ADARE® PHARMA SOLUTIONS

MEETING THE CHALLENGES OF PEDIATRIC ADHERENCE WITH PATIENT-CENTRIC FORMULATIONS

A Conversation With Srinivasan Shanmugam, PhD

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Developing effective therapies for pediatric populations involves unique and complex challenges. Key considerations include medication acceptance, patient-centered adherence strategies, and the pharmacokinetic and pharmacodynamic (PK/PD) challenges arising from the rapid anatomical and physiological development of pediatric patients. Additionally, pediatric medicine faces constraints such as a limited market size, complex formulation requirements, and specific regulatory demands.

In this interview, Srinivasan Shanmugam, PhD, Adare's Executive Director of Pharmaceutical Sciences, provides expert insights on these important topics.

What are the key causes of low compliance in pediatric populations, and how can these be addressed?

Swallowability and the bitter or unpleasant taste of medications are the main barriers to compliance in pediatric patients. By creating more palatable formulations using taste-masking technologies and developing easy-to-swallow options, we can significantly improve both acceptance and adherence, leading to better therapeutic outcomes for pediatric patients.

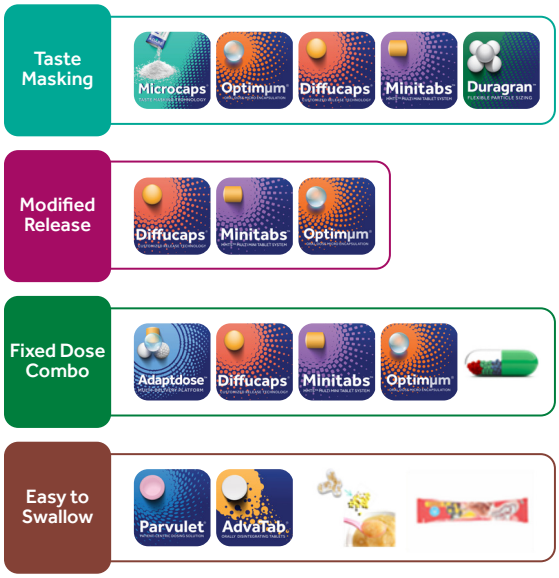
What are key components of the regulatory framework impacting pediatric drug development?

An effective regulatory framework for pediatric drug development includes a combination of legal mandates for compliance and incentives for pediatric labeling. It also incorporates scientific expertise in designing and developing age-appropriate formulations, ethical considerations for pediatric research such as pharmacokinetics/pharmacodynamics (PK/PD) and clinical studies, and collaborative efforts with stakeholders, especially regulatory agencies. These components ensure that safe and effective medications are available for children across various age groups.

What technologies does Adare offer to streamline pediatric clinical trial processes?

Adare provides comprehensive expertise in pediatric product development, from design through to commercialization, with a focus on efficient clinical study processes. Our key solutions offer clients a competitive edge through our platform technologies, which support scalable process development and provide analytical tools essential for clinical stage development.

Additionally, Adare offers various technologies aimed at overcoming the main barriers to pediatric acceptance and compliance, such as advanced taste-masking and enhanced swallowability options. For example, our mini tablets can be developed from the preclinical stage and scaled up through clinical trials to commercialization without the need for multiple formulation changes throughout the development lifecycle.



What are the key causes of low compliance in pediatric populations, and how can these be addressed?

Adare can make any typical size of stickpack, from a minimum of 17 mm x 40 mm (0.67" x 1.57") to a maximum of 40 mm x 200 mm (1.57" x 7.88").

Are oral films a viable option for pediatric populations?

Yes, orally disintegrating films (ODF) could be a viable option for pediatrics.

Minitablets are regarded as suitable for pediatric use, but is there a guideline stipulating the maximum size of minitabs for each pediatric age group?

Typically <2 mm minitabs in 2 years or less, and <3 mm for 2 years and above, have been found acceptable. Below are some references based on clinical study in pediatrics.

- Acceptance of 2 mm uncoated Minitablets resulted in better, or at least equivalent acceptance than that of a sweet-tasting liquid formulation—even for children aged 2 years or less (Spomer N. Et al. Arch Dis Child, Jan 17, 2012 online).
- Clinical trial in sixty 2- to 3-year-old children testing the acceptability of several mini-tablets administered at once showed that most of these children were able to swallow five to ten 2-and 3-mm mini-tablets with jelly food (Kluk A, Sznitowska M, Brandt A, Sznurkowska K, Plata-Nazar, K, Mysliwiec M, et al. Int J Pharm. 2015;485(1–2):1–6).

Can sensing technology provide reliable feedback on the bitterness of a drug, or on the effectiveness of taste-masking?

Sensing technologies have advanced significantly and now offer reproducible, high-throughput detection and feedback on the bitterness of drugs. However, the reliability of these results depends on multiple factors, including the expertise of highly skilled personnel who understand the intricacies of instrument sensitivity, detection concentration, and the impact of a drug's physicochemical properties, such as solubility and aftertaste. While these technologies are improving, they still need time to mature fully. Currently, they should be considered supplementary tools in pharmaceutical development, rather than definitive solutions.

Does a guideline exist detailing which excipients are acceptable in pediatric medicine — specifically, lactose? Stated differently, is it possible to have lactose in an oral pediatric formulation and/or with a max concentration?

According to the FDA's guidance for industry on pediatric drug development, lactose is generally considered acceptable in pediatric oral formulations. However, the use of lactose should be justified based on factors such as safety, tolerability, and age-appropriateness of the formulation.

Specific maximum concentrations of lactose may not be universally defined for all pediatric formulations. The acceptable concentration of lactose depends on factors such as the age group, dosage form, and known lactose tolerance of the pediatric population targeted by the medicine. For infants or children with lactose intolerance, alternative excipients or lactose-free formulations should be considered to ensure safety and efficacy.

In conclusion, lactose can be used in oral pediatric formulations based on regulatory guidelines, but its inclusion should be justified and appropriate for the target pediatric population. Manufacturers must conduct risk assessments and provide adequate labeling to ensure safe and effective use of pediatric medicines containing lactose.

What excipients are viable replacements for components like alcohol in pediatric formulations?

Replacing solvents like alcohol in pediatric formulations can be challenging, particularly for drugs that are poorly water-soluble and require liquid formulations. One approach is to minimize the use of such solvents by combining them with other similar ingredients at the lowest possible levels. In response to these challenges, regulatory bodies and pediatric industry experts are increasingly favoring solid oral formulations. These alternatives provide dose flexibility and allow for the use of safe and clean excipients suitable for pediatric patients.

Can we use real-word evidence (RWE) to support pediatric study/regulatory submissions, avoiding the need to conduct large clinical trials?

RWE can be helpful in post-market surveillance of pediatric medications and can help identify rare adverse events or long-term outcomes that may not be captured in clinical trials. Of course, RWE can be used to compare the effectiveness of different treatment options or dosing regiments in pediatric populations to inform treatment guidelines and optimize therapeutic strategies based on real world outcomes. Also, RWE can support label expansions for pediatric indications or help with post-approval commitments.

While RWE holds promise as a complementary source of evidence in pediatric drug development and regulatory submissions, it has a lot of challenges like data quality and reliability, confounding factors and possible bias, varying regulatory acceptance, and, most importantly, ethical and privacy considerations.

So, RWE should be applied judiciously and in alignment with regulatory standards. Collaboration among stakeholders, including researchers, clinicians, regulators, and industry partners, is essential to advance the use of RWE responsibly and effectively in supporting pediatric healthcare decisions. Regulatory agencies continue to develop guidelines and frameworks to facilitate the appropriate use of RWE while ensuring patient safety and public health.

My organization is developing an injectable drug for use in pediatric oncology. Are excipients in this delivery form also very different from those acceptable for adult patients?

Yes, excipients must be selected based on their safety profiles in pediatric populations, taking into account potential differences in metabolism, organ function, and susceptibility to adverse effects compared to adults. Although there may be some overlap in the excipients used in injectable formulations for both pediatric and adult oncology patients, the unique considerations related to pediatric patients and their specific oncologic conditions require meticulous selection and evaluation of excipients. This careful approach ensures optimal therapeutic outcomes and maximizes patient safety.

About the Author

Dr. Srinivasan Shanmugam has over 20 years of experience in designing and developing conventional, NDDS/alternate, advanced/modified drug delivery systems, and pharmaceutical platform technologies for oral and other routes of administration. His expertise includes stability, solubility/dissolution, permeability, and bioavailability enhancement techniques/technologies for challenging drugs, as well as patient-centric solutions focusing on pediatric and geriatric populations to achieve dose convenience, flexibility, and precision.

In his current position, Dr. Shanmugam is involved in the development and expansion of Adare's pharmaceutical technology portfolio and supports product development, co-development, and tech transfer opportunities. He holds a Ph.D. and a B.S. in Pharmacy. Dr. Shanmugam has published numerous research articles, holds multiple patents, and serves as a reviewer and editorial member for various prestigious journals. His recent work focuses on product development solutions for special patient populations, such as pediatric and geriatric populations.

About Adare Pharma Solutions

Adare Pharma Solutions is a global technology-driven CDMO providing end-to-end integrated services, from product development through commercial manufacturing and packaging, with small molecule expertise focusing on oral dosage forms. Adare's specialized technology platforms provide taste masking, customized release, solubility enhancement, and patient-centric dosing solutions. With a proven history in drug delivery, Adare's seven facilities in the US and Europe have developed and manufactured more than 65 products sold by customers worldwide.