dosage form

Developing pediatric dosage forms

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While tablets and capsules are often the preferred dosage forms of both patients and pharmaceutical companies, they can be difficult to swallow for children. This article presents the challenges associated with developing pediatric solid oral dosage forms (SODFs), discusses some alternatives, and describes efforts to develop more patient-centric pediatric drug products.

When developing a pediatric-focused drug product, pharmaceutical companies are faced with additional challenges than when developing a product for adults. It's insufficient merely to think of children as small adults and scale the dose down based on a child's body weight.

A pediatric dosage form must be safe, effective, palatable, and easy to administer. It must minimize dosing frequency and allow sufficient flexibility to meet children's needs at various stages of development. Also, it's critical

that the product be an appropriate size for a child to swallow safely. If a tablet or capsule is too large, the child could choke on it, and if it's too small, the child could aspirate the product into her lungs. Obviously, both of these situations are potentially very dangerous.

Children can differ greatly physically and physiologically from one another, even when their ages are similar. Drug permeation through the epithelial layer of the gastrointestinal tract is usually lower for children than for adults but may vary from one active pharmaceutical ingredient (API) to another, so developers must investigate this effect on a case-by-case basis. Plasma protein binding, metabolic enzymes, and total body water also vary as a person grows and matures, and there will be differences in the first-pass effect and glomerular filtration as well as in both renal secretion and absorption.

Furthermore, because a child's organ systems are still developing, a number of excipients that are acceptable for adult use are inappropriate for pediatric medicines.

To overcome the issue of dose variation, developers have used liquid oral formulations, allowing practitioners to tailor individual doses to patients. However, liquid formulations can introduce different challenges, such as a greater risk of microbial contamination and difficulties with maintaining the formulation's physical and chemical stability.

For companies that want to begin developing pediatric SODFs, outsourcing and collaborating with experts who are experienced in this area offers an obvious advantage.

Pediatric SODF challenges

For drug developers looking to bring new medicines to the market, SODFs are generally seen as the preferred option; but for pediatric medicines, SODFs may be the most challenging. Not only must you create a range of different doses and formulations in a variety of dosage forms, but you also must consider commercial and potential future profit implications, especially in the case of rare or orphan diseases with relatively small patient populations.

A further complication is that no standardized techniques to assess pediatric SODF product quality currently exist, which makes identifying an effective formulation complex and slow. The danger of this is that, if studies become protracted and iterative, costs in both time and money can increase, and the outcome could be an expensive, sub-optimal product. Companies must evaluate this balance of risk and potential reward—especially in a limited-population market—when planning a development program.

It's important to note that regulatory authorities understand these commercial realities well, and the pharmaceutical industry uses regulatory frameworks to make business decisions regarding pediatric clinical trials. Regulatory authorities have revised their recommendations and guidelines many times, both to clarify guidance and to offer incentives to companies for carrying out specific research and development of drugs for children. Regulators also design requirements to ensure that products are available for infants and children in different age groups and that the products have an acceptable risk-benefit profile.

Overcoming pediatric development challenges

For companies that want to begin developing pediatric SODFs, outsourcing and collaborating with experts who are experienced in this area offers an obvious advantage. There is no single solution for successful pediatric formulation, so having access to a broad range of expertise and drug development technologies can help companies overcome the numerous challenges they'll face and shorten the development process, bringing successful products to patients faster and with reduced costs.

For children that are old enough to swallow them, tablets or capsules may be a good option, but for babies and other patients who are unable or unwilling to swallow a full-sized tablet or capsule, formulations involving multi-particulates or granules may help to improve adherence.

For toddlers, mini-tablets are becoming a more popular delivery method, as clinical trials have shown that children as young as 2 years old can swallow multiple mini-tablets suspended in a spoonful of fruit-flavored jelly. Research and trials have also shown that mini-tablets can be more successful for newborn babies than syrups.

Chewable and orally disintegrating products remove the challenge of swallowing altogether. Developers must formulate these dosage forms, as well as those that contain multi-particulates or granules, to include taste-masking agents to ensure patient compliance. Children are less likely than adults to accept a bitter-tasting medicine, so no matter how effective a pediatric drug is, the dosage form is impractical if the child refuses to take it because of its taste. Taste-masking techniques are wide ranging, from simply adding

Photo 1: For babies and other patients who are unable or unwilling to swallow a full-sized tablet or capsule, formulations involving multi-particulates or granules may help to improve adherence.

Photo 2: No single solution exists for successful pediatric formulation, so having access to a broad range of expertise and drug development technologies can help companies overcome the numerous challenges and shorten the development process.

sweeteners and flavors to more advanced techniques such as complexation with ion-exchange resin and cyclodextrin, polymer-film coating, hot-melt coating, spray congealing, melt extrusion, or melt granulation.

An outsourcing partner with a broad toolkit of formulation technologies can help the developer consider the many options and find a product's optimal dosage form. However, even after establishing the dosage form, there must be flexibility within that form to ensure that the patient receives the correct dose of medication.

This is relatively straightforward for liquid formulations or soluble powders—simply adjust the dose by dispensing a different volume. The situation is less simple for an SODF. One approach is to create several conventional formulations in different dosage strengths, although this may bring about changes to the formulation. Another alternative would be to use a counting device filled with mini-tablets to dispense the appropriate number needed to meet the prescribed dose.

Collaborative approaches to pediatric drug development

Commercial outsourcing partners are taking the initiative to address the specific challenges of pediatric formulation and drug delivery, and a number of cross-industry consortiums have been created for this purpose. In 2017, for example, the Catalent Applied Drug Delivery Institute, which brings together medical physicians and experts from academia, pharmaceutical research, and technology innovation, entered into a collaboration with the department of pharmacy practice at Rutgers University to undertake further research into the development and administration of medicines to children.

In the UK, the Smart Paediatric Drug Development consortium (SPaeDD-UK) includes a number of academic and industry partners with the goal of establishing an industry standard framework and suite of tools to develop safe and efficacious pediatric dosage forms. The project will provide novel predictive analytical and in-silico tools to help companies select the most appropriate formulations to support for development and commercialization, making product development quicker, cheaper, and more efficient while also increasing the probability of regulatory and technical success.

Prioritizing the patient

As with all patients, children need safe and effective medicines; but the challenges of developing appropriate pediatric SODFs are significant. Overcoming those challenges remains an important goal for the industry and requires that companies carefully consider and investigate how drugs behave in children at different stages of physical development and the manner in which the product delivers the drug to the patient.

A pediatric dosage form must ensure maximum efficacy while offering the greatest level of acceptability to both children and their caregivers. Research pioneers and formulation experts should collaborate and use every available tool and technology to effectively and efficiently develop new drug products in this area, so children will have access to the next generation of potentially life-saving treatments. *T&C*

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