Novel oral dosage forms address formulation challenges across age groups.

Recognizing that physiological changes happen from birth through adolescence—leading to differences in pharmacokinetics (PK) and pharmacodynamics (PD)—developing medicines for the pediatric population can be challenging, requiring different formulations, different dosage forms and strengths, or different routes of administration depending on the patient’s age. *Pharmaceutical Technology* recently spoke with Pascale Clement, PhD, Director of Science and Technology, OptiForm Solution Suite and Softgels at Catalent, and Uwe Hanenberg, PhD, Director of Science and Technology, Oral Solids at Catalent, to learn more about new technologies for developing and delivering optimal dosage forms that address adherence and acceptability in pediatric populations.

**Pharmaceutical Technology:** What are some key development challenges for pediatric medicines?

**Clement:** The biggest challenge in pediatric formulation development is to create flexible dosage forms with measurable and easy-to-administer dosages. Improper dosing can lead to toxicity. Some dosage forms are associated with a risk of aspiration or choking, depending on the size and shape of the tablet or capsule. Special attention must be given to the use of appropriate excipients for children of various ages. The potential drug-vehicle interaction adds to the complexity.

**Pharmaceutical Technology:** Explain the PK–PD differences between adults and children.

**Hanenberg:** The differences in PK–PD are caused by the physical, metabolic, and physiological processes inherent in growth and reveal that children cannot be regarded as small adults. From birth through adulthood, several important factors that drive the PK–PD values are constantly changing. Gastric pH, especially in the first three years of life, can affect drug exposure.

A further difference is drug permeation through the GI tract’s epithelial layer, which has a smaller value in children than adults. API permeability must not be lower, as this may lead to a switch in the BCS class from BCS I (adults) to BCS III (children) or from II (adult) to IV (children) with a related impact on formulation and bioavailability enhancement requirements.

Finally, differences related to total body water, plasma protein binding, metabolic enzymes, first-pass effect, glomerular filtration, renal secretion, and renal absorption lead to differences in clearance between adults and children.
Pharmaceutical Technology: Do regulatory bodies reflect specifics of pediatric medicines?
Clement: The Pediatric Research Equity Act was made permanent under the Food and Drug Administration Safety and Innovation Act in 2012. In the European Union, pediatric regulations came into effect in 2007, and since then, no new drugs can be registered without the Pediatric Investigation Plan (PIP) being approved by the European Medicines Agency (EMA) Pediatric Committee. Regulatory authorities have published several useful guidelines and recommendations and they encourage the industry to conduct research and development of drugs in children.

For instance, a 2014 EMA guideline suggests how the route of administration and dosage form, dosing frequency, modified release preparations, excipient safety, and formulations should be adapted to the needs of children.

Another example is the six-month public consultation launched in October 2016 by the EMA on the addendum to the ICH E11, a guideline on the clinical investigation of medicinal products in the pediatric population. The proposed addendum intends to provide clarification and current regulatory perspective on various topics such as age classification and pediatric subgroups.

Pharmaceutical Technology: What are the specifics for developing pediatric medicines?
Hanenberg: Pediatric medication may need a different drug delivery technology than an adult medication using the same API. Not all excipients suitable for adults can be used in pediatric formulations, and selected excipients should be reduced to the minimum needed. Likewise, a minimum dosing frequency is desired. In addition, swallowability and choking risk must be considered. And, the treatment’s acceptance must be a strong focus, which is influenced by age, culture, health status, socioeconomic background, route of administration, taste of medication, duration of treatment, and convenience of administration.

Pharmaceutical Technology: Which oral dose form is most preferred by children?
Clement: Based on a 2014 FDA report, 69% of approved product labeling for pediatric use is in tablet form. However, we know that the preference toward dosage forms differs by age and prior use. About four years ago, the EMA recommended that an evaluation of pediatric acceptability be an integral part of pharmaceutical and clinical development.

We are now bridging the knowledge gap on acceptability of dosage forms based on evidence from clinical trials in children. For example, initial findings reveal minitablets and syrup are the most acceptable formulations to toddlers and infants. Another study demonstrated that two- to three-year-old children had no difficulty swallowing multiple minitablets suspended in jelly on a spoon. Another clinical trial reported that newborns have better swallowability of minitablets than syrup. Data published in November 2016 revealed a preference for chewable and orodispensible preparations compared with multiparticulate sprinkles across all ages.

Pharmaceutical Technology: How are drug companies meeting the need for weight- or age-dependent dosing of oral dosage forms?
Hanenberg: Industry is meeting the need for easy, reliable, and flexible dosing of pediatric oral formulations with technologies such as minitablets with a counting device, powders for reconstitution (such as powders in bottles or stick packs), liquids or syrups dosed by volume, and conventional solid formulations in various dosage strengths.

Pharmaceutical Technology: What are the most promising technologies for delivering pediatric formulations?
Clement: No single technology fits perfectly for every pediatric drug development application. Technologies that offer options for age-appropriate formulations would be desirable. Therefore, technologies that produce small oral dosage forms like minitablets, pellets, chewable, or orally disintegrating tablets have a promising chance for better compliance.

At Catalent, we develop pediatric-friendly softgels that are small and easy to swallow. For example, the OptiGel™ mini technology produces 30% smaller size than traditional softgels. To address dose titration, OptiGel Micro Technology can produce spherical capsules as small as 1 mm in diameter. These microcapsules can be packaged into a sachet to accommodate different dosing levels. Our Zydis® orally disintegrating tablets are also available for children and infants.

For more information, visit Catalent.com.