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WHITEPAPER

Are you prepared for the complexity of pediatric drug development?

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Abstract

The numerous controls and processes in place to ensure a medication is safe, effective, and manufactured with the utmost efficiency make drug development extremely complicated. The challenges of drug development can increase if a manufacturer assumes an existing formulation for an adult can also be used for a child. Pediatric drug development requires a formulation designed to fit the specific needs of that patient population. Not considering these requirements early enough could add significant delays and costs to the development process. A manufacturer must have the expertise and necessary dosage form options available to support pediatric drug development as well as the ability to scale these options up through commercial production.

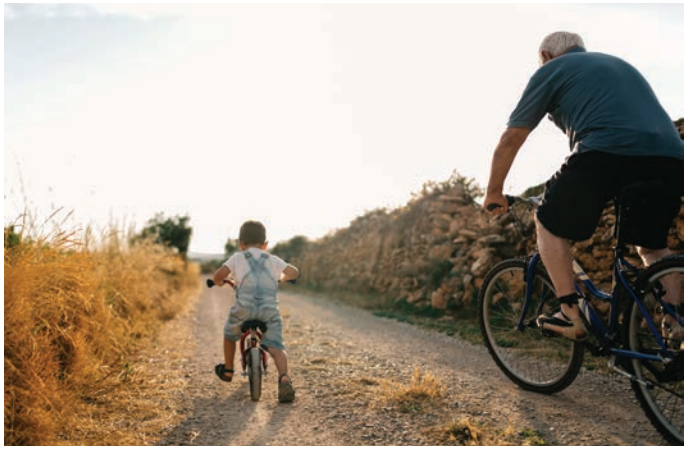
The unique challenges of pediatric medicine

Pediatric patients, or the pediatric population, are defined by the FDA as the age group "from birth to 16 years, including age groups often called neonate, infants, children, and adolescents[1]." One of the most important things to remember when developing drugs for this group is that children are not small adults. Just because a child is half the weight of an adult does not mean the dose he or she takes is also half. The dose range for pediatric drugs is much broader than that of adults. For example, a neonate requires completely different dosing than a child of 12 years. Dosage must be appropriate and flexible based on a child's weight, the release profile of the drug, and other factors, such as acceptability of the specific dosage form in children. For example, tablets and capsules are not preferred in children below the age of six, while the use of the selected excipients must also be justified in relation to their safety for pediatric use. These formulation challenges are often overlooked when submitting the pediatric investigation/study plan (known as PIP or PSP), leading to suboptimal formulations and concerns from health authorities[2].

Because it can be difficult to get a child to take medication, creating a formulation that is easy to administer by a parent and to ingest by a child is important.

Since regulatory authorities will not approve the use of tablets in children below the age of six, other formulation options must be available that can be easily administered by a parent[3]. These can include sprinkle capsules (used to quickly disperse medication into food), orally-disintegrating tablets, minitablets, and even proprietary technologies, such as chewable softgels (i.e., gummies).

Another option is a solution-based formulation, such as twist-off softgels, which can be used for both adults and children. This creates more flexibility in formulation development as well as offers higher dosing accuracy, as dosing with a cup or spoon can be inaccurate[4]. Because it can be difficult to get a child to take medication, creating a formulation that is easy to administer by a parent and to ingest by a child is important. In cases where the medication is used to treat a severe and/or life-threatening disease, it is crucial.



Another element that must be taken into account in pediatric drug development is that the excipients used for adult formulations are not always accepted in formulations for children. For example, colorants based on AZO-dyes used for a cosmetic coat can cause hyperactivity in children. The use of excipients with sugar requires a manufacturer to provide reasonable justification for its use in the formulation in relation to caloric intake and risk for tooth decay. The flavor of the medicine is another consideration for pediatric drugs, as many APIs have an unpleasant taste that must be masked. Children prefer fruit flavors, as opposed to flavors used for adults, such as mint. However, a manufacturer must be careful about making a pediatric formulation too sweet. If it could be perceived as candy, the appeal could be dangerous if a child accidentally gains access to the medication.

To avoid mistakes, manufacturers must have access to resources they can rely on for direction. An experienced formulation team and, if available, an internal toxicology group can provide guidance on the risk of any excipients being considered for a formulation.

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Some excipients used in pharmaceuticals are also used in food, so regulators have created reference material that includes a wide range of excipients with acceptable limits in children. Unfortunately, some excipients have not been tested in children, which means internal experts must be able to collect and evaluate related data to determine safety.

Ensuring these factors are considered during pediatric drug development is an arduous task. It is also an unavoidable one. If a company does not understand what regulators around the world require for a pediatric formulation, reformulation may be necessary, which could add a significant delay to the validation and approval of a new drug application.

Regulatory landscape of pediatric drug development

There are specific guidelines in place to ensure medicine developed for pediatric patients is properly evaluated. In the United States, the FDA has three laws for pediatric drug development[5]:

- Pediatric Research Equity Act (PREA)—requires companies to study the safety and effectiveness of their products in pediatric patients
- Best Pharmaceuticals for Children Act (BPCA)—offers financial incentive to companies that voluntarily conduct studies for pediatric drugs
- Title V of FDA Safety and Innovation Act (FDASIA)—enforces implementation of PREA and BPCA

Under PREA and Title V, a manufacturer developing a new drug must be able to provide a pediatric study plan (PSP). In some cases, a waiver may be granted, such as for indications that do not occur in children (e.g., benign prostatic hyperplasia).

A PSP must be approved by authorities before pediatric studies can be conducted. Unfortunately, opinions about what is acceptable vary among regulatory agencies. Some believe pediatric formulations should simply be a white tablet without any flavor, while others are more inclined to say it needs to be palatable for children. The disparity in viewpoints adds confusion to an already complicated matter.

In the EU, the European Medicines Agency (EMA) enforces the Paediatric Regulation, which oversees the development and availability of medicine for children[6]. It is comprised of:

- **Regulation (EC) No. 1901/2006**—requires oversight of drug development for pediatric populations to ensure ethical research of high quality, appropriate use of medications in children, and to improve the information available on the use of pediatric medicine
- **Regulation (EC) No. 1902/2006**—additional regulations to support the implementation of No. 1901/2006

The Paediatric Regulation also introduced the paediatric-use marketing authorisation (PUMA), which is "a dedicated marketing authorization covering the indication(s) and appropriate formulation(s) for medicines developed exclusively for use in the paediatric population[7]."

A path forward in pediatric development

Pediatric formulation development is an essential yet complex element of a development pathway and requires appropriate attention, expertise, and planning. If a company does not have in-house expertise available to guide them through pediatric formulation development, a CDMO partner with experience in this area can be critical.

By selecting a CDMO with a history of developing effective and accepted pediatric formulations, a company can take advantage of the knowledge necessary to navigate this difficult landscape

It is important to work with one that operates in a global fashion and offers the breadth of services required for pediatric development, including experience with multiple dosage forms that have been appropriate for pediatric use. By selecting a CDMO with a history of developing effective and accepted pediatric formulations, a company can take advantage of the knowledge necessary to navigate this difficult landscape.

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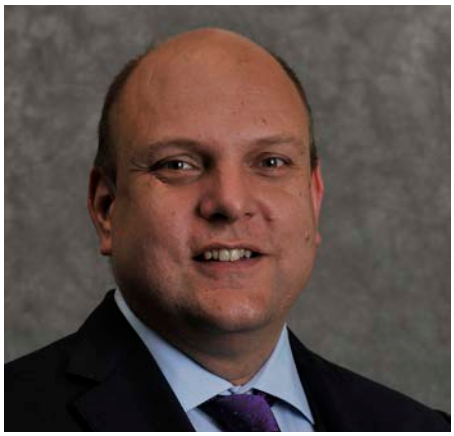

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Dr. van den Dries currently serves as Senior Director and Principle Scientist, Solid Dose Development at Thermo Fisher Scientific. With a Master's Degree in Pharmaceutical Sciences (University of Utrecht, the Netherlands) and a PhD degree in high shear granulation, Dr. van den Dries has spent a large portion of his career solving formulation and process challenges in solid dosage forms for, amongst others, poorly soluble compounds at Organon, Schering-Plough and Merck. In addition, Dr. van den Dries has experience serving as the global CMC project lead for the development, registration and commercialization of a late stage project that was ultimately selected as a pilot for quality-by-design, which included the implementation of quality risks management on in-line NIR blend control in commercial production. With extensive experience in pharmaceutical formulation development in softgel production, Dr. van den Dries eventually moved to Banner Pharmacaps, a well-established softgel manufacturer, as R&D Director to explore possibilities in drug delivery innovation based on soft gelatin technologies. This includes the upcoming regulatory approval of the first pharmaceutical chewable softgel formulation and the development of other delivery options based on softgels, which are in development in their R&D centers in Tilburg, the Netherlands, Mexico City and High Point, North Carolina.

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