Federal agency for medicines and health products

« Risques liés à l'utilisation d'excipients en pédiatrie»

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Disclaimer

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January 2007: Regulation (EC) N° 1901/2006 'on Medicinal Products for Paediatric Use' (and amendment 1902/2006)

- **Three domains of activity:**
  - **Promotion of paediatric clinical research**
  - **Information**
  - **Inclusion of a paediatric development plan into the business plan: PIP (paediatric investigation plan).**

What is a Paediatric Investigation Plan?

The PIP is submitted by the pharmaceutical companies, then reviewed and approved by the paediatric committee (PDCO, EMA, centralized procedure).

- **The document describes pre-clinical and clinical studies and trials necessary to develop the medicinal product in all relevant subsets of the paediatric population (birth to less than 18 years)**
- **It includes timelines**
- **It includes if appropriate requirement for age-appropriate formulation**
- ***It is binding on the company which has to implement it***

Age-appropriate formulation

- adapted:
  - route of administration (e.g. liquid oral formulations, iv solutions...)
  - strength,
  - volume,
  - size,
- excipients
- dosing device and/or medical device
- taste and acceptability (compliance)

Formulation working group

Excipients in the label and package leaflet of medicinal products for human use

(EC, ENTR/F2/BL), last revision: July 2003

- **Since the last revision of the EC Guideline on Excipients in the label and package leaflet of medicinal products for human use in July 2003, safety concerns regarding excipients have been identified which are not currently addressed in the guideline.**
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf
- **A concept paper on the need for revision of the Guideline was released in 2012:**
  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/03/WC500123804.pdf

Concept paper on the need for revision of the guideline on excipients in the label and package leaflet of medicinal products for human use (CPMP/463/00)

Safety concerns identified regarding excipients:

- The current guideline does not cover the paediatric population
- Pregnant women: safety labelling is needed for products intended for use in this population to ensure the safety of the unborn child(ren)
- Labelling: sometimes limited number of routes of administrations
- Additional excipients need to be added to the guideline to ensure consistency in the safety labelling of medicinal products.
- How warnings in the package leaflet should be addressed in the summary of product characteristics (SmPC) in accordance with Article 59 (1) of Directive 2001/83/EC.

Definition

In general, excipients may be defined as the constituents … other than the active substance:

- colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,
- the constituents intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products – capsules, gelatine capsules, rectal capsules etc.
- excipient mixtures, e.g. those used for example in direct compression or in a film coat or polish for an ingested dose form, pH adjusters ...

Residues of substances arising from the manufacturing process, impurities, residual solvents, degradation products etc. are not included.

Safety concerns in paediatrics:

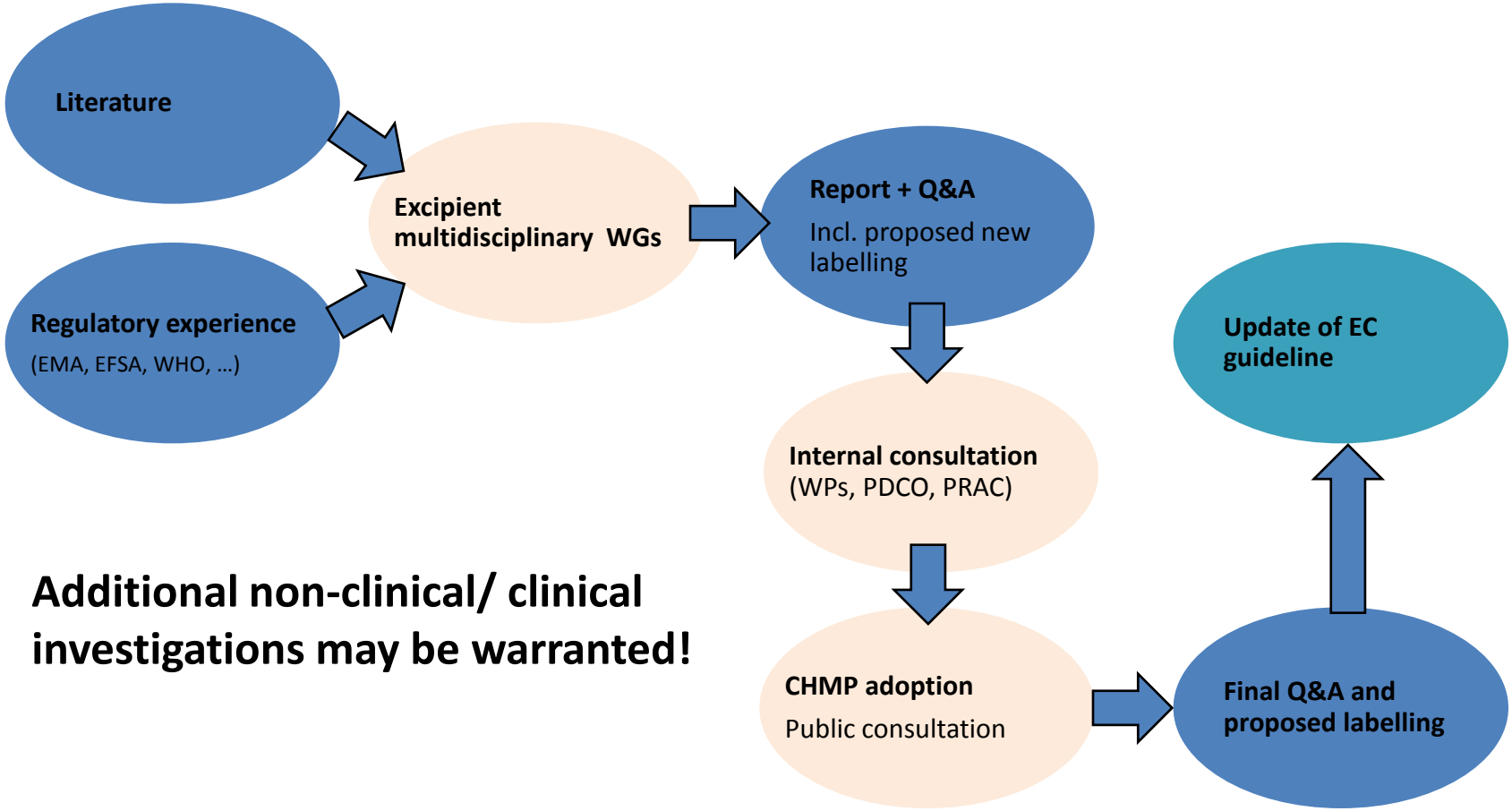
- The safety of excipients can affect children differently than adults due to the ongoing organ development and incomplete maturation depending on the age (e.g. pharmacokinetics: different metabolism, clearance, tissue distribution, skin penetration …)
- Excipients considered “inactive” and/or “safe” (?!)
- Products already on the market: more than 50% never tested in children
- Difficulty to discriminate symptoms due to the disease status/active substance from effects induced by the excipient(s)
- Most of the time, limited non-clinical (juvenile) data

Ongoing revision process

- 17 (+5?) excipients identified and prioritized based upon safety concerns
- Individual excipients attributed to multidisciplinary teams
- Internal (EMA) review followed by public consultation

Excipient in the label	Status
Phosphates in eye drops	Published
Benzyl alcohol	Draft published for public consultation
Benzoic acid and benzoates	
Ethanol	
Benzalkonium chloride	
Gluten	
Sodium	Draft for consultation by Q4-2014
Propylene glycol	
Cyclodextrins	
Boric acid	
Fragrances	

Revision process for each excipient



Additional non-clinical/ clinical investigations may be warranted!

Propylene glycol: Existing Recommendations

- **Dutch CTB (cough medicines): MTD 400 mg/kg/day (adults) – 200 mg/kg/day (children) (1994)**
- **WHO (food additives): PDI 25 mg/kg/day (1974)**
- **EU (excipients labelling): “May cause alcohol-like symptoms” above 400 mg/kg/day (adults) – 200 mg/kg/day (children) (2003)**

Propylene glycol: Safety concerns

- Hyperosmolality, lactic acidosis
- Renal dysfunction (acute tubular necrosis), acute renal failure
- Cardiotoxicity (arrhythmia, hypotension)
- Central nervous system (depression, coma, seizures)
- Respiratory depression, dyspnoea
- liver dysfunction
- haemolytic reaction (intravascular hemolysis) and haemoglobinuria
- multisystem organ dysfunction

- In children: immature metabolic pathway up to 5 years of age

Propylene glycol: Pharmacokinetics

- **ABSORPTION**
  - Similar for oral / i.v. / i.p. route (rapid and ~ complete absorption by oral route)
  - Rectal and inhalation route: limited data
  - Dermal route: negligible but increased if skin is damaged
- **DISTRIBUTION**
  - To aqueous compartment including CSF and fetus
- **METABOLISM**

  rate lim. Step

  ADH ALDH
  - PG → lactaldehyde → lactate → pyruvate + CO_2 + H_2O
  - Exaggerated formation of lactate → lactic acidosis
  - Saturation at lower doses in humans than in rats and rabbits
- **EXCRETION**
  - In adults ~ 50% metabolic clearance, 50% renal clearance.

Propylene glycol: Pharmacokinetics

- **ACCUMULATION**
  - **In case of saturation of metabolic clearance or impaired renal function**
  - **PG accumulates in serum → hyperosmolarity**
  - **Increased osmolar gap = predictive signal for PG toxicity**
- **Paediatrics:**
  - **Rapid oral absorption and extensive tissue distribution: → little impact of BBB maturation**
  - **One major metabolic pathway → potential DDI with other ADH substrats (Kaletra: PG + ethanol)**
  - **Neonates: most sensitive population because renal clearance very low, metabolic clearance limited → long elimination half life (30h vs 5h in adults),↑ risk of accumulation, acute toxicity (↑ exposure)**
  - **Infants up to 1 year: potentially limited renal clearance**
  - **Infants/children up to 4 years: ADH below adult level (~10% at birth)**

Propylene glycol: Non-Clinical Safety Assessment

- Repeat-dose toxicity
  - 2-year oral studies in rats (1972) and dogs (1971)
  - 90-day oral studies in mice, rats, dogs, monkeys (2010)
  - Lack of adverse effects in general. High dose effects at liver and hematologic system.
  - Oral NOAEL rats 2 g/kg/day, dogs 5 g/kg/day, mice 10 g/kg/day
- Genotoxicity potential low
- Carcinogenicity
  - Chronic studies in rats (diet, 1972) and mice (skin-painting, 1974) negative at highest dose tested: 2 g/kg/day (rats), 0,8 g/kg/d (mice)

Propylene glycol: Non-Clinical Safety Assessment

- Reproductive toxicity
  - Continuous breeding study in mice NOAEL F0 10 g/kg/day F1 14 g/kg/day (1989)
  - Prenatal developmental toxicity study in mice NOAEL 10 g/kg/day (1993)
  - Rat fertility study NOAEL 1 g/kg/day (2010)
  - Rat and rabbit teratology studies NOAEL 1 g/kg/day (2010)
- Juvenile toxicity
  - Single i.p. dose in mice:
    - apoptotic neurodegeneration in brain at 2 g/kg in animals aged PND 4, 7, 14 and 17 (no effects PND 24 or 30, attributed to effect on synaptogenesis)
    - at 10 g/kg animal death due to respiratory failure (2012)
- Local tolerance
  - Non-irritant
- Sensitisation
  - Negative guinea pig maximisation test, modified mouse ear swelling test and LLNA

Propylene glycol: Non-Clinical Safety Assessment

- low systemic toxicity in experimental adult animals

  (Oral NOAEL: rats 2 g/kg/day, dogs 5 g/kg/day, mice 10 g/kg/day)
- a juvenile mouse study shows that propylene glycol produces ethanol-like apoptotic neurodegeneration in the developing mouse CNS starting at doses of 2 g/kg (NOEL: 1 g/kg)
- based on non-clinical data the following conservative permitted daily exposures (PDEs) could be derived (note for guidance on impurities: Residual Solvents - ICH, 1998):

up to 4 years	5 years up to 17 years and adults
1 mg/kg	50 mg/kg

- below 5 years:
  - lesions are attributed to an effect on synaptogenesis; ~ week 4 in rodents, ~ year 5 in human
  - ADH maturation: ~ week 4 in rodents, ~ year 5 in human

Propylene glycol: Clinical Safety Assessment

- Detailed analysis of published case studies and retrospective/prospective observational safety studies
- Mainly data from iv infusion of lorazepam, benzodiazepine or etomidate in critically ill adults and children & iv administration of paracetamol in neonates
- Major effects (e.g. following oral, iv infusion): hyperosmolality & metabolic acidosis << renal dysfunction << acute renal failure and clinical deterioration
- Also CNS, CV and local vascular effects (e.g. following iv bolus)

Propylene glycol: Clinical Safety Assessment

ADULTS:

- **Manifestations of PG toxicity > 1g/kg/day**
- **Clinical deterioration > 3 g/kg/day**
- **Importance of treatment duration → up to 500 mg/kg/day can be administered safely for long term periods**
- **Metabolic changes and renal dysfuntion reverse upon weaning off – hemodialysis helpfull in more severe cases**

CHILDREN

- **No effects at a median PG dose of 34 mg/kg/day in neonates (2010) – short term treatment , no CNS evaluation**
- **Lack of solid data between neonates and 5 years of age!**

Propylene glycol: Derivation of Safety Limits

- **Based on the clinical data it was estimated that:**
  - **In adults, 500 mg/kg/day could be administered safely for long term periods**
  - **In children from two months of age to 4 years of age, 50 mg/kg could be adlministered safely for short term periods (!DDI)**
  - **In pre-term and term neonates up to 28 days of age, 1 mg/kg could be administered safely (DDI!)**

- **2 months up to 4 years:**
  - **conservative value based upon neonate study,**
  - **50 mg/kg < HED to NOAEL in juvenile mouse**

Propylene glycol: Derivation of Safety Limits

- **Pre-term and term neonates:**
  - Adverse events like heart, kidney & breathing problems reported in premature neonates
  - Total body clearance very low + contribution of renal clearance very low (15% of total clearance)
  - Metabolic DDI highly relevant in this population (e.g. with EtOH)
  - Proposed to restrict the dose limit to 1mg/kg in preterm neonates below 44 weeks of post menstrual age, or one month post natal age for term neonates.

neonates up to 1 month	2 months up to 4 years	5 years up to 17 years and adults
1 mg/kg	50 mg/kg	500 mg/kg

Recommendations

- The use of high amounts of propylene glycol in a drug product should be justified.
- Non clinical studies may have to be conducted in order to assess potential safety concerns particularly for children below 5 years of age
- The pivotal clinical studies will have to be performed using the final formulation. Signs of hyperosmolality, metabolic acidosis, and/or renal failure may have to be monitored. These signs include but are not limited to:
  - Propylene glycol serum concentration
  - Osmolality
  - Osmolar gap
  - Serum creatinine concentration, creatinine clearance
  - Serum lactate concentration
  - Serum bicarbonate concentration

Labelling

Name	Route of administration	Threshold	Information for package leaflet	Comments (for health care professionals)
Propylene glycol	Oral, parenteral, topical	1 mg/kg/day	This product contains XXX [concentration] propylene glycol as an ingredient necessary for the medicine to work properly.	Content to be also in the SmPC to reflect this PL information.
			Talk to your doctor or pharmacist before giving this medicine to your child if (s)he is a pre-term or full-term neonate.	Co-administration with any substrate of alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates. Minute amounts of propylene glycol in the composition of other excipients such as flavours or colouring agents would not produce any detectable increase in propylene glycol serum concentration.

Labelling

Name	Route of administration	Threshold	Information for package leaflet	Comments (for health care professionals)
Propylene glycol	Oral, parenteral, topical	50 mg/kg/day	This product contains XXX [concentration] propylene glycol as an ingredient necessary for the medicine to work properly.	Propylene glycol could cause the following adverse events: • Hyperosmolality, lactic acidosis; • Renal dysfunction (acute tubular necrosis), acute renal failure; • Cardiotoxicity (arrhythmia, hypotension); • Central nervous system (alcohol like symptoms such as depression, coma, seizures); • Respiratory depression, dyspnoea; • Liver dysfunction; • Haemolytic reaction (intravascular hemolysis) and haemoglobinuria; • Multisystem organ dysfunction. Adverse events usually reverse following weaning off propylene glycol, and in more severe cases following hemodialysis.
			Talk to your doctor or pharmacist before giving this medicine to your child if (s)he is below 5 years of age	PG may be toxic in children less than 5 years old in particular when co-administration with any substrate of alcohol dehydrogenase such as ethanol.
			If you are pregnant or breast feeding or if you suffer from a liver or kidney disease, talk to your doctor or pharmacist before taking this medicine because of its content in propylene glycol.	Propylene glycol administration should be monitored with caution in patients with impaired renal or hepatic functions.

Thank you for your attention!

Your medicines and health products, our concern

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Update of the annex of the guideline

Trigger information in PL

Information for the **patient**

Additional info for **healthcare professionals**

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzalkonium chloride	Ocular	Zero	May cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Known to discolour soft contact lenses.	
	Topical		Irritant, may cause skin reactions.	
	Respiratory	10 micrograms / delivered dose	May cause bronchospasm.	