Table I: Examples of excipient-related adverse events in pediatric patients, patients with metabolic disorders, and hypersensitive patients.

Excipient	Route of administration	Adverse event
Neonates and infants <6 months of age		
Benzyl alcohol[30,31]	Oral, parenteral	Neurotoxicity, metabolic acidosis, gasping syndrome, risk of hyperbilirubinaemia in neonates.
Propylene glycol	Oral, parenteral[8,20,31]	Seizures, hyperosmolarity, neurotoxicity.
	Topical[18,30,31]	Skin irritation, contact dermatitis.
Polyethylene glycol[20]	Parenteral	Metabolic acidosis.
Polysorbate 20 & 80[20]	Parenteral	Liver and kidney failure.
Polysorbate 80[30]	Topical	E-Ferol syndrome—thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension, metabolic acidosis.Inhibition of p-glycoprotein with potential effects on the blood–brain barrier and drug–drug interactions.
Ethanol[30,31]	Oral, parenteral	CNS depression—muscle incoordination, visual impairment. Negative synergic effects on CNS when associated with propylene glycol. Chronic toxicity.
Propylparaben[30,31]	Oral	Hyperbilirubinemia in neonates. Hypersensitivity reactions. Agonistic activity at hormone receptors.
Patients with a metabolic disorder		
Aspartame[8]	Oral	Phenylketonuria (source of phenylalanine).
Fructose, sucrose[20]	Oral, parenteral	Hereditary fructose intolerance.
Sorbitol[20]	Oral	Hereditary fructose intolerance.
Lactose[8]	Oral	Lactose intolerance, galactosemia, diarrhoea.
Hypersensitive patients		
Azo dyes[8]	Oral	Allergenic potential, should not be used in children.
Parabens[20]	Oral, ocular, topical	Allergies, contact dermatitis.
Sulfites, bisulfites[30,31]	Oral, parenteral, topical	Rashes, abdominal upset. Hypersensitivity, paradoxical bronchospasm, wheezing, dyspnoea and chest tightness in asthmatic children.
Lanolin[20]	Topical	Contact dermatitis, urticaria.

formulations.[20] Precedence of use of excipients or excipient concentrations in commercially available drug products for adults may not be appropriate for use in pediatric patients, or for children of different ages. Excipients may also have different effects on developing organ systems, depending on the child's age and developmental stage. In addition, metabolic capacity is restricted in young children, especially during the first months of life. These factors can result in elevated toxicological risks in children compared to adults for some excipients.[21] As an example, propylene glycol is commonly used to solubilise drugs in oral, parenteral and topical formulations; in the body it is partially excreted by the kidneys unchanged and partially oxidized to lactic and pyruvic acid, entering the glycolic pathway and ultimately resulting in the production of carbon dioxide and water. The half-life of propylene glycol in adults is 5 hours compared to 16.9 hours in a neonate; adverse events reported in neonates include metabolic acidosis (due to lactic acid) and serum hyperosmolarity (due to propylene glycol accumulation) after intravenous administration and topical administration on burn wounds.[22] As such, the use in a product for pediatric use should be carefully considered and justified in line with current safety information and regulatory requirements.[23]

Specific hypersensitivities associated with certain excipients (e.g. azo-dyes, lanolin), as well as metabolic disorders (e.g. phenylketonuria) also need to be considered when selecting excipients; however this does not exclusively apply to the pediatric population.

Table I provides examples of reported adverse events with a number of excipients commonly used in pediatric formulations.

The STEP (Safety and Toxicity of Excipients for Paediatrics) database, jointly developed by the European Paediatric Formulation Initiative (EuPFI) and the US Pediatric Formulation Initiative (USPFI), collates preclinical and clinical safety and toxicity data for excipients commonly used in pediatric dosage forms. The STEP database is a useful repository for the formulator when assessing excipient safety for different pediatric age groups and routes of administration.[24–26]

Other sources of safety information on excipients include the EMA web page 'excipients labelling',[27] which contains a growing number of question and answer documents that have been generated following a decision by the European Commission (EC) to revise the guidance on excipients in the label and package leaflet of medicinal products for human use. The guidance documents with specific reference to pediatrics include; ethanol, propylene glycol, sodium methyl/propyl paraben and boric acid. In the US, the FDA Inactive Ingredient Database (IID) provides information on the quantities of excipients found in US approved drug products; such information can be useful to determine previous precedence of use. However, such information in isolation is not sufficient to justify the use of an excipient in a formulation.

Justification of Excipients - Regulatory Considerations

The EU Paediatric Regulation outlined the requirement for the submission and approval of a PIP. The PIP must be approved prior to the application for a Marketing Authorisation Application (MAA) for a new medicinal product in the EU, or following significant changes to an existing product already approved and on-patent such as a new indication, pharmaceutical form, or route of administration. Within the quality sections of the PIP, the applicant is expected to provide a justification for the pharmaceutical form for the intended pediatric population, which would include the excipient justification for review by the Paediatric Committee (PDCO).

The Formulation Working Group (FWG) supports the PDCO in the review process providing input on formulation aspects. In 2013, the EMA published a list of criteria for screening PIPs with regard to pediatric specific quality issues and referring them to the PDCO and the FWG for discussion. Included are aspects related to the age appropriateness of the formulation, considerations for administration (including palatability and the safety evaluations for the chosen excipients with respect to the target population), dosing, and duration of exposure.[28]