

**Chapter Title:**

**Paediatric Pharmaceutics – Science of formulating medicines for children**

**Chapter Outline:**

- 1. Introduction**
  - a. Children & their specific needs**
  - b. Children & their medicines**
  - c. Children & regulations around their medicine**
  
- 2. Paediatric drug development: Key attributes**
  - a. Dosage form design**
  - b. Excipients**
  - c. Administration**
  
- 3. Patient centricity and future vision**

**Full postal addresses and emails for all authors**

Mine Orlu<sup>1</sup>, Smita Salunke<sup>1</sup>, Catherine Tuleu<sup>1</sup>

<sup>1</sup>UCL School of Pharmacy, Department of Pharmaceutics, 29 - 39 Brunswick Square, , London  
WC1N 1AX

[m.orlu@ucl.ac.uk](mailto:m.orlu@ucl.ac.uk); [s.salunke@ucl.ac.uk](mailto:s.salunke@ucl.ac.uk); [c.tuleu@ucl.ac.uk](mailto:c.tuleu@ucl.ac.uk)

**Paediatrics** (also spelled **pediatrics**) is the branch of medicine that deals with the medical care of neonates, infants, children, and adolescents, and the age limit usually ranges from birth up to 18 years. Child health is key to overall human life expectancy, whereas paediatric diseases may have a lifelong effect on quality of life. On global scale nearly 5.8 million children under age 5 died in 2015, representing a 52% decline in the number of under-5 deaths since 1990. Neonatal deaths fell at a slower pace since 1990, decreasing 42% to 2.6 million; stillbirths declined 47% to 2.1 million. Although the life expectancy has improved around the world between 1990 and 2015, it still remains the case that people in look forward to longer and healthier lives. One of the factors driving the increases in life expectancy at birth is better health outcomes for young children, implying urgent need for medicines that keep children healthy.

Children have the right to access medicines that are appropriate to their unique needs and have adequate assurance of their quality, safety and efficacy. This has been widely acknowledged on a worldwide platform and prompted global initiatives and legislative changes that have transformed this once niche area into an integral part of the drug development process that requires adequate understanding of relationship between medicine pharmaceutical design and how child's growth affects the medicine's safety, efficacy and its usability in daily practice.

This chapter discusses the specific needs of children, how the implementation of paediatric regulation has influenced/promoted the research into previously neglected population and key attributes to consider during the designing and development of paediatric dosage forms to provide adequate paediatric therapies.

## 1. Introduction

### a. Children & their specific needs

Children are a heterogeneous population that includes new-borns (term or pre-term), infants, toddlers, pre-schoolers, school-age children, and adolescents(1). The stages of developmental physiological changes throughout childhood complicate pharmacotherapy. A complete consensus does not exist about the age ranges that define infancy, childhood and adolescence. The term 'child' has been used broadly to refer to individual ages 0 to 18 years. Biologically, a **child** (plural: **children**) is generally a human between the stages of birth and puberty. The guideline on clinical investigation of medicinal products in the paediatric population uses the age groups in relation to developmental stages. It reflects biological changes – the changes after birth; the early growth spurt; gradual growth from 2-12 years; the pubertal and adolescent growth spurt and development towards adult maturity (2). The subsets of the paediatric population widely differ in their therapeutic requirements due to their developmental and behavioural stage. From birth into adulthood, children change and develop physically, cognitively, socially, and emotionally. Physical growth during childhood is apparent to the eye, but less obvious is the on-going maturation of organ function. The physiological make-up of children differs not only from adults but also within their own age group. During the first few weeks and months of their life, changes occur in saliva production, body composition (e.g., body water and fat content, protein binding characteristics), organ weight and maturity (eg. renal maturation, hepatic maturation) (3). This can affect the absorption, distribution, metabolism and excretion of drugs and excipients and in turn can cause toxicity (4) Additionally, there is extensive inter-individual variation; children of the same age may vary according to weight, height, body surface area and maturity (3). There will always be an overlap in developmental stages. Understanding the physiological development differences and changes during the earliest period of life is important in paediatric drug testing (5). One area that needs special attention is neonatal (in first month life) deaths which are falling more slowly than under-5 deaths and accounted for nearly half (2.6 million) of all deaths in children under 5 in 2015. Preterm birth complications and birth asphyxia and trauma are now the leading causes of deaths in children younger than 5 years worldwide, highlighting the slower progress in reducing neonatal conditions compared with communicable diseases in childhood. Hence, when designing a paediatric drug product it is important to take into consideration the specific age category.

## **b. Children & their medicines**

Lack of authorised medicines and consequent off-label use of adult's medicines is a significant problem in the paediatric population. In neonates, the situation is particularly challenging due to the vulnerability of newborns and even lower patient numbers. Children are not young adults then why are they prescribed adult medicines on an "off-label" basis? Authorised medicines that are not available on the market do not bring any benefit to a child. The percentage of authorised and dose capable medicines with a suitable dosage forms increases with age. The American Academy of Pediatrics has argued that the shortage of pediatric research creates an ethical dilemma for physicians, who "must frequently either not treat children with potentially beneficial medications or treat them with medications based on adult studies or anecdotal empirical experience in children". Research with adults cannot simply be generalized or extrapolated to infants, children, and adolescents and hence research-involving children is essential if children are to share fully in the benefits derived from advances in medical science. Several challenges including the relatively small numbers of children with serious medical problems, the need for developmentally appropriate outcome measures for children of different ages, the complexities of parental involvement and family decision making, and the adaptations required in research procedures and settings to accommodate children's physical, cognitive, and emotional development make the research in paediatrics more challenging than adults. Specific clinical investigations in paediatric populations are normally required due to age-related differences in the drug handling or drug effects which may lead to different dose requirements to achieve efficacy or to avoid adverse effects. The development of medicines tailored for children needs implies that a specific drug may be needed to be available in various dosage forms and/or strengths. Thus several medicinal drug product may be needed in order to treat a broad patient population from birth into adulthood. The dose capability and suitability of dosage form are considered for any authorised paediatric medicine. (e.g., for acetaminophen, two strengths of chewable tablets, a low-strength "swallowable" tablet, a syrup, and drops in a different concentration for infants). Furthermore, compared to adults, children generally represent a smaller market for commercial sponsors of research. The commercial value of various preventive, diagnostic, and therapeutic options for children, especially for rare diseases, may not be enough to offset the costs of developing them. On one hand there are several formulation, clinical and regulatory requirements for developing paediatric formulation while on other hand the widespread use of off label drugs does not incentivize companies to finance paediatric research on drugs that are already approved for use by adults. Challenges in carrying out

paediatric research include the rarity of many childhood diseases, heterogeneity of the population and issues regarding consent. Efforts are needed to obtain good evidence with as few subjects as possible and prevent unnecessary clinical trials. Approaches such as extrapolation and modelling and simulation are increasingly becoming part of paediatric medicine development to optimise available data from other populations and reduce the number of children needed in clinical studies, however, clinical research with children is essential for paediatric drug development in the majority of cases. Much progress has been made on understanding how diseases differ in children and adults, but more concerted effort is needed towards understanding the patient.

In general, several features distinguish pharmacotherapy in children from that in adults and explain why medicines must be studied in research with children to ensure their safe and effective use (3).

These features include

- Lack of age-appropriate formulations that allow the accurate, safe, and palatable administration of medicines to children of a wide range of developmental characteristics such as weight, height, body surface area and maturity
- Age and development dependent changes in how medicines are distributed in and eliminated from the body (pharmacokinetics);
- age and development dependent changes in the response to medicines (pharmacodynamics);
- age and development dependent changes in the adverse effects of medicines, both short and long term; and
- unique pediatric diseases that require development of unique pediatric medications.

### **c. Children & regulations around their medicine**

Historically, paediatric drug development was mainly promoted and incentivized as a voluntary process. However, this voluntary market forces alone had proven to be insufficient to stimulate research or address the lack of dosage forms for children. The unmet need for safe and better medicines for children was well recognized by various agencies governing pharmaceutical regulations across the globe and has resulted in a dramatic progress and growing interest in the development of age appropriate formulations to better serve the needs of the paediatric population (6). Legislative and regulatory reforms were initially led by the United States (US) Food and Drug Administration (FDA) to increase the information in the drug label on use of medicines in children. The FDA Amendments Act (FDAAA) in 2007 was an important landmark, which included reauthorisation of the 2002 Best Pharmaceuticals for Children Act (BPCA) and the 2003 Pediatric Research Equity Act (PREA). The BPCA grants 6-months market exclusivity as an incentive to conduct necessary paediatric studies (voluntarily), while PREA codified the authority of the FDA to mandate studies for certain drugs and biological

products. The FDA Safety and Innovation Act (FDASIA) in 2012 made both the BPCA and PREA permanent. Subject to PREA, sponsors are required to provide information related to the development of paediatric formulations as part of a Pediatric Study Plan (PSP) submitted at the end of Phase 2 research. The European Union (EU) adopted its own comprehensive reforms when Regulation (EC) No. 1901/2006 or the “Paediatric Regulation” came into force in January 2007. The paediatric regulation aims to improve the health of children of Europe by a system of obligations and rewards facilitating the development and availability of appropriately authorized medicines for children between birth and 18 years; by improving the information on the actual use of medicines in children; by ensuring that medicines for use in children are of high quality and ethically researched (7). The regulation requires companies to develop Paediatric Investigation Plan (PIP) at an early phase in the development of a new medicine, new route of administration or new indication or for any variations to patented authorised medicines (unless a waiver is granted). The PIP describes the plan for paediatric development of medicines, including the pharmaceutical design of the preparation(s) to be developed for each of the target age group (8) (9) (10). The PIP is assessed and subjected to agreement upon by a scientific Paediatric Committee (PDCO) of the European Medicines Agency (EMA). The EMA/PDCO PIP decisions are binding at the time of marketing authorisation and industry can only apply for marketing authorisation of the (adult) medicine when the EMA has confirmed that the PIP was followed or a deferral was obtained. In contrast with the US PSP, the EU PIP is agreed at the end of Phase 1, though deferrals can be agreed for the initiation or completion of initial proposals if justified. Both legislations provide frameworks together with the incentives and rewards and ensure that new medicines are adapted to children needs and that the paediatric population is not neglected despite the forces of the market. However, a more harmonised approach across these jurisdictions would be beneficial (11). The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (which brings together authorities and industries in the EU, US and Japan) also adopted a guideline, ICH E11, addressing the conduct of clinical trials in the paediatric population (12). Notably, this guideline categorises the paediatric population into 5 distinct age groups, including “children” aged 2 to 11 years and adolescents aged 12 years and above (for the purposes of this research, this includes persons aged 12 to 17 years old). While these groups reflect clinical applications, the EMA further subdivided children into “pre-school children” aged 2 to 5 years and “school-children” aged 6 to 11 years in relation to formulation development considerations (2). These remain the principal regulatory reforms and there has been comparatively little progress in other countries. Acknowledging that the majority of children in less developed countries live less healthy life as compared to more developed countries, the limited availability of appropriate medicines for children is key concern to the World Health Organization (WHO). It has spearheaded important campaigns promoting awareness and accelerating action to address three challenges associated with paediatric medicines, namely availability, accessibility and affordability. These were aptly entitled ‘Making Medicines Child Size’ and the ‘Better

Medicines for Children Project', and notable outcomes of these initiatives include the WHO Model List of Essential Medicines for Children and a 'points to consider' document on the formulation of paediatric medicines (13). The objective was to inform regulatory authorities and manufacturers on issues that require special attention in pharmaceutical formulation. In 2010, the WHO published a Model Formulary for Children built on the EML that provides prescribing guidance on use of the essential medicines. As a result, for the first time medical practitioners worldwide have access to standardized information on the recommended use, dosage, adverse effects, and contraindications of these medicines for use in children (14). Recommendations to improve children's access to better medicines had also been made by other Australian professional and government advisory groups since the late 1990s, but with little resulting action.

The changing regulatory landscape has generated a need of research to create better and safer medicines for children and advance the current platforms and technologies that are already used in this patient population (15). Pharmaceutical sponsors, regulatory agencies and allied stakeholders have reached an influential period in the new era of developing paediatric medicines. Given the lengthy drug development process, it is somewhat premature to measure the overall global impact of these legislations and initiatives. Nevertheless, proof of concept and progress to date has been encouraging, including improved drug labelling, completion of PIPs with new paediatric indications and formulations, and emerging research into the previously neglected areas of neonatology and off-patent medicines (11). Some argue that economic barriers and lack of adequate incentives continue to impede the necessary focus on unmet clinical need, and instead, development of paediatric medicines seems to shadow drug development in adults (16, 17). While these reforms continue to serve as platforms steering research and development, distinctive opportunities and challenges in the field also emerge.

With the mission of better medicines for children finally on the global agenda, the challenges are now to collaboratively further shape the paediatric drug development agenda and effectively use the existing data to address these challenges in formulating medicines for children and to bridge the adult-children medicine gap. Researchers and academics are putting in all the efforts to respond to many unanswered questions about medicines for children, through research and international collaboration both at country or regional levels and at the global level. Key developments include the range of pioneering paediatric drug development initiatives such as formation of the International Alliance for Better Medicines for Children (IABMC) in 2006; establishment of the Paediatric Task Force by The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) in 2008; and establishment of European Paediatric formulation Initiative (EuPFI)<sup>1</sup> in 2007. The European

---

<sup>1</sup> The European Paediatric Formulation Initiative (EuPFI) is a consortium founded in 2007 and working in a pre-competitive way on paediatric drug formulations. Members are from academia, hospital pharmacies,

Union funded Global Research in Paediatrics (GRIP) project that brings together over twenty collaborating organizations and more than a thousand researchers to harmonize paediatric research tools and share research strategies. However, despite the expansion of research in the development of paediatric medicinal products, there is still an unmet need and challenges for medicines for children. These research efforts have resulted in some progress in medicines with a larger market (e.g. anti-infectives, antibacterials, medicines for the respiratory and central nervous system) but not in all areas of priority paediatric health need (18). Younger and more vulnerable age groups, where the need for better evidence is even greater, have been less well studied and many of the off-patent medicines remain unevaluated. Hurdles such as regulatory capacity, affordability and patient and caregiver acceptance still hinder access to safe and appropriate medicines for children. In addition, research is still needed to define appropriate dosages and formulations for other priority medicines for children.

## **2. Paediatric drug development: key attributes**

### **a. Dosage form design**

Appropriate dosage form design is essential for any type of drug product development to help ensure safety, efficacy and quality. When designing a paediatric drug product it is also important to consider the age-related physiological and behavioural growth and their influence on the pharmacokinetics / pharmacodynamics and medicine use. The variance across the paediatric population is also an important factor determining the appropriateness of the formulation. The dosage form design should be tailored according to the specific needs of paediatric subsets ranging from neonates to adolescents. The European Medicines Agency has issued a specific guideline related to the pharmaceutical development of medicines for paediatric use in 2013. This key reference describes the regulatory expectations for a paediatric medicinal product design including the end-user acceptability to optimize therapeutic outcomes.

The design of paediatric dosage form is driven by the key points to consider listed below (19).

#### **1. Efficacy**

- a. Adequate bioavailability to ensure pharmacotherapeutic effect
- b. Disease to be treated (chronic or acute condition)
- c. Dose flexibility (enabling dosing to different age-subsets, acceptable dose size)

#### **2. Safety**

- a. Dosing accuracy (minimal risk of dosing error, no requirement for manipulation prior to use)

---

pharmaceutical industry (Innovators, Generics, Contract Research Organizations (CRO), Specials and Excipient Manufacturers) with European Medicine Agency (EMA) as an observer. The main objective of the members is to resolve scientific, regulatory and technological issues associated with paediatric formulation development.



- b. Excipients (determination of qualitative and quantitative composition considering patient`s tolerability)
  - c. Stability (shelf-life and in-use stability)
- 3. Patient access
  - a. Manufacturability (availability of robust process, ease of production, transport and storage, commercial viability)
  - b. Cost (affordability for patient / healthcare provider)
- 4. Patient acceptability and adherence
  - a. Patient age subset
  - b. Patient ability (suits patient capability)
  - c. Patient willingness (meets patient preferences)
  - d. Administration related requirements (easy and convenient preparation of point of care, acceptable for care-givers and healthcare professionals)
  - e. Compliance (minimal impact on life style)

Oral drug delivery is the most widely preferred route of administration of paediatric medicine (20). Historically liquid formulations have been reflected as the choice of formulation as the main barrier is the swallowability of intact conventional solid oral dosage forms for younger children. However the issues related to the need of use of specific excipients (e.g. co-solvents, preservatives, sweeteners, flavours) and packaging / administration devices may be the barrier for the use of liquid formulations to treat childhood conditions.

The progress in the development of novel drug delivery systems has enabled solid oral dosage forms as age-appropriate formulations for paediatric use. The World Health Organization suggests the use of flexible solid oral dosage forms as the preferred way of administering medicines to children. The flexible solid oral dosage forms include dispersibles, orodispersibles and multiparticulates. The design of age appropriate formulations consider the aspects of the Quality Target Product Profile relating to patient and caregiver`s needs, capabilities and preferences. Dispersibles are presented as solid dosage forms that are dispersed or dissolved in a liquid to form a solution or suspension prior to administration. Oral liquid dosage forms are normally considered acceptable from birth, taking into consideration appropriateness of volume, composition and palatability (7). Dispersible and soluble tablets should disintegrate within three minutes in a small amount of water, to yield a homogenous dispersion or solution. Orodispersible formulations include tablets (ODT) and oral thin oral dispersible films (ODFs) that rapidly disintegrate in saliva, usually within seconds. These formulations are well suited for drugs with high aqueous solubility; however, their applicability in practice may be restricted by limited drug loading. Multiparticulates describe powders, granules, pellets and minitablets that are presented as multiple, discrete unit dosage forms. The flexibility of the multiparticulates is due to the possibility of administering with sprinkling on soft food (21). The points to consider for paediatric dosage form design are explained using the recent development of lopinavir/ritonavir sprinkle formulation as follows.

The recognition of the challenge related to the traditionally available antiretrovirals in liquid and conventional solid formulations led to the development of paediatric lopinavir/ritonavir in a new formulation. Lopinavir/ritonavir are produced in pellets by melt-extrusion technology and are enclosed in capsules. The dosage form has enabled the dose flexibility via the possibility of sprinkling the oral pellets on a compatible soft food prior to administration to infants. The medicinal product is also possible to be taken as a whole capsule by older children. This new design has also addressed the demand for a heat-stable and easy to transport/store formulation. The pellets are also functionalized by taste masking. The palatability is one of the key requirements for acceptability of orally administered dosage forms. The acceptability may be perceived as a pre-condition to long term adherence. In this respect, the new sprinkle pellet formulation shows promise for higher patient acceptability and adherence. A multi-discipline approach may be required (collaboration with experts from pre-clinical, packaging and devices as well as behavioral science) to have a further understanding on the overall acceptability and longer term adherence to paediatric medicinal products.

#### **b. Excipients**

Excipients play a fundamental role in medicines. They are included in a dosage form to convert a pharmacologically active compound/drug substance into a pharmaceutical product that can be administered to or taken by the patient and that is acceptable to them. Although not pharmacologically active, they can enhance product performance by assuring the stability of the active substance, or to protect against microbial contamination during use (eg, parabens, benzoic acid). Some excipients (eg. polyethylene glycol, sodium pyrophosphate, mannitol) can in fact accelerate the passage of oral administered active substances through the intestinal tract thus adversely influencing the gastrointestinal absorption of active principle (22-24). There are many instances in which excipients have been shown to have a significant effect on the bioavailability of the drug (25). They can contribute to reactions leading to degradation or to interactions between the drug and the excipient (26, 27). To further complicate the issue, these effects can be drug, dose, formulation and/or subject dependent. For instance by modifying absorption for parenteral products, excipients can change exposure patterns and thus influence both safety and efficacy outcomes (28).

Advancements in functionality of excipients have now rendered the traditional view of excipients as “*simple inert pharmaceutical fillers*” obsolete. Today excipients, which have a critical effect on the quality and bioavailability of some drug products and novel dosage forms, do not anymore fit within the traditional definition as “*an inert substance used as diluent or vehicle for a drug*” (29). The evolution of the excipient definition from “*the inert substance used as a medium for giving a medicament*” to “*any constituent of a medicinal product other than the active substance*” is summarised in Figure 1

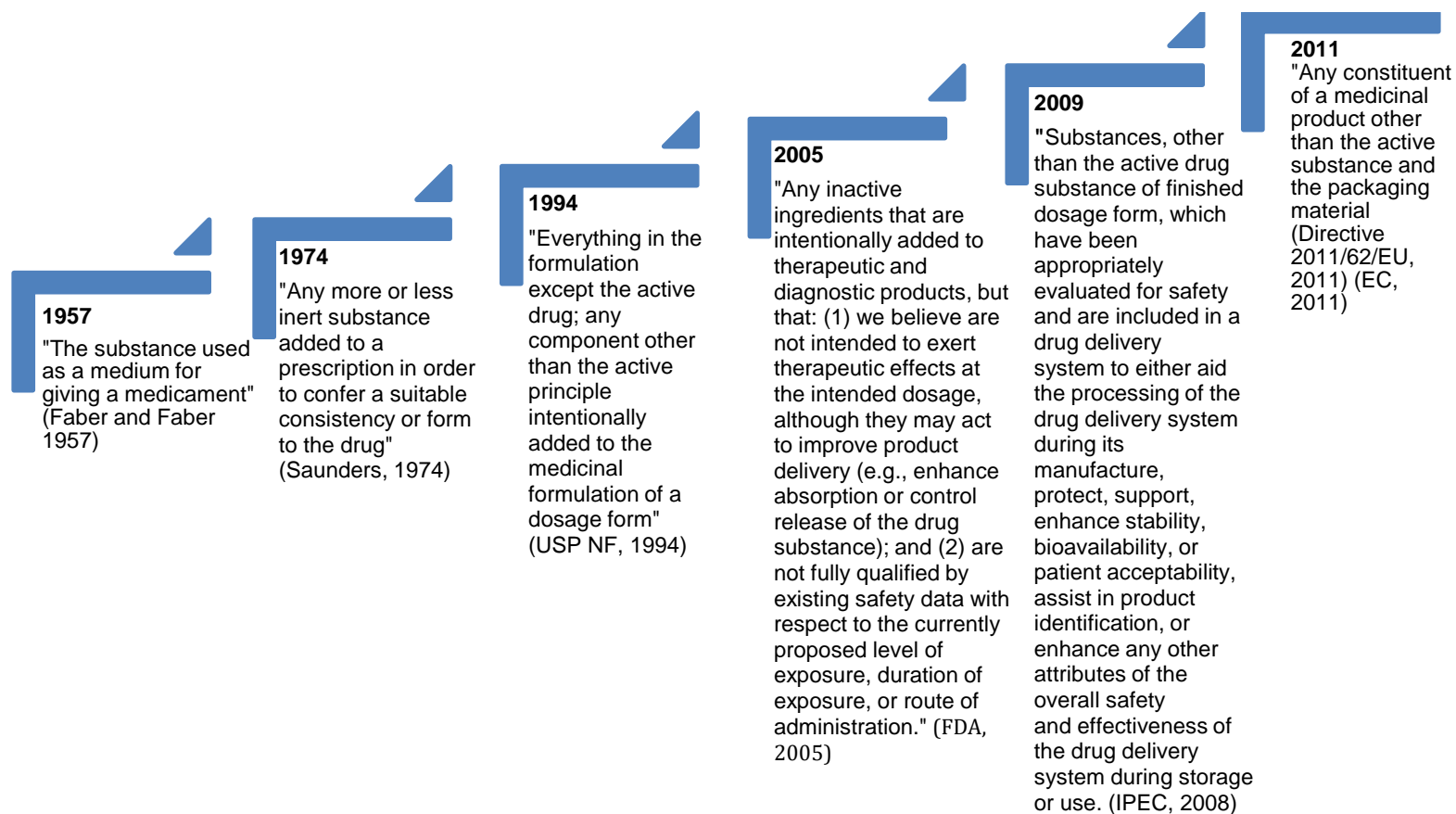


Figure 1: Evolution of definition of excipients  
(30-34)

## **Issues of excipients in paediatrics**

An objective of development of medicines for the relevant paediatric subsets is providing formulations that have sufficient bioavailability, acceptable palatability, acceptable dose uniformity and stability. Developing such age appropriate formulations is more complex and may involve a broader range of excipients than for adult dosage forms (35). There are many aspects to be considered when selecting an appropriate excipient such as: influence of excipient on the overall quality, stability, and effectiveness of drug product, compatibility with drug, route of administration, dosage form, their quantities in relation to the target age group, treatment duration and severity of disease, patient acceptability and safety profile (2). The current literature indicates that certain excipients acceptable in adult formulations (e.g. benzyl alcohol, ethanol, propylene glycol, ethanol, parabens) are associated with elevated toxicological risks and safety issues when used in children, even in proportional lower concentrations (36). Nevertheless, excipients with a potential cause for concern may be essential to the development of a specific dosage form. Hence, the screening and careful selection of excipients in a paediatric medicinal product is one of the key elements of pharmaceutical development (7) and the excipients chosen, their concentration, and the attributes relevant to their function in the drug product needs to be justified in terms of safety for the targeted age group, treatment, route of administration, duration, allergies, and severity of disease in their PIP application (37). EMA recommends that selection of a particular excipient and excipient quantity should be justified based on overall risk to benefit evaluation of the product itself for its intended use and target age group (7). For example, an excipient, which raises a minor safety concern, may still be allowed in exceptional cases taking into account the seriousness of the clinical indication or the advantages offered by a particular pharmaceutical form, route of administration, etc.

A combination of clinical, formulation and regulatory challenges (Figure 2) have to be addressed in the process of selecting and justifying the excipients for paediatric preparations.

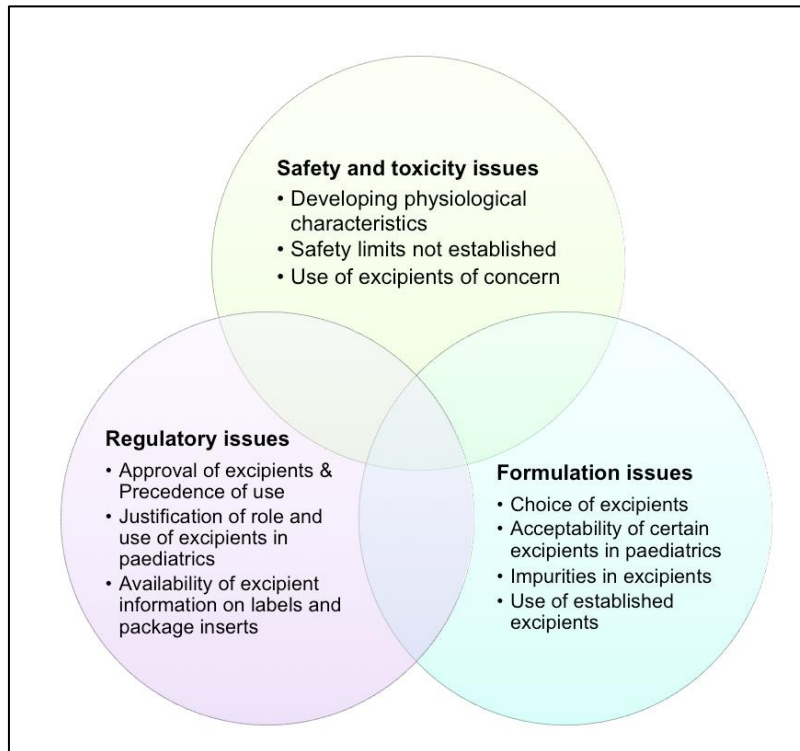


Figure 2: Issues of excipients in paediatrics

**Clinical issues**

The five-year report to the European Commission (EC) on the public health effects of the Paediatric Regulation indicated that safety of excipients is one of three major topics discussed by the Paediatric Committee Formulation Working Group (PDCO FWG) members (38). The WHO ‘Points to Consider’ document (20), the EMA reflection paper (2), and EMA Guideline on Pharmaceutical Development of Medicines for Paediatric Use, list known concerns about the use of excipients in paediatric patients. There are a number of reviews on the risks and benefits of excipients in compounded formulations (39-41), which are mainly used in children due to unavailability of medicines for children. Table 1 summarises the adverse effects of commonly used excipients in paediatrics. There are the theoretical arguments on why the use of the excipients in children is matter of concern. These include: the developing physiological characteristics of children, inappropriate labelling of excipients on paediatric medicines and non-established safety limits of excipients in paediatrics.

Table 1: Reported adverse effects caused by excipients especially in children

Lactose	Diarrhoea, malabsorption, vomiting, flatulence (in patients with lactose-intolerance) Jaundice, hypoglycaemia, CNS	(42) ; (43); (44)
---------	--	-------------------

	symptoms, cataracts (in patients with galactosemia)	
<b>Sweeteners and flavouring agents:</b>		
Aspartame	Headache, grand mal seizures, memory loss, gastrointestinal symptoms, dermatological symptoms (large quantities). Potentially toxic metabolites methanol, aspartic acid and phenylalanine. Phenylalanine is harmful in patients with phenylketonuria. Aspartic acid is neurotoxic and epileptogenic. Lastly, aspartame has been blamed for causing hyperactivity in children; the US the acceptable daily intake is 50mg/kg/day.	(36); (45) (46); (47)
Fructose	Hypoglycemia (in patients with fructose intolerance)	(44)
Menthol	Hypersensitivity reactions, systemic allergic reactions. In infants cause isolated cases of spasm of the larynx. Few cases of nervous or digestive system disturbance have been associated with excessive inhalation or oral exposure to menthol.	(45), (44)
Peppermint oil	Atrial fibrillation, muscle pain, cooling or burning sensations	(44)
Saccharin sodium	Irritability, hypertonia, insomnia, opisthotonus and strabismus, cross-sensitivity with sulfonamides; The most frequently described adverse reactions are dermatological and represented by urticaria, pruritus, dermatitis and photosensitivity. Other systemic reactions have been however reported: irritability, insomnia, opisthotonos and strabismus in children assuming saccharin-containing feed formulas. Approved for children >3 years. Banned in canada, allowed in USA and Europe. The American Medical Association recommended to limit the use of this synthetic sweetener in food and pharmaceutical products intended for paediatric population, the average acceptable intake of 0.6–0.9mg/kg/day for the general population and 0.6–2.3mg/kg/day for diabetic patients.	(36); (46) (48)
Sodium cyclamate	Incidence of bladder cancer increased in rats Use is restricted in many countries, Banned in USA and canada, allowed in Europe	(48)

Sorbitol, mannitol, xylitol	Large amounts: osmotic diarrhoea; "fructose intolerance" 0.15g/kg/day is well tolerated in males and 0.3g in females. The medicinal intake of sorbitol in paediatric population has been associated with disorders of the gastrointestinal tract, above all diarrhoea and malabsorption. A maximum intake limit neither for the paediatric population nor for adults has been defined, however, it has been suggested that a 20g daily intake should possibly represent a reasonable limit for an average weight adult.	(36); (46)
Sucrose	Tooth decay Carcinogenicity, increased degradation of active drug, allergic reactions (very rare); Diabetes mellitus or rare hereditary problems of fructose intolerance, glucose–galactose malabsorption, or sucrose–isomaltase insufficiency represent risk factors for sucrose adverse effects.	(45); (48); (44)
<b>Colouring agents:</b>		
Azo dyes	Anaphylactic reactions, angioedema, asthma, urticaria, hyperkinesia, cross-sensitivity with acetylsalicylic acid, sodium benzoate and indomethacin (tartrazine FD&C yellow5 = E102, sunset yellow FD&C 6 = E110)	(46)
Quinoline dyes	Contact dermatitis	(46)
Triphenylmethane dyes	Bronchoconstriction (brilliant blue FCF: FD&C blue1 = E133), erythema multiforme-like skin rash (fast green FCF: FD&C green3), anaphylaxis, angioedema (fluorescein: FD&C yellow7)	(46)
Xanthine dyes	Photosensitizer (eosin: FD&C red22), carcinogenicity (erythrosine: FD&C 3 = E127)	(46)
<b>Preservatives and antibacterial agents:</b>		
Benzalkonium chloride	Dose-related bronchoconstriction, cough, burning sensation, occasionally facial flushing, pruritus	(48); (47)
Benzoic acids and benzoates	Displacement of bile from albumin binding sites in premature neonates, 'gaspings syndrome'	(48) (49)
Benzyl alcohol	A number of neonatal deaths and severe respiratory and metabolic complications (32–105 mg/kg/d), bronchitis, haemoptysis, hypersensitivity reactions (rare)	(47)

Boric acid	Is not used internally owing to its toxicity: death from ingestion of <5g in young children	(45)
Parabens	Skin sensitization and cross-sensitization with each other Concern has been expressed over the use of methylparaben in infants' parenteral products because bilirubin binding may be affected, which is potentially hazardous in hyperbilirubinemic neonates. The WHO has set an estimated total acceptable daily intake for methyl-, ethyl-, and propylparabens at no more than 10 mg/kg	(45); (48) (49)
Sodium benzoate	Nonimmunological contact urticaria, anaphylaxis It has been recommended that sodium benzoate injection should not be used in neonates	(45)
Sodium borate	Damaged skin, severe toxicity (vomiting, diarrhoea, erythema, CNS depression, kidney damage) Lethal oral intake 5g in children	(45)
<b>Surfactants and solubilising agents:</b>		
Ethanol	Accumulation of acetaldehyde In the USA, the maximum quantity of alcohol included in OTC medicines is: 10% v/v for use by individuals of 12 years of age and older, 5% v/v for children aged 6–12 years of age, and 0.5% v/v for children under 6 years of age In Europe there are no limits set	(45); (48); (46)
Ethylene glycol	Renal failure (in 1937, children treated with sulphanilamide elixir developed renal failure traceable to the ethylene glycol which had been used as a solvent) The WHO has set an estimated acceptable daily intake of polyethylene glycols at no more than 10 mg/kg	(45); (46)
Glycerol	>40% in volume: mucositis, diarrhoea, electrolyte disturbances	(46)
Polysorbate	Hypersensitivity, Serious adverse effects (E-Ferol syndrome: thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension and metabolic acidosis, including some deaths, in low-birth weight infants. The WHO has set an estimated acceptable daily intake at no more than 25 mg/kg	(45); (48)
Propylene glycol	One-third as intoxicating as ethanol, Effects on central nervous system, Ototoxicity, cardiac arrhythmias, seizures, osmotic laxative effects, contact dermatitis lactic acidosis	(45); (48); (47)



	(especially in neonates and children <4 years of age) Acceptable daily intake up to 25 mg/kg Not recommended for children <4 years (limited alcohol dehydrogenase) Half-life 17h in neonates (5h in adults)	
Polyethylene glycol	Metabolic acidosis in neonates and infants <6mths. Children between 1-6 yrs: 6.5g to treat constipation	(45)
<b>Miscellaneous groups, e.g. antioxidants, lubricants, etc:</b>		
Liquid paraffin	Lipoid pneumonia caused by aspiration or use of ophthalmic preparations. Should not be used in very young children	(45)
Potassium metabisulphite	Bronchospasm, anaphylaxis (especially in those with a history of asthma or atopic allergy)	(45)
Povidone	Anaphylactic reaction	(48)
Sulphites	Wheezing, dyspnoea, chest tightness (in patients with known reactive airway disease). Anaphylaxis, hives, itching	(50) ;(47)
Thymol	Respiratory arrest, nasal congestion edema (reported in newborn). Not for children under 5 years	(45)

#### Developing physiological characteristics of children

Physiological differences between children and adults may affect the ways in which any xenobiotic work in the body. Agents that are effective with adults are not always effective with children. Infants have slower gastric emptying time, but faster intramuscular (IM) absorption, limited protein binding and immature enzymes. Their livers are immature and may not metabolise excipients as rapidly as expected; their kidneys are also small and immature. The immaturity of an infant's physiology (e.g. glomerular filtration rate, nervous system, etc.) may contribute to elimination and functional sensitivities of chemical exposure (51, 52). The differential hepatic and renal clearance mechanisms, coupled with the immaturity of the blood brain barrier in new-borns may lead to possible accumulation of excipients, which can lead to toxicity such as central nervous system depression, renal failure, metabolic acidosis and seizures, as seen with propylene glycol, benzyl alcohol and benzoic acid (53-55). Furthermore, children have larger liver/body and brain/body weight ratios and higher blood-brain barrier permeability, and small infants often have a two to three times longer half-life for elimination of medicines than adults, requiring lower doses of medicines. Consequently, even when a medicine has a known effect in adults, a linear dose-per-kg correlation often does not hold true with regards to small children. Dose related adverse effects of excipients are of particular concern in preterm low birth weight infant because of the known immaturity of hepatic and renal function in this population. For instance, dose related reversible Central Nervous System (CNS) effects have been reported in children after receiving intravenous injection for long term therapy

in which propylene glycol was a cosolvent (56-58). Furthermore, the growth is not a linear process; age associated changes in body composition and organ functions are dynamic and can be discordant during the first decade of life (3). Compared to adults, neonates and infants can be anticipated to have the greatest differences in pharmacokinetics and susceptibility to excipient toxicity—the youngest being the most likely to exhibit aberrant responses. It is difficult to generalize about age-dependent deficiencies in the metabolism of excipients because different enzymatic pathways seem to exhibit dissimilar maturational patterns (3). It is dependent on the timing of the exposure during developmental life-stages, the kinetic and dynamic characteristics of the specific excipient, and the exposure situation (59-61) The toxicity of some common excipients, like lactose, may differ across the various paediatric sub-groups and between paediatrics and adult patient groups (62). More than one system can be susceptible and different pathology may occur depending on the dose and timing of exposure of excipients. Also depending on the dose and timing of exposure during gestation, effects may be severe and immediately obvious, or subtle and delayed. Certain excipients may lead to life threatening toxicity in paediatric patients when multiple doses of medications with the same preservative are employed (e.g. benzyl alcohol and benzoic acid) (63).

#### Safety limits not established for paediatrics

The literature available on excipient use in the paediatric population reveals that the harm caused due to the excipients is often associated with use of higher amounts of excipients than Acceptable Daily Intake (ADI)<sup>2</sup> for adults. For instance, neonates receiving propylene glycol in doses exceeding 2000 mg/kg/day exhibited significantly higher degrees of hyperosmolality than their counterparts receiving >200 mg/kg/day (64). High doses of propylene glycol have been associated with cardiovascular, hepatic, respiratory adverse events and with toxic effects on central nervous system in new-borns and infants (65). In a UK based study Whittaker et al. described that during their hospital stay, 38 infants were exposed to over 20 excipients including ethanol, propylene glycol and high concentrations of sorbitol. By calculating age-corrected exposure, the authors showed that in several neonates weekly exposure of excipients exceeded the limit that was considered safe in adults.

The underlying issue is that the accepted daily and cumulative intake of excipients has usually not been established for paediatrics and the applicability of the adults ADI to infants and children is questionable. The Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organisation of the United Nations (FAO) and World Health Organisation (WHO) set ADI for substances used as food additives. No limit of acceptable exposure has been defined for substances used as an excipient in medicinal product formulations, neither for the adult nor for the paediatric population. The issue of sensitivity of children compared with adults has been largely ignored. Children are more likely than adults to exceed the ADI or

---

<sup>2</sup> The ADI is “an estimate of the amount of a food additive, expressed as µg or mg per kg body weight, that can be ingested daily over a lifetime by humans without appreciable health risk” (WHO 1987)

Tolerable Daily Intake (TDI)<sup>3</sup>, due their low body weight. The concern is even greater for children from six months to twelve years. Poly-pharmacy increases the probability of common excipients exceeding safe threshold levels, potentially putting patients at an increased risk of developing adverse effects. The need for the development of a child and neonatal specific ADI has been highlighted in the literature (66). The Permissible Daily Intake (PDE) for excipients are determined for few excipients as part of revision of “Guideline on Excipients in the Label and Package Leaflet of Medicinal Products for Human Use (67). For instance, a recent refaction paper from EMA has suggested PDE for propyl paraben. However PDE has not been set for children under 2 years old because of the uncertainty about the metabolizing capacity at this very early age, and the absence of animal data corresponding to this age group (68).

In such scenarios, safety assessment of excipients in paediatrics has to be considered on case-by-case basis by systematically assessing the available literature. It would be useful for formulators to have the list of an acceptable range/level or consolidated information on safety and toxicity studies on excipients, to establish the acceptable level for the most common excipients used in paediatric formulation products.

### **Formulation Issues**

A key consideration for paediatric dosage forms is to understand the limitations in the type of excipient that can be used and also the amounts & concentrations that can be administered. For instance, injectable products require a unique formulation strategy. The formulated product must be sterile, pyrogen-free, and, in the case of solution, free of particulate matter. No colouring agent may be added solely for the purpose of colouring the parenteral preparation. The formulation should preferably be isotonic, and sterility requirements demand that an excipient is able to withstand terminal sterilization or aseptic processing. These factors limit the choice of excipients available (28). For formulation of oral liquids, several excipients may be needed as solvents, bulking agents, viscosity modifiers, wetting agents etc. to make a solution or suspension suitable for volumetric dosing. This may result in a higher potential for drug/excipient and for excipient/excipient incompatibilities and, thus adds to the complexity of preformulation studies. Also, excipients may contain (or develop over time) trace amounts of their own degradation products that may negatively impact the stability of the API, the color and/or the level of taste masking in the formulation. Examples are aldehydes and peroxides. Modern concepts of design of experiment (DoE) and quality by design (QbD) need to be applied to understand the robustness of such formulation and to establish the critical quality attributes of excipients to be used for routine manufacturing of the pediatric product (35). Hence, from a formulator’s perspective, one of the challenges in working with excipients may relate to limited

---

<sup>3</sup> A TDI is an estimate of the amount of a substance in air, food or drinking water that can be taken in daily over a lifetime without appreciable health risk. TDIs are calculated on the basis of laboratory toxicity data to which uncertainty factors are applied.

choice. There is no reference list available on excipients generally considered safe for use in paediatric formulations.

#### Acceptability of certain excipients in paediatrics

There are limitations on choice and concentration of certain groups of excipients for paediatric patients. The selection of colourants, sweeteners, and preservatives is based on several acceptance criteria. These include regulatory acceptance; toxicity; function such as mouthfeel, viscosity and taste; disease state (acute versus chronic, and the disease itself); administration (dose strength, volume, and frequency); patient population; market potential; and dosage-form characteristics.

#### Sweeteners

A key stumbling block to administering medicine orally to children is 'taste', with over 90% of paediatricians reporting that a drug's taste and palatability were the biggest barriers to completing treatment. Taste (and aftertaste) are particularly crucial for compliance in children (69). Therefore, natural (e.g. sucrose, dextrose, fructose and lactose) or artificial (e.g. saccharin, cyclamate and aspartame) sweeteners and flavouring agents are frequently used to improve the palatability of medications and ensure good compliance. The choice of natural versus artificial sweeteners (e.g. syrup versus sugar free SF preparations) is critical. Artificial sweeteners although typically well tolerated, may have adverse reactions when used in children (70). Hence sweeteners and their levels have to be judiciously chosen. The decision in choosing sweeteners has to be balanced with supportive information and not overly constraining. Trade-offs have to be identified and carefully considered by all stakeholders (e.g., clinical, regulatory, pharmaceutical development, and marketing). For example, paediatric drug products may need more than one type of sweetener and taste modifier to effectively mask the bitterness of the API that is strong in intensity and long in duration. Nutritive sweeteners and sugar alcohols alone do not provide relative sweetness. High-intensity sweeteners do not provide bulk, build viscosity, or provide beneficial mouth feel effects and as such do not work in formulations by themselves (71). Thus, they are often used in combination with each other. As long as there is evidence of absence of adverse effects, multiple sweeteners may be acceptable, however pharmaceutical companies have to provide thorough justification or clarification on the need and concentration of the sweeteners or reduce the number of sweeteners.

#### Colourants

Colourants are dyes, pigments, or other substances that can impart colour when added or applied to foods, drugs, cosmetics, medical devices, or the human body. Selection of the appropriate colourant and its purpose in specific pharmaceutical dosage form plays an important role in manufacturing of pharmaceutical dosage forms. In selecting a colourant for a given application, prime consideration is given to the type of formulation in which the colourant

is to be incorporated. Colour also influences the taste and flavour perception and may affect patient compliance (72). Tablet colour has been linked with taste, where pink is considered to be sweeter than red, and yellow is considered to be salty irrespective of its actual ingredients (73). Colour preferences among children have shown to be stereotypically gender dependent, and they seem to prefer brightly coloured medicines (74)

The number of colouring agents that are acceptable for use in medicines is limited but their wide use in food industry has indicated that a number of colouring agents in current use have been associated with reports of hypersensitivity and hyperkinetic activity, especially among children (75)). The safety of azodyes remains to be a big issue (76). Some of these dyes are no longer used in food, but the restrictions do not extend to many medicines designed for children. For instance, Allura Red AC is not recommended for children. It is banned in selected countries like Denmark, Belgium, France, Switzerland, and Sweden. The use of azo dyes for paediatric medicines is discouraged. The 2007 "Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product" clearly indicates that azo dyes (and other synthetic colouring agents) should not be used in (new applications for) paediatric drug products (77).

Several regulations are available on the aspects of colourants including their procedures for use, provisionally and permanently certified and uncertified colour additives, and use levels and restrictions for each colouring additive (78) (79, 80). Restrictions or bans on the use of some colouring agents have been imposed in some countries, while the same colours may be permitted for use in a different country. As a result the same colour may have a different regulatory status in different territories of the world (81). With the differences in colourant regulations worldwide and the need for various performance attributes based on the dosage form, there are numerous considerations that must be assessed.

### Preservatives

Antimicrobial preservatives are normally added to prevent microbial proliferation arising under in use conditions. The use of preservatives is currently one of the most controversial issues in paediatric drug development. The use of preservatives is discouraged in general, especially when considering the suitability of related formulations to the paediatric population. Two general issues are linked to the use of these preservatives, one of which is the choice of materials. Plastic containers and dispensing devices pose problems such as permeation of preservatives through the container or interaction with the plastic materials. A second issue is high incidence of local side effects attributed to preservatives. The discussion is controversial, and published preclinical and clinical studies are not always consistent. It seems to be clear that short-term use of preparations containing preservatives at low concentrations is well tolerated, but preservatives can cause serious inflammatory effects with long-term use (82). The adverse effects may include chemical irritation, hyperactivity and allergic reactions. Hence

evidence of safety of preservatives used is required, together with thorough justification for the choice of the preservative. Typically, the use of the older preservatives (e.g. imidurea, bronopol, hexachlorpene) in new products has been largely discontinued because of safety considerations (83). There is a limited number of approved preservatives available for multi-use oral or topical products, and options are even more limited for dosage forms such as parenteral. For instance, benzyl alcohol is not recommended for use in parenteral products due to fatal toxic syndrome in low weight neonates (84). The long chain alkyl alcohols, cetyl and stearyl alcohol used as preservatives in topical products can lead to contact allergies and irritant reactions (85). 2-Phenylethanol can be mildly irritant to skin, eye and mucous membranes. A large number of clinical and experimental studies reveal that preservatives in topical ophthalmic medications have been demonstrated to produce effects from inflammation/ hypersensitivity to permanent cytotoxic effects involving all structures of the eye (86). Benzalkonium chloride and other quaternary ammonium preservatives have direct toxic effects on the cells and damage the cornea (87).

Alternatively, it is known that a combination of preservatives can have a synergistic effect on antimicrobial efficacy, allowing smaller amounts to be used, in total and per excipient and this approach might be considered if they are known to be safe e.g. Benzalkonium chloride (BKC) is ineffective against some strains of *Pseudomonas aeruginosa*, *Mycobacterium* and *Trichophyton*, but combinations with benzyl alcohol, 2-phenylethanol or 3-phenylpropanol enhances anti-*Pseudomonad* activity probably by increasing the permeability of the cells to the antimicrobial agents (88).

There is a regulatory expectation that the reason for preservative inclusion, proof of efficacy, safety information, control methods in finished product and details of labelling in the finished product should all be addressed by the applicant (89). The EMA has recommended that the levels of preservatives within a formulation should be maintained at the minimum concentration consistent with antimicrobial effectiveness in each individual preparation (68). Pharma companies are encouraged to formulate preservative-free products. Preservative-free approaches are still in their infancy and much more research and analysis of existing information is required before they can be considered on an equal footing with preserved approaches.

### **Regulatory approval of excipients & Precedence of use**

There is no general approval process for excipients and they are approved together with a drug (as drug product) under particular settings (e.g., indication, route, dose-levels). The excipients are scrutinized through cross-references to pharma/ food/ cosmetic compendia, reference in an Abbreviated New Drug Application (ANDA) or NDA for a particular function in a drug product and permitted list of colours and flavours in EU food legislation. The precedence of use of marketed excipients is assessed by reference to FDA's Inactive Ingredients Database (IID), the

Japanese Pharmaceutical Excipients Dictionary (JPED), and drug catalogues such as Dictionnaire Vidal or Rote Liste. However, if there is no precedence of use in a drug product, then the excipient is considered as new excipient and the manufacturer has to develop the safety information appropriate to their intended use. The FDA has issued a Guidance concerning the safety testing required for novel excipients (34). The IPEC Europe Safety Committee also has published a guide for the qualification of excipient ingredients by excipient suppliers and pharmaceutical users (31). The additional safety data is required to introduce a novel excipient to a pharmaceutical product. The resources and time associated with this requirement makes formulation scientists hesitant to try new excipients. Hence the biggest challenge for formulators is the limited and scattered information of known and approved excipients available for use in paediatrics.

#### Justification of role and use of excipients in paediatrics

Excipients may have avoided detailed regulatory attention because it was not always perceived that they have a purpose but now marketing authorisation (MA) applicants are required to state and justify the role an excipient has to play. Recent legislative changes require that companies provide the supportive data and complete justification on use of excipients in paediatric formulation proposed in PIP. However, insufficient justification of the chosen excipients related to age, daily dose of excipient(s) and insufficient discussion on the feasibility of replacing excipients with potential safety issue are concerns the regulators often encounter in PIPs (90).

With the regulators point of view, it is not yet clear to which extent a precautionary approach to the excipient composition should be envisaged in the PIPs. For example, it is not clear whether to accept or ask companies to replace the excipients that may cause problems in children with less common deficiencies, e.g. hereditary fructose/galactose intolerance? or lactose (which may cause problems in some children with lactose intolerance) (91). A structured risk analysis framework (11) assessing the available information may allow a informed discussion among regulators, industry and academia and come up with a transparent and consistent approach on this dilemma for future applications.

#### Availability of excipient information on labels and package inserts

With regard to labelling of the medicinal products, Article 54 (1) (c) of Council Directive 2001/83/EEC requires that excipients known to have a recognized action or effect need to be declared on the labelling of all other medicinal products. According to Article 59 (1) (a) a full statement of the active substance and excipients should be included in the package leaflet. Also all excipients, which are present in the product, should be listed in the Summary of Manufacturing Product Characteristics (SmPCs), even those present in small amounts. Recently, EMA has undertaken the task of updating the information in the package leaflet to update the thresholds and toxicological profile and to adjust them in relation to different age groups. A concept paper on the need for revision of the Guideline was released in 2012.

However regulatory authorities do not yet adequately regulate or enforce its guidelines on the requirements of quantitative information of excipients on package inserts or labels. Although it is acceptable that safeguard is granted to the intellectual property of drug developers (namely, quantitative details), information on excipients should be sufficient to allow precautions to be taken when needed. The need for drug users (health care professionals, patients, caregivers) to obtain adequate information on the drug product excipient composition is commonly acknowledged (92, 93). Information on excipient content could prove helpful in a clinical setting where no alternatives are available.

In a regulatory context, it is important to consider all the existing guidance documents that support the development of paediatric formulations known to be safe and effective for neonates, infants and children of all ages. The pharmaceutical companies are struggling to find the existing information on safety and toxicity of excipients in paediatrics as it is scattered around various sources. In general, there is a tendency to apply the precautionary principle as justification for excluding excipients from medicines given to paediatric population. However excluding excipients is not always appropriate. The Safety and Toxicity of Excipients for Paediatrics (STEP) database project was hence developed by EuPFI consortium in collaboration with USPFI<sup>4</sup>, to bridge the gap in resources for safety and toxicity of excipients for paediatrics and address the challenges in information gathering and evaluation. Similar discussions were being carried out in Pediatric Formulation Initiative (PFI) in United States to address safety issues and problems associated with the lack of adequate pediatric<sup>5</sup> formulations.

## **Administration**

The non-acceptability of medicine can have major implications ranging from medicine errors, under- / over- dosing, poor adherence and therefore suboptimal therapy. Patient acceptability defined by the EMA as the overall ability and willingness of the patient to use and its caregiver to administer the medicine as intended. The higher acceptability render the medicine less prone to any type of modification prior to administration. All major components of formulation design can influence the patient acceptability. The key design aspects include composition (qualitative and quantitative), route of administration, dosage form, dosing frequency, packaging, administration device and user`s instructions. The understanding of paediatric patient acceptability to formulations has not been fully established yet. There is lack of standardization of the measurement of acceptability and data interpretation, nevertheless

---

<sup>4</sup> The United States Pediatric Formulation Initiative (US-PFI) is a project of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The PFI was established in 2005 to address the issue of the lack of appropriate formulations in children and to use this activity as a means to improve paediatric formulations.

<sup>5</sup> The European spelling "paediatric" is used throughout the thesis unless specifically referring to the US. In case of the US reference the US spelling "pediatric" has been adopted.



further research is expected to be conducted to define the dosage form attributes and their perception to determine the patient acceptability.

Acceptability is a term different than palatability or swallowability for orally administered formulations. Palatability is known as the overall appreciation of a medicinal product in relation to its smell, taste, aftertaste and texture. The sensory evaluation of the dosage form influence the patient's ability and willingness to take the medicine. The gold standard to assess the sensory attributes of dosage forms is human panel study. Providing the evidence for the correlation between in vivo animal / in vitro characterization studies and human panel data, predictive methodologies can also be applied to understand the patient acceptability. Taste has been the mostly studied among the other sensory attributes. The taste assessment can be performed by applying in vitro and in vivo methods. The in vitro tool, e-tongue has been studied to evaluate the taste of medicinal formulations, though there are limitations of the method depending on the physicochemical properties of the drug molecule. The in vivo animal model (Brief Access Taste Aversion) is promising as a predictive method to assess the perceived aversive taste of drug formulations.

Acceptability is also not a synonym term to medicine adherence (or compliance) which is generally defined as the extent to which patients take medications as agreed with their healthcare providers. Acceptability can be seen being the first stage of adherence due to its impact on the agreement of the child to take the medicine, it does not result in the optimum adherence as controlled by multiple factors ranging from the clinical condition to the treatment setting. The age subset of the paediatric population also has an effect on the compliance with the medicine. Adolescents may show different adherence profile due to their autonomy and self-management of their medicine compared to younger children.

### **3. Patient Centric Pharmaceutical Drug Product Design and future vision**

The objectives of the Paediatric Regulation in Europe (2017) was to stimulate the development of paediatric medicines but also to provide more information on their use, as a response to the lack of evidence and approval of medicines for children. In fact similar initiatives started in the 80s in the USA.

The tools in place in the European Union encompass the Paediatric Committee (PDCO), the European Network for Paediatric Research (Enpr-EMA), Paediatric Use Marketing Authorizations (PUMA) and importantly Paediatric Investigation Plans (PIPs). Although an holistic approach in paediatric drug development is required with concomitant advances in clever clinical trial designs, modelling/simulation approaches, refining endpoints, and biomarkers, PIPs are crucial as they offer a framework to develop clinically and age relevant paediatric dosage forms so that children of all ages and their caregivers have access to safe and accurate medicines.

There has been a lack of evidence to guide the design of age-appropriate and acceptable dosage forms and resulted in a longstanding knowledge gap in paediatric formulation development. A list of criteria for screening PIPs with regard to paediatric specific quality issues and referring them to the PDCO Formulation Working Group for discussion is published [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2014/01/WC500159380.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/01/WC500159380.pdf). This provides a structured framework for pharmaceutical design options against pre-determined criteria relating to efficacy, safety and patient access, this latter being particularly complex due to the diverse paediatric population.

There is a drive now to carefully consider and balance the quality target product profile against not only technical challenges and development feasibility but also the varied needs and ability of children as well as their carers. Patient centricity can be defined as *'Putting the patient first in an open and sustained engagement of the patient to respectfully and compassionately achieve the best experience and outcome for that person and their family'*. No doubt the binding elements of the paediatric regulation has steered research with and for children and their family to refine end-user requirements in order to guide dosage form design and formulation selection.

In a decade, the Paediatric Regulation has certainly had a positive impact on paediatric drug development yet the years to come will reveal the true extent of this impact as we catch up with long deferrals for completion of paediatric studies requested by pharmaceutical companies and gather real life outcomes from post marketing studies.

1. ICH. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population, Note for guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99). 2001.
2. EMA. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP), Reflection paper: Formulations of choice for the paediatric population. 2006.
3. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *The New England journal of medicine*. 2003 Sep 18;349(12):1157-67. PubMed PMID: 13679531. Epub 2003/09/19. eng.
4. Molteni M, Clementi E, Zuccotti G. Introduction to the new "Perspectives in Paediatric Pharmacology" series. *Pharmacological Research*. 2011;63(5):361-.
5. FDA. General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, Guidance for Industry. US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Available at <https://www.fda.gov/downloads/drugs/guidances/ucm425885.pdf>. 2014.
6. Lopez FL, Ernest TB, Tuleu C, Gul MO. Formulation approaches to pediatric oral drug delivery: benefits and limitations of current platforms. *Expert opinion on drug delivery*. 2015;12(11):1727-40. PubMed PMID: 26165848. Pubmed Central PMCID: PMC4673516. Epub 2015/07/15. eng.
7. EMA. European Medicines Agency Committee for Medicinal Products for Human Use and Paediatric Committee (2013) Guideline on the pharmaceutical development of medicines for paediatric use. 2013.
8. K. WER. *The Global Framework of Paediatric Drug Development, European Union Paediatric Regulation: Theory and Practice, Guide to Paediatric Drug Development and Clinical Research*. Basel, Karger, 2010, pp I–XX (DOI:10.1159/000315565). Rose K vdAJ, editor2010.
9. Rocchi F TP. The development of medicines for children. Part of a series on Pediatric Pharmacology guest edited by Gianvincenzo Zuccotti, Emilio Clementi, and Massimo Molteni. *Pharmacol Res* ;64(3):169-175. 2011.
10. D.A. VR-N. *Child friendly medicines: availability, pharmaceutical design, usability and patient outcomes.*: Thesis Utrecht University; 2014.
11. Turner MA, Duncan JC, Shah U, Metsvaht T, Varendi H, Nellis G, et al. Risk assessment of neonatal excipient exposure: Lessons from food safety and other areas. *Advanced drug delivery reviews*. 2014 6/30/;73:89-101.
12. EMA. ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population. 2001.
13. WHO. World Health Organization, Forty Sixth Report: Development of Pediatric Medicines: Points to consider in formulation. WHO Technical Report Series. 2012;790.
14. WHO. World Health Organization. *Model Formulary for Children WHO Library Cataloguing-in-Publication Data*2010.
15. Abdulla S, Sagara I. Dispersible formulation of artemether/lumefantrine: specifically developed for infants and young children. *Malaria Journal* 2009;8(Suppl 1):S7.
16. Milne C, Bruss JB. The economics of pediatric formulation development for off-patent drugs. *Clinical Therapeutics* 2008;30(11):2133-45.
17. Ivanovska V RC, van Dijk L, Mantel-Teeuwisse AK. . Pediatric drug formulations: a review of challenges and progress. *Pediatrics* 2014;34(2):361-72.
18. Van Riet-Nales D, de Jager K, Schobben A, Egberts T, Rademaker C. The availability and age-appropriateness of medicines authorized for children in The Netherlands. *British Journal of Clinical Pharmacology*. 2011;72(3):465-73.
19. Sam T, Ernest TB, Walsh J, Williams JL. A benefit/risk approach towards selecting appropriate pharmaceutical dosage forms - an application for paediatric

- dosage form selection. *International Journal of Pharmaceutics*. 2012 Oct 5;435(2):115-23. PubMed PMID: 22626885. Epub 2012/05/26. eng.
20. WHO. World Health Organization (WHO), Development of paediatric medicines: points to consider in pharmaceutical development. QAS/08.257/Rev.3 2011.
21. Ranmal S. Acceptable medicines for children: End-user insights to support dosage form design. Doctoral thesis, UCL (University College London). 2015.
22. Adkin D, Davis S, Sparrow R, Huckle P, Wilding I. The Effect of Mannitol on the Oral Bioavailability of Cimetidine. *Journal of Pharmaceutical Sciences*. 1995;84(12):1405-9.
23. Basit AW, Podczeczek F, Newton JM, Waddington WA, Ell PJ, Lacey LF. Influence of polyethylene glycol 400 on the gastrointestinal absorption of ranitidine. *Pharmaceutical research*. 2002 Sep;19(9):1368-74. PubMed PMID: 12403075. Epub 2002/10/31. eng.
24. Rostami-Hodjegan A, Shiran MR, Ayesh R, Grattan TJ, Burnett I, Darby-Dowman A, et al. A new rapidly absorbed paracetamol tablet containing sodium bicarbonate. I. A four-way crossover study to compare the concentration-time profile of paracetamol from the new paracetamol/sodium bicarbonate tablet and a conventional paracetamol tablet in fed and fasted volunteers. *Drug development and industrial pharmacy*. 2002 May;28(5):523-31. PubMed PMID: 12098841. Epub 2002/07/09. eng.
25. García-Arieta A. Interactions between active pharmaceutical ingredients and excipients affecting bioavailability: Impact on bioequivalence. *European Journal of Pharmaceutical Sciences*. 2014 12/18;65:89-97.
26. Crowley P, Martini, LG. Excipients in Pharmaceutical Products: Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker Inc; 2002.
27. Nishath F, Tirunagar, M., Husna Kanwal, Q., Nandagopal, A., Jangala VR., Drug-excipient interaction and its importance in dosage form development. *Journal of Applied Pharmaceutical Science*. 2011;01(06):5.
28. Pramanick S, Singodia D, Chandel V. Excipient selection in parenteral formulation development. *Pharma Times* 2013;45(3):65.
29. Webster. Webster's II New College Dictionary. Boston: Houghton Mifflin Company; 1995.
30. Saunders W. Dorland's Medical Dictionary (25th ed.), W.B. Saunders, Philadelphia, PA 1974.
31. IPEC. The International Pharmaceutical Excipients Council, Qualification of Excipients for Use in Pharmaceuticals. 2008.
32. EC. Council and the European Parliament, the Falsified Medicines Directive (Directive 2011/62/EU). Official Journal of the European Union. 2011.
33. Faber & Faber. Morton's, The Nurse Dictionary, 24th ed., London. 1957.
34. FDA. Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients. 2005.
35. Maldonado S, Schaufelberger D. Pediatric Formulations. *American Pharmaceutical Review* 2011.
36. Fabiano V, Mameli C, Zuccotti GV. Paediatric pharmacology: Remember the excipients. *Pharmacological Research*. 2011;In Press, Corrected Proof.
37. ICH. Pharmaceutical Development Q8(R2). 2009.
38. EMA. 5-year Report to the European Commission General report on the experience acquired as a result of the application of the Paediatric Regulation. 2012.
39. Lowey A, Jackson M. Handbook of Extemporaneous Formulation - A guide to pharmaceutical compounding. London: Pharmaceutical Press; 2010.
40. Nahata M. Safety of 'inert' additives or excipients in paediatric medicines. *Archives of Disease in Childhood - Fetal and Neonatal Edition*. 2009;94:392-93.
41. Whittaker A, Currie AE, Turner MA, Field DJ, Mulla H, Pandya HC. Toxic additives in medication for preterm infants. *Archives of Disease in Childhood Fetal and*

- Neonatal Edition. 2009 Jul;94(4):F236-40. PubMed PMID: 19158148. Epub 2009/01/23. eng.
42. He et al. TH, M.G. Priebe, H.J. Harmsen, F. Stellaard, X. Sun, G.W. Welling and R.J. Vonk, . . Colonic fermentation may play a role in lactose intolerance in humanS. *J Nutr.* (2006);136 1 (pp. 58-63. ).
  43. Campbell AK, Waud, J.P., Matthews,S.B. The molecular basis of lactose intolerance. *Sci Prog.*, 2005;88 Pt 3( ):pp. 157-202. .
  44. Kumar A, Aitas AT, Hunter AG, Beaman DC. Sweeteners, dyes, and other excipients in vitamin and mineral preparations. . *Clinical Pediatrics*: . 1996;September:443-50,.
  45. Rowe et al. R, R.C., Quinn, M.E., Sheskey, P.J., . *Handbook of Pharmaceutical Excipients*. sixth ed. ed: Pharmaceutical Press; 2009.
  46. Pawar S, Kumar A. Issues in the Formulation of Drugs for Oral Use in Children: Role of Excipients. *Pediatric Drugs*. 2002;4(6):371-9.
  47. Anonymous. "Inactive" ingredients in pharmaceutical products: update (subject review). *American Academy of Pediatrics Committee on DrugsPediatrics*. 1997;99 2 (1997):pp. 268-78.
  48. Costello I, Long P, Wong I, Tuleu C, Yeung V. *Paediatric drug handling*. Cornwall: Pharmaceutical Press; 2007.
  49. Kumar A, Rawlings R, Beaman D. The mystery ingredients: sweeteners, flavorings, dyes, and preservatives in analgesic/antipyretic, antihistamine/decongestant, cough and cold, antidiarrheal, and liquid theophylline preparations. *Pediatrics* 1993;91:927-33. .
  50. Pagliaro A. Administering drugs to infants, children, and adolescents. In: *Problems in pediatric drug therapy*. 4th ed ed. Ed. Pagliaro LA PA, editor. Washington: American Pharmaceutical Association; 2002.
  51. Larsen JC, Pascal G. Workshop on the applicability of the ADI to infants and children: Consensus summary. *Food Additives & Contaminants*. 1998 1998/01/01;15(sup001):1-9.
  52. Peters P. Developmental toxicology: Adequacy of current methods. *Food Additives & Contaminants*. 2009;15(S1):55-62.
  53. Allegaert K, Vanhaesebrouck S, Kulo A, Cosaert K, Verbesselt R, Debeer A, et al. Prospective assessment of short-term propylene glycol tolerance in neonates. *Archives of Disease in Childhood* 2010;95(12):1054-8.
  54. Kulo A, Smits A, Naulaers G, de Hoon J, Allegaert K. Biochemical tolerance during low dose propylene glycol exposure in neonates: A formulation-controlled evaluation. *DARU Journal of Pharmaceutical Sciences*. 2012 07/19 04/25/received 07/19/accepted;20(1):5-. PubMed PMID: PMC3517950.
  55. Shehab N, Streetman, DD., Donn, SM.,. Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. *Pediatric Critical Care Medicine*. 2009;10(2):256-9
  56. Glover ML, Reed MD. Propylene glycol: the safe diluent that continues to cause harm. *Pharmacotherapy*. 1996 Jul-Aug;16(4):690-3. PubMed PMID: 8840379. Epub 1996/07/01. eng.
  57. Lolin Y, Francis DA, Flanagan RJ, Little P, Lascelles PT. Cerebral depression due to propylene glycol in a patient with chronic epilepsy--the value of the plasma osmolal gap in diagnosis. *Postgraduate medical journal*. 1988 Aug;64(754):610-3. PubMed PMID: 3249707. Pubmed Central PMCID: PMC2428931. Epub 1988/08/01. eng.
  58. Kelner MJ, Bailey DN. Propylene glycol as a cause of lactic acidosis. *Journal of analytical toxicology*. 1985 Jan-Feb;9(1):40-2. PubMed PMID: 3981973. Epub 1985/01/01. eng.
  59. Hasegawa R, Hirata-Koizumi M, Dourson M, Parker A, Hirose A, Nakai S, et al. Pediatric susceptibility to 18 industrial chemicals: A comparative analysis of

- newborn with young animals. *Regulatory Toxicology and Pharmacology*. 2007 4//;47(3):296-307.
60. Olin SS, Sonawane BR. Workshop to develop a framework for assessing risks to children from exposure to environmental agents. *Environmental Health Perspectives*. 2003;111(12):1524-6. PubMed PMID: PMC1241657.
  61. Ostergaard G, Knudsen I. The applicability of the ADI (Acceptable Daily Intake) for food additives to infants and children. *Food Additives & Contaminants*. 1998;15 Suppl:63-74. PubMed PMID: 9602914. Epub 1998/05/29. eng.
  62. Edge S, Kibbe A, Kussendrager K. Handbook of pharmaceutical excipients. RC R, Sheskey, P, Owen S, (Eds), editor. London: Pharmaceutical Press; 2005.
  63. Glass B, Haywood A. Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. *Journal of Pharmacy & Pharmaceutical Sciences*. 2006;9:398-426.
  64. MacDonald M, Getson P, Glasgow A, Miller M, Boeckx R, Johnson E. Propylene glycol: increased incidence of seizures in low birth weight infants. *Pediatrics*. 1987;79(4):622-5.
  65. Arulanantham K, Genel M. Central nervous system toxicity associated with ingestion of propylene glycol. *Journal of Pediatrics*. 1978;93:pp. 515-6.
  66. Nydert P, Ali, M. Methyl paraben, usage of preservatives in drugs for premature neonates. 2007.
  67. EMA. 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). 2012.
  68. EMA. Committee for Medicinal Products for Human Use (CHMP), Reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use. EMA/CHMP/SWP/272921/2012. 2015.
  69. Milne C. The pediatric studies initiative. In: Mathieu M, ed. *New Drug Development: A Regulatory Overview*. 8th ed, Revised. Waltham, Mass: PAREXEL International. 2005.
  70. Walsh J, Cram A, Woertz K, Breikreutz J, Winzenburg G, Turner R, et al. Playing hide and seek with poorly tasting paediatric medicines: do not forget the excipients. *Advanced drug delivery reviews*. 2014 Jun;73:14-33. PubMed PMID: 24614069. Epub 2014/03/13. eng.
  71. Chattopadhyay S, Raychaudhuri, U., & Chakraborty, R. Artificial sweeteners – a review. *Journal of Food Science and Technology*. 2014;51(4):611-21.
  72. Delwiche J. The impact of perceptual interactions on perceived flavor. *Food Quality and Preference*. 2004;15:137-46.
  73. Srivastava R, More A. Some aesthetic considerations for over the- counter (OTC) pharmaceutical products. 2010;11:267–283. *International Journal of Biotechnology*. 2010;11(267-283).
  74. Smith C, Sammons H, Fakis A, Conroy S. A prospective study to assess the palatability of analgesic medicines in children. *Journal of advanced nursing*. 2013 Mar;69(3):655-63. PubMed PMID: 22671021. Epub 2012/06/08. eng.
  75. Pollock I, Young E, Stoneham M, Slater N, Wilkinson JD, Warner JO. Survey of colourings and preservatives in drugs. *British Medical Journal*. 1989 Sep 9;299(6700):649-51. PubMed PMID: 2508849. Pubmed Central PMCID: PMC1837544. Epub 1989/09/09. eng.
  76. McCann D, Barrett A, Cooper A, Crumpler D, Dalen L, Grimshaw K, et al. Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. *Lancet (London, England)*. 2007 Nov 3;370(9598):1560-7. PubMed PMID: 17825405. Epub 2007/09/11. eng.
  77. EMA. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP): Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product. CHMP/QWP/396951/06 2007.

78. FDA. Food and Drug Administration, CFR - Code of Federal Regulations Title 2, Subchapter A—General, Part 70 Color Additives. 2015.
79. EC. European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuff. Official Journal of the European Communities 1994.
80. EC. Opinions - Scientific Committee on Medicinal Products and Medical Devices. 1998.
81. Kumar A, Madan AK. Color additives: legislative perspective in the United States, Europe, Australia, and India. International journal of pharmaceutical compounding. 2014 Jul-Aug;18(4):293-300. PubMed PMID: 25474858. Epub 2014/12/06. eng.
82. Tu E. Balancing antimicrobial efficacy and toxicity of currently available topical ophthalmic preservatives. Saudi Journal of Ophthalmology. 2014 06/23 03/25/received 05/27/revised 06/15/accepted;28(3):182-7. PubMed PMID: PMC4181434.
83. Elder D, Crowley P. Antimicrobial Preservatives Part One: Choosing a Preservative System. American Pharmaceutical Review 2012.
84. Gershanik J, Boecler B, Ensley H, McCloskey S, George W. The Gasping Syndrome and Benzyl Alcohol Poisoning. New England Journal of Medicine. 1982;307(22):1384-8. PubMed PMID: 7133084.
85. Aakhus AE, Warshaw EM. Allergic contact dermatitis from cetyl alcohol. Dermatitis : contact, atopic, occupational, drug. 2011 Jan-Feb;22(1):56-7. PubMed PMID: 21291645. Epub 2011/02/05. eng.
86. Hong J, Bielory L. Allergy to ophthalmic preservatives. Current opinion in allergy and clinical immunology. 2009 Oct;9(5):447-53. PubMed PMID: 19697451. Epub 2009/08/22. eng.
87. Rosin L, Bell N. Preservative toxicity in glaucoma medication: clinical evaluation of benzalkonium chloride-free 0.5% timolol eye drops. Clinical Ophthalmology 2013 10/30;7:2131-5. PubMed PMID: PMC3817055.
88. Brown M, Richards R. Effect of ethylenediaminetetraacetic acid on the resistance of *Pseudomonas aeruginosa* to antibacterial agents. Nature. 1965;207(1391-1393).
89. BfArM. Bescheid des Bundesinstitut für Arzneimittel und Medizinprodukte für benzalkoniumchlorid-haltige Arzneimittel zur Anwendung in der Nase, A 37489/38186/03 Bonn, Dezember 2003. 2003.
90. Quijano R, Desfontaine E, Arenas-López S, Wang S. Pediatric formulation issues identified in Paediatric Investigation Plans. Expert Review of Clinical Pharmacology. 2014;7(1):25-30. PubMed PMID: 24308789.
91. Van Riet-Nales D, Kozarewicz P, Aylward B, de Vries R, Egberts T, Rademaker C, et al. Paediatric Drug Development and Formulation Design—a European Perspective. AAPS PharmSciTech. 2016:1-9.
92. Lass J, Naelapaa K, Shah U, Kaar R, Varendi H, Turner M, et al. Hospitalised neonates in Estonia commonly receive potentially harmful excipients. BMC Pediatrics. 2012;12(1):136. PubMed PMID: doi:10.1186/1471-2431-12-136.
93. Corder C, Caldwell N, Elliot P. What else is in our children's medicine? Archives of Disease in Childhood. 2012 May 1, 2012;97(5):e2-e3.