function of the excipient, the safety profile of the excipient with regard to the target age group, the exposure and the duration of use, the condition that is to be treated, patient acceptability, palatability and any known allergies and sensitisation concerns.

In order to develop an acceptable age appropriate formulation some excipients are more commonly used in dosage form development for the pediatric patient group. These include, amongst others, excipients to improve formulation palatability and provide taste-masking (e.g. sweeteners and flavouring agents), and excipients which facilitate formulation of oral solution and suspension products (e.g. solubilisers, preservatives, and suspending agents). Consequently, pediatric formulations may include a broader range of excipients than adult dosage forms, all of which should be justified.

Acceptable palatability is a key consideration when developing pediatric oral dosage forms as it directly impacts patient adherence. Taste-masking should be considered for all oral presentations, but this is challenging in oral liquid dosage forms, where the dissolved drug comes into direct contact with the taste receptors on the tongue. A range of excipients and technologies are available to the formulator to mask the unpleasant taste of drugs in different oral dosage forms. Examples include covering up unpleasant taste with flavours and sweeteners, complexation with ion-exchange-resins or cyclodextrins, and barrier approaches using polymer coatings or lipidic excipients.[13]

Dosage form stability and excipient compatibility studies are also an important aspect of formulation design; however requirements for pediatric dosage forms are largely the same as for adult preparations. When pediatric formulations are designed to be mixed with food or drink (e.g. multiparticulate or sprinkle dosage forms), stability and compatibility of the dosage form with the proposed food or drink needs to be confirmed. This is of particular importance for dosage forms with a functional film coat (for example providing taste-masking or modified release) where mixing with foodstuffs must not impact on dosage form performance prior to administration.

A key element in pediatric dosage form development is the choice of suitable excipient types and concentrations. In addition to ensuring the correct excipient is selected on the basis of its role, there are also biopharmaceutical, safety and regulatory considerations that need to be addressed for pediatric patients.

Biopharmaceutical Effect of Excipients

Physiology changes rapidly with age, impacting both pharmacokinetics and pharmacodynamic responses to drugs. For instance, the residence time of a dosage form in various portions of the gastrointestinal (GI) tract, the pH of the GI tract, the maturation of biliary excretions, and the presence and activity of different enzymes and transporters, can be significantly different in adults and in pediatric patients. Physiological changes can also vary significantly within the pediatric population (e.g. between neonates and older children).[7,8] For example, gastric pH and emptying can have a major impact on drug bioavailability through their effect on certain drugs (e.g. solubility, absorption, metabolism, stability) or pH sensitive dosage forms (e.g. enteric coated formulations).[14] Pediatric patients demonstrate a variable but age-related trend from birth well into infancy and childhood, with the greatest changes occurring during the neonate's first month. At birth, gastric pH is in the neutral range, between pH 6 and 8, but falls to between pH 1.5 and 3 within a day. Following this, up to 10 days from birth, gastric pH increases again to between 6 and 7, and remains in the neutral range for approximately 28 days. This is followed by a gradual reduction to adult capacity of pH 1 to 2 by the age of approximately 3 years. In addition, the rate of gastric emptying during the neonatal period is both variable and prolonged.[15]

Technologies and associated functional excipients, such as film coating of pediatric multiparticulate formulations (e.g. used for taste-masking purposes or gastric protection), also have the potential to alter drug bioavailability. For example, enteric coatings are commonly used to coat dosage forms either to protect the stomach from the drug, or protect the drug from the low pH typically seen in the stomach. However, the neutral pH conditions in the oral cavity can result in a loss of integrity of sensitive enteric coatings of tablet or granule formulations if the dosage form is not swallowed immediately, but kept in the mouth longer; this could be a consideration for pediatric administration. As another example, solid oral dosage forms may use barrier membrane systems based on a pH trigger (e.g. reverse enteric membranes). These systems have the advantage that they can achieve good taste-masking as they do not release drug under the neutral conditions of the mouth. Typical reverse enteric systems need to be in an acidic environment (the stomach) for a sufficient period of time in order to fully dissolve and release the drug. GI transit in the pediatric population can be very variable and age-dependent and similarly, there is also a risk that in certain pediatric age groups or disease states, the required acidic pH to cause complete dissolution of the film coat may not exist. All these factors need to be considered when assessing bioperformance risks associated with products containing these excipients.[15]

Other common excipients used in pediatric formulations may have unintended influence on the bioavailability of a drug. For example, they can affect absorption (e.g. surfactants or excipients that may affect transport transit proteins), *in vivo* solubility (e.g. co-solvents), or *in vivo* stability of the active substance.[16]

Excipients that accelerate transit through the small intestine (e.g. polyethylene glycol, sodium acid pyrophosphate, and poly-alcohols, such as mannitol and sorbitol) reduce gastrointestinal absorption of medicines primarily absorbed at this site (e.g. ranitidine, cimetidine). Diarrhoea has been reported for sorbitol-containing formulations as well as a decrease in maximum serum concentration (C_{max}) and total exposure (area under curve) for some drugs. In those cases, a relatively minor formulation change such as the use of a different sweetener in an oral formulation can have a significant effect on bioavailability of the drug.[17] The bioavailability of a drug may also be reduced when it forms a poorly soluble, non-absorbable complex with an excipient (e.g. tetracycline with calcium phosphate; amfetamine with sodium carboxymethylcellulose; or phenobarbital with polyethylene glycol 4000).[18,19]

Safety of Excipients

The justification of selecting excipients for pediatric dosage forms needs to take into account a range of safety-related factors, including patient age, route of administration, dose levels and frequency (e.g. acute or chronic dosing). The condition to be treated and the safety in the targeted age group at the proposed exposure levels also needs to be considered. The number and concentration of each excipient used in a formulation should be kept to the minimum necessary to achieve the required target product profile criteria such as product quality, stability, bioavailability and patient adherence. It should also be noted that previously authorized pediatric products may contain concentrations of excipients, which are now no longer recommended for use in children. Previous approval of an excipient in a pediatric drug formulation may not automatically qualify its safe use in another pediatric formulation, route or age group.

The EMA *Guideline on Pharmaceutical Development of Medicines for Paediatric Use*[5] contains guidance on the choice of excipients for pediatric products, along with suggested sources of information to assess the excipient safety. It also provides a hierarchical decision tree to guide the developer through the various sources of information already available to support the justification or to determine whether additional safety studies may be required.

The 'Acceptable daily intake' (ADI) established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) provides an acceptable mass of excipient per unit body weight per day (mg/kg/day) for the adult population. However ADI figures are commonly used for the risk assessment of excipients in pediatric