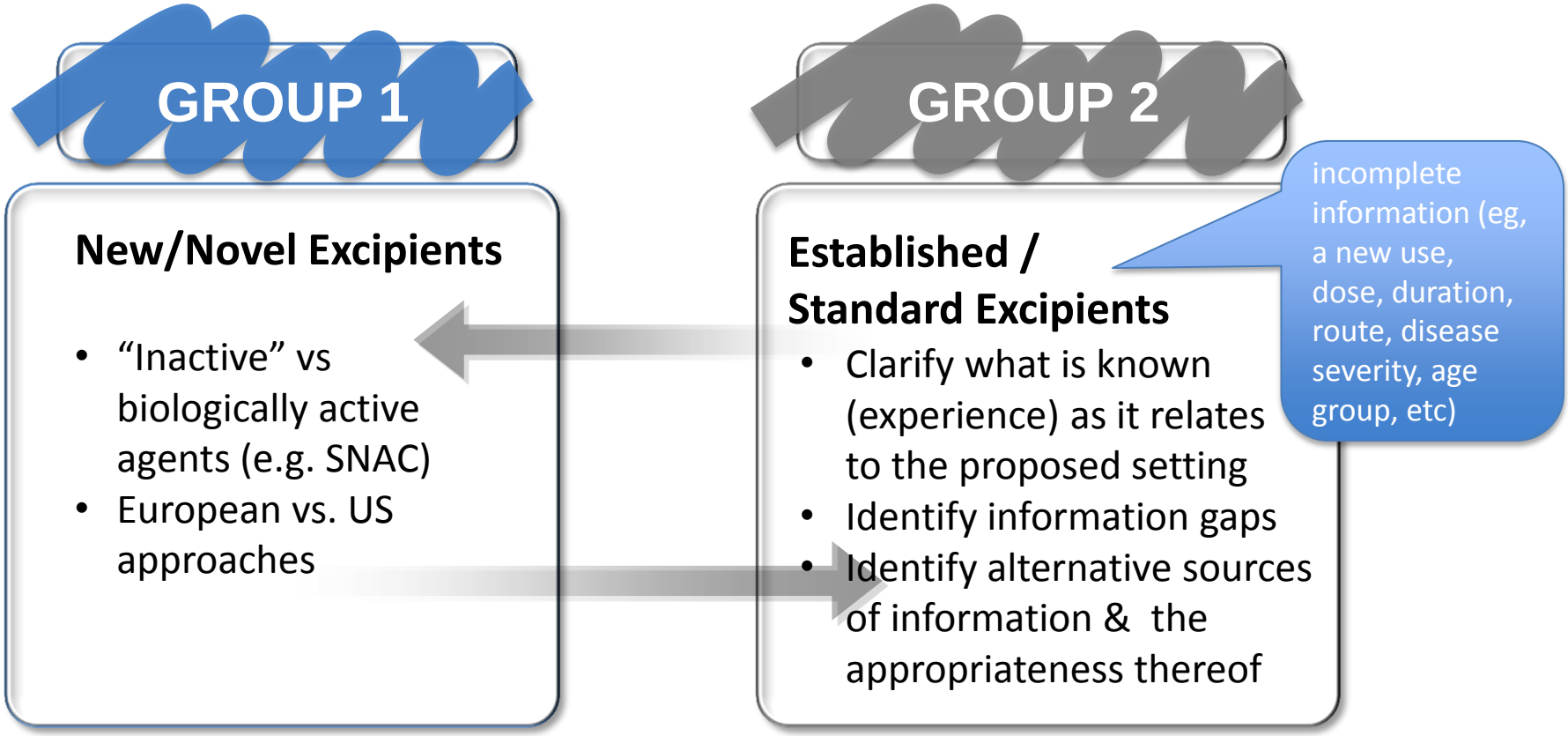
- Lack of standardization with regard to what is adequate / necessary to sufficiently characterize risk:benefit for excipient use in (various) pediatric patients and disease states

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:



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?