EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Excipients general approach

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AGENDA

- Objectives
- Reminder about excipients
- Background & References
- Excipients
- Case Studies
- Conclusion

OBJECTIVES

•To present the current knowledge and references for the excipients

• To present challenges with excipients in PIP case studies.

BACKGROUND

- Medicines primarily developed **for adults**
- Children's doses were **unknown**
- Small children were treated as small adults
- Excipients chosen were the same for adults and children
- Safety reports have shown that some excipients were not safe for children

http://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childrens.pdf
(benzyl alcohol safety in neonates)

REMINDER Excipients

The definition has evolved…[1]

1) *"Inert substance that forms a vehicle"*

2) *"Additives used to convert active substances into pharmaceutical forms"*

1-Excipients Toxicity and Safety by M.L Weiner and A. Kotkoskie, Drugs and the Pharmaceutical Sciences, volume 103

and Handbook of pharmaceutical excipients

REMINDER Excipients 2

Excipients can be used for:

- Aid processing during manufacture
- Improve physical and chemical attributes of the active substance
- Protect, enhance stability
- Enhance any other attribute of the Safety and Effectiveness (use or storage)

Excipients and functions

Examples for oral formulation:

filler or diluent, preservative, binder, disintegrant, lubricants, antiadherents, glidants, wetting agents, colorants, sweeteners, antioxidants, adjuvants, flavours, taste masking…

Examples for parenteral forms:

diluent, solubiliser, buffer, antioxidant, antimicrobial agent…etc

1–Paediatric drug handling by Costello, Long, Wong, Tuleu, Yeung, Pharmaceutical Press

2-Toxic Additives in Medications for Preterm Infants Arch. Dis. Child. Fetal Neonatal Ed. published online 21 Jan 2009 by Whittaker, Mulla, Turner, Currie, Field and Pandya

SO WHERE TO START ?

What are the main issues….?

What guidance is out there concerning excipients…… ?

Critical points for paediatric formulations

- Route of administration.
- Appropriate dosage forms.
- **Excipients - 50% of the PIPs – choice , safety, level, side effects……**
- Acceptability and palatability
- Delivery devices.
- Rate of infusion.
- Volume to be administered.
- Wastage.

REFERENCES 1

Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product (CHMP/QWP/396951/06, revised 2008).

Excipients in the Label and Package leaflet of Medicinal Products for Human Use (Eudralex 3BC7A)

REFERENCES 2

Food Directives (i.e. Directive 2009/35/EC – colorants in medicines).

EFSA & CHMP Opinions

Literature

External sources (WHO, FDA, Databases, external groups EuPFI...).

REFERENCES 3

Reflection paper (EMEA/CHMP/PEG/194810/2005) on "Formulation of choice for the paediatric population" (not a guideline!).

Concept paper (EMEA/138931/2008) – future quality guideline.

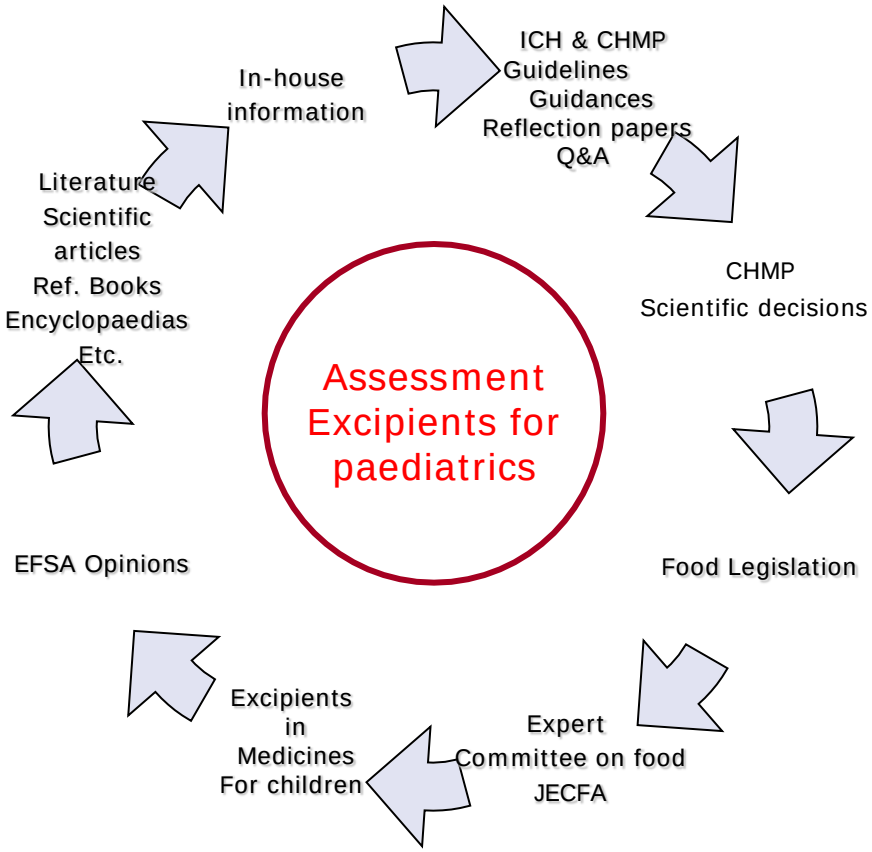
Guideline on pharmaceutical development of medicines for paediatric use (EMEA/CHMP/QWP/180157/2011) – under consultation.

Guideline on the investigation of Medicinal Product in the Term and Pre-term Neonate (EMEA/536810/2008)

REFERENCES 4

Guideline on pharmaceutical development of medicines for paediatric use (EMEA/CHMP/QWP/180157/2011) – under consultation

Information sources on excipients for paediatrics



Selection of excipients for paediatric formulations

- Pharmaceutical form;
- Well-known safety profile in paediatric population;
- The expected duration of treatment (short & Long term);
- Potential allergies and sensitization;
- Excipients used in paediatric formulations with no adverse events;
- Novel excipients with lack of safety information in children should be avoided;

Excipients for paediatrics - Safety concerns

• Justification on the safety profile of an excipient should be provided;

• Toxicology data may be requested if no information is available in children;

Excipients - Colouring agents

- Colouring agents allowed in foodstuffs might be used in medicines;

- Colouring agents should be avoided as much as possible;

- Use of a colouring agent to be discussed and justified;

Excipients - Flavours agents

- Palatability extremely important;
- Use and selection of flavours should be justified;
- Qualitative and quantitative composition to be provided (MAA);
- Any safety concerns should be addressed;

Excipients - Preservatives

- The choice of the preservative system should be discussed

- The lowest concentration should be used

- The selection of the preservative system should take into account the target age group

Excipients - Sugar *versus* sweeteners

The selection should take into account:

- Cariogenic effect of sugar
- Dosing frequency
- Duration of treatment
- High concentration of sugar =>additional preservatives
- Possible side effects
- Compatibility with other ingredients

CASE STUDY 1

Formulation issue:

- Capsules and oral solution
- Indicated for melanoma
- Long-term for patients above 12 years old
- **Issue:** sorbitol quantity, citric acid, and composition of oral solution

CASE STUDY 1 - continues

Discussion:

- Composition of the oral solution
- Impact of the citric acid (teeth erosion) may be considered
- Taking into account the quantities agreed- sorbitol not an issue

Conclusion:

- No major concerns regarding of the quality of oral solution
- Final composition of the oral solution should be provided

CASE STUDY 2

Formulation issue:

- Oral solution
- Indication: Treatment of HIV
- Life long treatment from the age of 14 days (infants)
- **Issue:** Composition

CASE STUDY 2 - continues

Discussion:

- This product already exists as tablets, soft capsules and oral solution (patients who cannot swallow and below 6 years)
- Issue with concentration of propylene glycol and ethanol

Conclusion: The PDCO FWG requested:

- To provide data on exposure of propylene glycol and ethanol in infants (SWP to review, especially chronic and risk accumulation)

CASE Study 3

Formulation issue:

- Two formulations (IV form- for the neonate and oral suspension).
- Indication: Fungal infection.
- Short term use from neonates

- **Issues:**
- IV form contains Cyclodextrin derivative (CD Sulfobutylethyl β).
- Oral form contains benzyl alcohol, propylene glycol and liquid glucose- "sensitive" excipients

CASE Study 3- continues

Discussion

- IV formulation: contains cyclodextrin derivative (CD Sulfobutylethyl β). Applicant asked to provide safety studies conducted on juvenile animals
- Oral suspension: agreed no concern since excipients present in the flavouring (quantities below authorised limits)

Conclusion

- PDCO FWG wanted more data from the applicant on safety of Cyclodextrin used

CASE STUDY 4

Formulation issue:

- Solution for injection
- Treatment for hypotension
- Long term extremely low gestational age newborn and children to 18 years
- **Issue:** sodium metabisulfite

CASE STUDY 4 - continues

Discussion:

- High-content of sodium metabisulfite- potential toxicity (hypersensitivity)

Conclusion:

- sodium metabisulfite: justify high content/replace by alternative antioxidant with a better safety profile
- Further follow-up needed = remove/minimise the amount of the antioxidant as key binding element

CONCLUSIONS

- Critical points for paediatric formulations
- Safety profile of excipient extremely important
- Excipients allowed in adult formulations might be different in paediatric formulations
- Assessment of excipient - Information source
- Need for further research and collaboration (on-going ESNEE, EuPFI STEP database)

STEP database http://www.eupfi.org/ and ESNEE project part of the EC Research Funding FP7

THANK YOU FOR YOUR ATTENTION. ANY QUESTIONS?

Thanks to the entire Quality & Paediatric Teams