

Demonstrating Evidence of Acceptability: The “Catch-22” of Pediatric Formulation Development

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Both researchers and practitioners have reached an influential period in the new era of developing pediatric medicines. Evolving regulatory reforms and guidance continue to serve as platforms steering research and development while distinctive opportunities and challenges in the field emerge. An advancing research need involves gaining a better understanding of end-user requirements and acceptability of formulations. This review considers solid oral forms to demonstrate the importance of such research to stakeholders in policy and practice.

In the global objective of developing better medicines for children, a recurring question in the field of drug delivery remains: “from what age can solid oral dosage forms be developed and safely prescribed for children?” Solid formulations offer numerous advantages over liquids, both from a pharmaceutical development and end-user perspective. This includes superior taste masking opportunities, a requirement for fewer excipients, easy and complete dose delivery, and the capability to include functionalities such as modified-release systems. Conventional tablets and capsules have been the principal means of oral drug delivery for nearly a century, while the emergence of innovative multiparticulate, (oro-)dispersible, and mini-tablet technologies enables the same dosing flexibility and ease of ingestion that have traditionally heralded liquids as the “gold standard” in pediatrics.

Provision of a suitable dosage form is an important factor that governs the age appropriateness of pediatric formulations, yet there is little evidence to support their suitability and acceptability among this population. Furthermore, there are few data to demonstrate how specific characteristics such as size and shape should be addressed to render these forms appropriate for children. Until recently, there has been little primary research addressing this issue, as well as a lack of important formulation information being published in pediatric trials and few studies addressing patient-related outcomes such as formulation acceptance and adherence.¹ Nevertheless, research in this area is emerging, driven by legislative changes and evolving regulatory guidance.

REGULATORY DEVELOPMENTS

The requirement for an age-appropriate formulation is stipulated in global legislation: the “Paediatric Regulation” in the European Union mandates a pediatric investigation plan

describing “measures to adapt the formulation ... to make its use more acceptable, easier, safer or more effective,” whereas under the US Pediatric Research Equity Act, pediatric assessments should gather data “using appropriate formulations for each age group.” An initial reflection paper published by the European Medicines Agency (EMA) acknowledged the question of formulation suitability. While recognizing the inherent variability among children, as well as the influence of a multitude of patient- and disease-related factors, 6 years was proposed as the approximate age from which solid forms such as tablets and capsules could be taken.² Despite some caution, particularly due to its insufficient evidence base, this reflection paper remained a strong point of reference and had a major impact on the evaluation of early regulatory submissions.

This resource has been somewhat superseded by the recent draft publication of the much-anticipated EMA guideline, another important milestone in the area of pediatric formulations.³ Benefiting from some emerging data, particularly in the case of multiparticulates and mini-tablets, a more comprehensive approach was initially proposed, notably in the appraisal of acceptable tablet sizes as a function of age. Dosage form size is fundamental to a child’s ability to swallow, and it was proposed that, unless justified by appropriate studies or clinical evidence, the specific dimensions shown in **Table 1** would be deemed appropriate for tablets.

Following release for public consultation, these proposals were criticized for lacking an adequate evidence base, despite the need for investigators to fully justify and support deviations with an appropriate level of corroboration. On the other hand, some commenters requested further definitive guidance, including provision of specific capsule size limits in relation to age.⁴ The

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Received 11 June 2013; accepted 20 July 2013; advance online publication 11 September 2013. doi:[10.1038/clpt.2013.154](https://doi.org/10.1038/clpt.2013.154)

Table 1 Suitable dimensions for tablets (width or length, whichever is longest), as initially proposed in the “EMA Guideline on Pharmaceutical Development of Medicines for Paediatric Use”

Age	Acceptable tablet diameter
6 Months to <2 years	None; multiparticulates (powders, granules, or pellets) acceptable
2–5 Years	3–5 mm (Small tablets)
6–11 Years	5–10 mm (Medium tablets)
12–18 Years	10–15 mm (Large tablets)

EMA, European Medicines Agency.

From ref. 3.

need for systematic and transparent regulatory evaluation is well established, and, understandably, developers seek to follow duly endorsed scientific advice. Herein lies the “catch-22”—regulators are unable to provide rigorous guidance in light of the well-acknowledged paucity of evidence available, yet when proposing formulation development strategies, investigators need to support their approach with the same.

Although stakeholders’ reservations toward this prescriptive guidance are justified, its logic-based approach is nevertheless a step in the right direction; it initiates discussion and highlights how formulation-related factors need to be considered alongside those of the intended population and therapeutic indication. Although this prohibitive level of detail has been removed from the next revision, “a more general requirement for justification by applicants” is still required.⁵ However, even a more communicative approach that discusses the benefit–risk profile of the formulation strategy still requires supporting evidence. Likewise, although the US Food and Drug Administration has given no specific direction regarding this issue, it is envisaged that substantiation of acceptability will similarly support regulatory evaluations in the United States. The need to understand how the interplay of population, disease, and formulation-related factors can affect children’s ability and willingness to accept formulations is thus a pertinent research need.

Initiatives such as the Seventh Programme Framework in the European Union and National Institutes of Health program announcements (e.g., PAR-11-301 to PAR-11-305) in the United States show government support toward pediatric formulation research, to help close the gap of the current catch-22. Nonetheless, both the EU and US regulations are oriented toward interactions between regulatory authorities and usually pharmaceutical companies. For formulations developed in an academic setting, subsequent linkage with regulators is less defined, posing the risk that innovative formulations developed in an academic institution may never positively impact pediatric therapeutics, unless purchased by a manufacturer.

POLICY TO PRACTICE

In the era of evidence-based medicine, guidance toward choosing the most suitable formulation is another important factor that would contribute to ensuring optimum therapeutics in children. Even the most efficacious drug therapies will be futile if not acceptable or adhered to by patients. Furthermore, the

attitudes and choices of health-care providers strongly influence which formulations are administered to patients in clinical practice, and this is an important link yet to receive adequate consideration. In the case of oral medicines, for example, the age from which children are prescribed solid forms over liquids is subject to the judgment and experience of the clinician. Assessing the perceptions of stakeholders at the bedside, including patients, caregivers, and health-care professionals, is an important area that needs to be addressed in order to ensure that evolving regulatory guidelines fully reflect pediatric medicines use in practice.

Currently, EMA guidance specifies the need to assess the acceptability of pediatric medicinal products as an integral part of pharmaceutical development studies, primarily with children themselves but also giving due consideration to the needs of caregivers.⁵ Clinical practitioners should be aware of this as an anticipated outcome measure in impending clinical studies. Assessing this aspect of therapeutics may be beneficial further, as incompatibility between the medicinal product and patient, or likewise the caregiver, could potentially affect adherence to treatment regimens and even patient retention in clinical trials.

METHODOLOGICAL CONSIDERATIONS

Investigators must duly consider and justify their methodological approach toward evaluating this latent variable, including the means of assessment and outcome measures. Currently, few data exist in both typical and atypical populations, and small, nonrepresentative samples invariably lead to inconsistent and limited findings. In the case of swallowability, there is little consensus regarding the relationship between dosage form geometry and the influence of patient-related factors, including age, developmental capability (e.g., swallowing coordination), and prior experience. From a traditionalist view, considering solid forms for infants and toddlers would be implausible; however, the emergence of multiparticulate technologies reforms this. These formulations offer greater ease of swallowing and show potential for use from ~6 months of age, when infants start to accept semisolid foods. An emerging research issue is establishing the dose quantity (or volume) of multiparticulates that would be appropriate for different ages.

The validity and reliability of study designs are also important. Exploratory studies using placebos of these novel forms are valuable to show their proof-of-concept but may not be comparable to extended investigations with the intended clinical populations to indicate long-term acceptability. Furthermore, by agreeing to take part in such research, participants inherently have a positive attitude to the formulation being investigated, a bias that can threaten the validity of findings. Understanding reasons for dissent and exploring perceptions of formulations overall would also be informative to help identify potential barriers to acceptance.

Furthermore, a lack of formulation-related problems reported during studies may not necessarily be a reliable indication of appropriateness or acceptability because it is well acknowledged that patients and caregivers often adopt pragmatic measures to administer medicines, including modification of dosage forms. Rather than solely relying on patient or carer self-reports, including an objective, researcher-observed measure might be

preferable. Although the EMA states that adequate assurance of acceptability is “not to be understood as 100% acceptance” in the target population,⁵ a threshold from which formulations can be deemed acceptable is yet to be defined.

CONCLUSIONS

Determining end-user acceptability of pediatric medicines is a challenging and evolving research need for which a multi-focal and multidisciplinary approach is needed. The EMA's requirement to assess this aspect will have a positive impact on pediatric therapeutics. Aside from published literature evidence, outcomes of any clinical studies could provide the vital evidence required to guide formulation development, although availability in a public domain is not guaranteed. An important objective of the EU regulation was to improve the availability of information on the use of medicines without subjecting children to unnecessary trials. In light of this, establishing an arena to share essential formulation information may be a pivotal step in the future of pediatric formulation development.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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