EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Excipients: Safe or not safe?

Viewpoint from the EMA

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Agenda

- Objective
- Regulatory references
- Points to consider for paediatric formulations
- What do we mean by excipients ?
- Focus on few excipients (i.e. colorants…)
- Case studies
- Conclusion

Objective

- To present the challenges and issues encountered during the assessment of the PIPs (focus on the excipients)

- To share our experience and open the discussion

Regulatory references

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

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

Regulatory references 2

Food Directive Legislation

BUT

Safety profiles and warning statements are based mostly on data in **adults**.

Excipients and functions

The definition has evolved…[1]

1) Inert substance

2) Any substance other than AS - evaluated from a Safety Efficacy point of view that can be used for the following…

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

Excipients and functions

Excipients can be used for:

- Aid processing during manufacture
- Protect, support, enhance stability and BA
- Assist in product identification
- Enhance any other attribute of the Safety and Effectiveness (use or storage)

Excipients and functions

Examples for oral formulation:

filler or diluent, binder, disintegrant, colorants, flavours, taste masking…

Examples for parenteral forms:

diluent, solubiliser, buffer, antioxidant, antimicrobial agent…

Critical Points for Paediatric Formulations

- Route of administration
- Appropriate dosage forms
- **Excipients / Safety (i.e. Antioxidants, Colorants, sweeteners…)**
- Taste and palatability
- Delivery devices

How to select the "safe" excipients ? [1, 2]

For instance with oral formulations:

- Taste-masking; often use of sweeteners
- Addition of co-solvents to improve drug solubility
- Antioxidants to protect the formulation
- Colorants to differentiate strengths

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

How to select excipients 2

What do we know ?

What are the concerns : reported cases (with patients) or potential risks ?

How to select excipients 3

Taste-masking agents & techniques:[1]

- Common excipients used: flavours, sweeteners (i.e. aspartame),
- Taste-masking techniques such as coating (i.e. cellulose), encapsulation (i.e. cyclodextrins)

1- Taste masking technologies in oral pharmaceuticals: recent development and approaches by Sohi H. et Al, Drug Development and Industrial Pharmacy, 2004, vol 30, n 5, 429-448

How to select excipients 3 -continues

Flavours, Sweeteners, taste-masking agents, complexation…

- Flavours: complex mix ? natural or synthetic ? Composition ?
- Excipients for coating, encapsulating, solubilisation (Oral or Parenteral)? Toxicity ?
- Sweeteners: Mix of sweeteners ? Toxicity ? ADI established ? Literature info ?

How to select excipients 4

Colorants

- Natural or synthetic ? composition ?
- Natural colorants can present allergy risks[1]
- Synthetic azo-dyes are not recommended

1-The safety of pharmaceutical excipients by Pifferi G. and Restani P. Il Farmaco 58, 2003, 541-550

Case 1 – complexation of AS

Formulation issue: Powder for concentrate for solution for infusion (Intravenous use), developed for adults. The same formulation is proposed for the paediatric patients.

The AS slightly soluble in water and in other organic solvents. Formulated with HP-β-cyclodextrin as solubiliser.

Case 1 – continues

Discussion: Major concern PDCO + extensive discussion CHMP

Conclusion: PIP modification requested:

- HP-ß-CD is nephrotoxic. More investigation needed.

- The applicant claims HP-ß-CD reduces nephrotoxic potential of the AS (answer provided to CHMP).

- This hypothesis should be explained + same effect in children?

Case 2 – Sweeteners & flavours

Formulation:

It is a licensed product. The applicant is now proposing a new indication in children.

The applicant does not intend to develop specific paediatric formulation (plans to use the authorised adult's one).

Case 2 – continues

Discussion: exact composition of used formulations unknown.

+ 3 sweeteners (sucrose, mannitol and aspartam)
+ several flavours

Unclear whether the applicant plans to use just one of them or all ?

Conclusion: It was agreed that the applicant should be asked to reduce the number of sweeteners and flavours (or to clarify/justify).

Case 3 – Colorants

Formulation issue:

oral tablets used for Cystic Fibrosis treatment

long term treatment (above 6 years of age)

use of colorants necessary ?

Case 3 – continues

Discussion: The usage of colorants for purely cosmetic reason is considered not acceptable. Company should be encouraged to use other differentiators (e.g. different shapes or embossing) when variety of strengths.

Conclusion: minimize the amount of dye per tablet (colour via a non-functional film coat) - acknowledged.

Data needed to support their claim that CF patients prefer oval shaped tablets for ease of swallowing.

Conclusion

- Apply:
  - The Precautionary principle
  - Benefit/Risk arguments
- Excipients - Need to develop further research and collaboration
- Need to develop further guidance

Thank you for your attention.
Any question?