



## Paediatric Formulation Development: Challenges and Opportunities

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### ABSTRACT

The design and selection of new pharmaceutical dosage forms involves the careful consideration and balancing of a quality target product profile against technical challenges and development feasibility. There is an important need for research and development into paediatric medicines. Only a small fraction of the drugs marketed and utilized as therapeutic agents in children have been clinically evaluated. It may not always be possible to provide authorized, commercially manufactured, age appropriate, ready to administer preparations. In terms of assurance of quality and bioavailability there is a gamut from this ideal through intermediate products through authorized compounding and manipulation of commercial dosage forms to ad hoc compounding using only the skills and experience of the individual pharmacist. Additionally, it is widely known that caregivers may manipulate medicines at home, for example by segmenting tablets and by addition to foods or liquids. Clinical trials are subject to detailed scrutiny by the various regulatory bodies that have recently recognized the need for pharmaceutical companies to invest in paediatric medicines. The costs associated with paediatric product development could result in poor or negative return on investment and so incentives have been proposed by the EU and US regulatory bodies. Additionally, some commonly used excipients may be unsuitable for use in children; and some dosage forms may be undesirable to the paediatric population.

**Keywords:** Paediatric Dosage Form, Manipulation, Authorized, Non-authorized.

### INTRODUCTION

For many years children have been described as 'therapeutic orphans'<sup>1</sup> to indicate that medicines research, regulation and formulation development has mainly focused on disease in adults. With so few medicines containing adequate labeling information to guide their use, off-label use of medicines has become, unfortunately, a necessary and accepted part of pediatric medical practice<sup>2</sup>. Off-label prescribing includes the use of drugs for unapproved indications, in a different age group, or with a different dosage, frequency, or route of administration. Off-label prescribing also includes the administration of extemporaneous formulations (e.g., oral suspensions made from adult tablets) with untested bioavailability and stability.

The majority of marketed drugs are either not labelled, or inadequately labelled, for use in paediatric patients. Approximately 80% of listed patient information leaflets (PILs) in the US either disclaimed usage or lacked specific dosing information for paediatrics. Less than 30% of drugs approved by the US Food and Drug Administration<sup>3</sup> were authorized for paediatric use. Additionally, only 38% of new medicinal products, which were potentially of benefit in paediatric therapy, were initially labelled for paediatric use<sup>4</sup>.

A recent Australian survey of available PILs for paediatric patients<sup>5</sup> showed either inadequate information (~70% of cases), or in those cases where there was specific paediatric information, absence of a suitable paediatric dosage form (~22% of cases). Considering that in many ways the diethylene glycol poisoning tragedy of the 1930s in the US was prompted by the unavailability of a child-

friendly liquid preparation of the then new low solubility drug sulphanilamide, and as a result, chemists at the Massengill pharmaceutical company formulated the drug in a non-aqueous solvent (diethylene glycol<sup>6</sup>), it appears that paediatric dosage form development has not moved on significantly in the succeeding 70 years.

In January 2007 the European paediatric regulation (EMA, 2007), came into force, requiring (and rewarding) manufacturers to study their medicines in children along agreed timelines if they were also seeking Marketing Authorization (MA) for that particular medicine in the adult population. A Paediatric Investigation Plan (PIP) must be agreed with the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) describing the clinical studies that will be undertaken and including information on formulation development indicating suitability for children.

For new drugs or MA variations there is an opportunity to apply modern formulation technology to ensure that all relevant ages can receive a commercially manufactured, authorized dosage form – whilst traditional tablets and liquids will be suitable in some cases, orodispersible and dispersible tablets, coated granules, mini-tablets and multi-particulates offer other opportunities which may be more acceptable in others. Traditional manufacturing methods for less stable drugs desired to be administered in liquid form may be utilized to manufacture granules or a powder containing taste-masking agents and other excipients to be reconstituted before use. Such dosage form design, also offers an opportunity to manufacture an appropriate medicine rather than relying on ad hoc



adaptation of an authorized dosage form by the dispensing pharmacist or care giver.

The aim of this review is to illustrate the need for paediatric medicines and to identify the various challenges associated with the development of paediatric medicines.

### **Dosage form selection as part of modern pharmaceutical development**

The goal for any new drug product is a safe, effective dosage form that facilitates maximum compliance through the course of treatment. Formulations for pediatrics usually must cover a broad age range. Selecting and designing an appropriate dosage form for the paediatric population is particularly challenging. In addition to those challenges usually encountered when developing adult dosage forms; developing a dosage form for children poses other challenges such as the diversity of the patient population both in terms of size and physiological and biological maturation; specific patient compliance challenges such as swallowing difficulties and low tolerance to unacceptable taste; and specific safety concerns associated with the required excipients<sup>7-9</sup>.

As with adult patients, the oral route of drug administration is the most commonly used for paediatric patients. This poses the additional challenges of developing dosage forms that are easily swallowed and have acceptable palatability. Many oral dosage forms are available, each with their advantages and disadvantages, which formulators will take into account when assessing the strategy for developing a paediatric product for a specific situation.

Drugs that must be dosed based on body weight or endocrine status (e.g., puberty) require either solid doses that are scored or different doses. Children under 12 years of age often have difficulty swallowing capsules and/or chewing tablets. A liquid formulation, therefore, is often chosen for pediatric administration. Liquid formulations facilitate dose titration and are easily administered. Liquid formulations, however, have certain constraints. Taste is an important issue for pediatric formulations, and the more frequent the dosing, the more critical this issue can be. Stability of the liquid in multiple-dose bottles must be maintained, often by using preservatives. Taste-masking agents, preservatives, and solubilizing excipients must have an acceptable safety profile in pediatrics.

Special considerations must be taken to reformulate currently approved adult drugs to be a pediatric friendly product. As an example, Madeira Therapeutics is developing a pediatric formulation of a marketed statin for a population with an inherited cholesterol gene that often leads to early heart disease<sup>10</sup>. This product requires flexibility in dosing as the amount of drug required can be variable. To meet the requirements of a flexible dose level and integrate the characteristics of the active pharmaceutical ingredient (API), an oral syrup

formulation was identified as the target formulation. As expected, many of the formulation steps are the same as with any drug-development program. The physical and chemical properties, such as solubility, salt form, stability, and the taste of the API must be known or established.

The major difference for a pediatric formulation compared with an adult formulation is an added layer of investigation when choosing excipients. The traditional sources, the generally regarded as safe (GRAS) list (i.e., 21 CFR Parts 182, 184, and 186) and FDA's *Inactive Ingredients Guide* are based on the safety obtained primarily in adult subjects. Investigation into the safety data in the pediatric population available for the potential excipients to be used should be performed. The specific excipients chosen must be determined based on the drug under development as well as the pediatric product profile under consideration.

On some occasions it may be acceptable to provide manipulation or compounding instructions for the marketed dosage form, either for early clinical studies in pediatrics or, more rarely, as the intended future commercial presentation. In considering formulation development challenges such as aqueous stability, intermediate preparations for reconstitution may also be justifiable as viable commercial formulations in certain circumstances thus negating the need to develop more sophisticated formulations that require no such reconstitution (terminology: intermediate dosage form – intended future commercial presentation).

In addition to new products being developed by the industry, there are many off-patent medicines that are already licensed for adults but still require clinical data to be generated in paediatric populations. In these cases clinical phase appropriate/intermediate preparations may have utility to generate clinical data in a more timely and cost-effective way compared to the manufacture of specific and sophisticated medicines.

### **Compounding and manipulation**

The EMA reflection paper on 'Formulations of choice for the paediatric population' summarizes much of the background to the issues of access to age-appropriate preparations (EMA, 2006).

The reflection paper encourages manufacturers to produce and provide relevant data and information to practitioners. The paper goes on to state that 'in essence, the pharmaceutical industry should be aware that an 'adult' formulation may be manipulated for paediatric use and provide any such information about the product that would allow the pharmacist to design a satisfactory formulation. Depending on the evaluation of such data by the competent authorities, validated formulations for extemporaneous dispensing may be considered acceptable for inclusion in the Summary of Product Characteristics (SmPC) and package leaflet'. (Note: The reflection paper uses the term 'manipulation' to include compounding by the pharmacist.)



It is to be anticipated that the majority of new medicines developed through the PIP process will have age-appropriate formulations manufactured so that the need for compounding or manipulation is minimal. However, many older medicines (often 'adult' medicines used off-label) may never have suitable commercial dosage forms made for children and it remains likely that caregivers will continue to manipulate medicines at the point of administration to cope with the abilities and preferences of children and in some cases it will be preferable for the pharmacist to produce a medicine that the child finds acceptable. It is important that the regulatory agencies, academia and industry work together to enable provision of data supporting these activities. Typically, any kind of modification or manipulation of a drug product prior to administration has been termed 'extemporaneous'.

Extemporaneous or magistral products are produced for an individual patient to the specific order of a clinician by a pharmacist<sup>11</sup>. Extemporaneous or magistral preparation describes the manipulation by pharmacists of various drug and chemical ingredients using traditional compounding techniques to produce suitable medicines when no commercial form is available. However, this definition does not distinguish between ad hoc preparation by the pharmacist using his knowledge and experience and preparation according to a manufacturer's instructions which may have been approved by the regulator and included in the SmPC.

In many parts of the world extemporaneous dispensing or preparation is known as compounding. It may involve the bench top modification and incorporation of an 'adult' dosage form (e.g. tablets) or an active ingredient, with other ingredients, to produce an age appropriate paediatric formulation such as an oral liquid. Because the term extemporaneous is poorly defined, the term 'compounding' should be used for the process undertaken by the individual pharmacist who creates a medicine from active drug substance and excipients or from an authorized dosage form and excipients when no suitable paediatric dosage form is commercially or locally available.

Few European countries have standards for the preparation of compounded preparations with the result that reproducibility and safety are potential issues<sup>12</sup>. Sometimes compounded preparations are used on a large scale and may be prepared in larger quantities (batches), usually from actives and excipients. Exemptions in medicines legislation may allow this to be classed as 'dispensing' (with little quality assurance) but commercial or health service units may also produce such unlicensed preparations to GMP standard. In the UK such medicines are known as 'specials' but when requesting a product there is often confusion as to what standard has been used in their preparation<sup>13</sup>. Although aspects of quality may be assured, there may be inconsistency between producers with bioavailability differences, colour, taste and strength variation. 'Manipulation' has been described as the physical alteration of a dosage form to achieve

administration of that dosage form usually, for children, in a smaller age/weight-related dosage than in the original dosage form. This is usually undertaken by the care giver at the time of administration and may also include modification of the dosage form for addition to food or liquid to facilitate administration. Segmenting of tablets is the most common manipulation of a dosage form but dispersion or dissolution of tablets or capsule in liquid and proportional dosing; mini-tablets in capsules for adults, to be counted for different ages of children or reducing the size of a suppository by cutting might also be considered. The term 'industry-verified' has been used to describe preparations and methods of preparation verified by approved manufacturers based on supportive scientific data (pharmaceutical and sometimes clinical), which can provide a much higher degree of control and assurance than traditional compounded preparations.

Where compounded or manipulated preparations are proposed for paediatric use authorized by the regulatory authority, it is expected that the manufacturer will have investigated appropriate pharmaceutical and bioavailability aspects of the products paying particular attention to accuracy of dose delivery, bioavailability and uniformity of preparation. Pharmacopoeial and other tests and standards applied must be described and justified in the PIP as part of formulation development. It is preferable that such industry-generated data are reviewed and approved by the competent authority and included in the approved SmPC.

#### **Development of palatable formulations for children**

Many existing medicinal formulations are not designed as suitable for children. Therefore, the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act were introduced in the United States, and legislation governing the development and authorization of medicines for use in children was also recently introduced in the European Union to stimulate pediatric formulation development through a combination of market incentives and regulatory requirements<sup>14-16</sup>. The goals of these initiatives, however, are difficult to reach if the challenges in pediatric formulation and taste optimization are not well managed<sup>17</sup>. A majority of formulations for children have complex compositions in a less desirable physical state, (e.g., liquid state) to provide dose flexibility and facilitate dose administration (e.g., ease-of-swallowing). These formulations are more susceptible to taste, physical, chemical, microbiology, and pharmacokinetics issues than those of conventional solid oral dosages for adults. Advanced knowledge in formulation (e.g., reaction kinetics, physical chemistry of drug solubility and forms, and special technologies for taste-masking), taste assessment/optimization, and bio pharmaceuticals are required.

A hallmark of many successful pediatric formulation development programs is an integrated team of formulation and sensory scientists. A typical development program for pediatric formulations involves:



1. An exploratory and preparation stage for the development team consisting of formulation and sensory scientists to provide interdisciplinary input on formulation composition, and sensory characteristics (e.g., basic tastes, aroma, texture, mouth feel, and aftertaste) to clearly define the development strategy
2. An experimental stage for the development team to establish viable options
3. An optimization stage to finalize the formulation and establish product, process, and design space; for example such as for preservative levels
4. A confirmatory stage to verify the flavor quality (i.e., palatability) of formulations (e.g., on aged products) and conduct stability/clinical/bioavailability programs in preparation for product registration.

It is important for the project team to define the strategies to address excipient compatibility, physical and chemical stability, taste, preservative, bioavailability, regulatory, and packaging issues as early as possible<sup>18</sup>. For excipient compatibility, it is unlikely that all combinations of excipients can be tested. To reduce technical risk and late-stage setbacks, an approach based on drug substance chemistry, drug/excipient sensory characteristics, excipient properties, and statistical design-of-experiments is recommended to generate data to set the direction for taste-masking and dosage-form selection and development. The excipients, including colorants, sweeteners, and flavors for consideration can be based on several acceptance criteria. These factors include regulatory acceptance; toxicity; function such as mouth feel, viscosity and taste; disease state (acute versus chronic, and the disease itself); administration (dose strength, volume, and frequency); patient population; market potential; and dosage-form characteristics<sup>19</sup>. For example, the use of sucrose may be more suitable for acute therapy than for long-term therapy such as in the treatment of HIV, provided patient compliance is not compromised. The decision in choosing excipients must be balanced and not overly constraining. Trade-offs should be identified and carefully considered by all stakeholders (e.g., clinical, regulatory, pharmaceutical development, and marketing). For example, pediatric drug products often need more than one type of sweetener and taste modifier to effectively mask the bitterness of the active pharmaceutical ingredient (API) that is strong in intensity and long in duration. Nutritive sweeteners and sugar alcohols alone do not provide lingering sweetness. High-intensity sweeteners do not provide bulk, build viscosity, or provide beneficial mouth feel effects and as such do not work in most systems by themselves.

The development of palatable drug formulations requires human input for taste assessment and optimization. Sensory analysis methods are applied to create great tasting food products for decades and are increasingly being adopted in the pharmaceutical industry to develop

palatable drug products. With qualified taste panels, analytical sensory tests are used to accurately identify and quantify perceived sensory characteristics of APIs, excipients, and products under controlled laboratory conditions to guide development programs<sup>20-21</sup>. To minimize exposure to drug substances, proper precautions, including good clinical practices for investigational new drugs, are taken to ensure the safety<sup>22</sup> of the evaluators. For example, "sip and spit" tasting protocols and the use of surrogates of generally recognized as safe (GRAS) ingredient compositions are employed. Human taste panels require proper calibration, standardized sampling procedures, and reference standards to generate objective and reproducible data. Knowledge of flavor construction is required to properly translate the data to pediatric drug products. Instrumental taste measurement is finding application in quality control to detect lot-to-lot variations and reduce the sample testing burden on human taste panels. However, there are comparatively few applications of these instrumental techniques in formulation development owing to the general lack of API-specific data correlating human taste panel with instrumental output.

A good understanding of the technical, clinical, regulatory and market requirements using a multidisciplinary development approach, with solid scientific principles is critical for developing formulations that meet today's needs in pediatric medicine.

#### **Thin-film technology<sup>23</sup>**

The oral thin film (OTF) platform is a proven and accepted form of drug delivery for pediatric products. Its premeasured format provides an accurate and easily ingested dose without water that allows for portable and convenient "give and go" administration by a parent or caregiver. Patient compliance can be improved because of an OTF's ease of administration and subsequent difficulty in expectoration. The dosage format offers flexibility in base chemistry and base formulation development from raw material selection to final packaging configurations as well as an established and well-understood manufacturing path. Based on the continuous nature of production, formulators can also approach pediatric films as either unique, single-product formulations, or as a dosage modification of a preexisting product.

#### **Tolerability and disintegration**

Beyond efficacy, most OTF development for pediatric products focuses on two key attributes: tolerability and disintegration. Depending on the age range, region, and marketing needs, formulators can use various flavors and compendial excipients to create a child-friendly formula. They can also choose to develop dye-free and alcohol-free products, add sensory components such as heating or cooling sensations, and/or modify texture. Different taste-masking approaches can be incorporated, and the dosage unit area can be modified to hit specific



taste and disintegration profiles ranging from less than five seconds to multiple minutes. Additionally, dissolvable films may be formulated to demonstrate adhesion properties for use with other devices currently used by younger populations to deliver medications or vitamins. With a standard active pharmaceutical ingredient (API) loading level of 50% of the final unit mass and an adjustable final unit area, formulators have a lot of latitude in both how much API can be loaded and how other product attributes can be tailored for each product.

### Other approaches in OTFs

Another approach to development is to leverage higher-dose, preexisting formulations for pediatric populations. Dissolvable films are currently manufactured as a continuous roll stock that is unitized during final packaging. With this approach, the packager cuts the film strip to an alternative size to achieve a different dose. For example, a 10-mg dose could become a 5-mg dose by halving the unit size. This approach is attractive because only one formulation is developed, but two or more products and dosage forms can be marketed. Examples of this approach have been launched in the pediatric market, including cough/cold and gastrointestinal products.

Precision-coating techniques derived from transdermal and filled-pad production translate base chemistries into final dosage units with unit tolerances as tight as  $\pm 2.5\%$  around the potency target. Specialized coat weight monitoring systems and liquid deposition techniques enable any OTF product to hold and maintain consistent cross and downstream uniformity during manufacture. These manufacturing approaches are well understood and controlled, enabling robust, efficient development from bench to commercial scale.

The flexibility in base chemistry combined with an established production process enables formulators to present a new platform to the patient. From a materials-selection standpoint, the OTF format provides formulators with the flexibility to add or omit ingredients that are more or less desirable for pediatric populations while still producing a scalable product. Table III provides examples of commercially available thin-film over-the-counter pediatric products.

The dose accuracy, ease-of-use, convenience, and potential for improved compliance of dissolvable films continue to drive new formulations and applications for pediatric populations. New programs are emerging for topical, transdermal, and oral modified release pediatric products. In addition, OTFs have the potential to extend product life cycles for approved oral APIs via a simplified filing path such as a 505 (b)(2). OTF's flexibility in base formulations make them a viable strategy in pediatric formulations.

### Oral thin-film delivery via a pacifier<sup>23</sup>

The pediatric population represents one of the most challenging patient groups for administering drugs as

compliance, proper dosing, and safety are difficult to manage with most standard modes of drug delivery. Thin-film dosage-form technology has become more prominent in pediatrics because it provides an accurate, convenient, and effective way to deliver medications to infants and young children. Thin films are easy to administer and fast-acting and does not require the patient to actively swallow or chew the dosage unit as is required with a liquid or chewable tablet. Thin film is a highly flexible drug-delivery technology. The strips can be manufactured to different sizes and tastes, can carry various drugs, and be applied to a host of surfaces within the oral cavity to enable the desired drug delivery outcomes.

An infant's natural propensity to suckle makes pacifiers and bottle nipples useful devices for administering medication and vitamins. MonoSol Rx has developed a patented technology for administering film dosage units to infants and young children using this approach.

The system relates to the delivery of drugs and/or vitamins contained in a thin film that is attached or placed inside of a pacifier or porous nipple member such as the tip of a baby bottle. Affixing a quick dissolving thin film into the porous nipple of a bottle or pacifier ensures that the active ingredient is immediately released into the oral cavity upon contact with saliva or liquid from the bottle. Delivery of a complete and accurate dose is confirmed as the thin film dissolves and disappears from the inside surface of the pacifier or porous nipple.

The dissolvable thin film is attached to the inner surface of the nipple and held in place with retaining fingers. The porous nipple member can possess holes or slits, which allow saliva to enter the inside of the nipple member and drug from the dissolved thin film to be suckled into the oral cavity. The pacifier or nipple member can be developed as a single-use application or as a reusable system.

Flavoring agents and/or coated drug particles can easily be added to the thin film for the purpose of taste-masking. This property enhances the likelihood that the infant or young child will continue to suckle the nipple member, further ensuring that the entire dose is consumed. In addition, a translucent material can be used for the nipple member, so the parent or caregiver can visually determine that the thin film has been completely dissolved and that the entire dose has been administered.

Distinct attributes of the thin-film dosage also make it advantageous for pediatric use without the pacifier or nipple member delivery method. Since the polymeric films are very thin (i.e., typically 50 to 150 microns), the technology ensures rapid disintegration due to a larger surface area for wetting and subsequent dissolution. It is virtually impossible for a film strip to be swallowed intact when placed on the tongue because the rapid wetting of the film generally causes adhesion to the tongue or other oral mucosal surface immediately. The film quickly



dissolves and is ingested along with the saliva into the gastrointestinal tract.

Thin-film drug-delivery also offers the potential for reduction of dosing errors in a healthcare-provider setting because the dosage forms are usually supplied in printed individual pouches. The thin quick-dissolving film and low-dosage mass also allow for a shorter residence time in the oral cavity, which eliminates the possibility of the child spitting out the medication.

Thin film is likely to play a larger role in pediatric drug delivery in the future. Likely applications will include the delivery of prescription drugs, oral vaccines, nutritional supplements, and over-the-counter medications.

### Other approaches to paediatric formulations

There is a clear need for specific paediatric formulations that permit accurate dosing and enhance compliance by this unique patient group(s). Other paediatric-friendly dosage forms are melt forms, needle-free injections, nasal solutions, nasal drops, eardrops, ear ointments, eye drops and ointments, scalp applications and other dermal applications (creams, ointments, lotions) and powders (nutritional powders, powders for reconstitution, sprinkles, etc.). Suitability for paediatric administration is based on the requirement not to dilute to strength, and that strength matched the dosing instructions<sup>5</sup>. These formulations in turn may require different flavours and colours for different markets, based on cultural preferences. These formulations may require different concentrations from the existing, registered adult formulation, and these differences may go beyond merely prorated differences in mg/kg dosing regimens. There are also age related differences in sensory discrimination of the tongue, sensory discrimination decreasing with increasing age<sup>24</sup>.

Controlled-release multiparticulate dosage forms offer a distinct advantage over many conventional dosage forms used in paediatric medicine. In addition to their small size helping overcome issues associated with dysphagia, they may be designed to taste mask whilst also modifying the release of the active drug substance from the formulation. Controlled release dosage forms have the potential to extend the period of time between dosing, reducing the number of doses required per day, enhancing patient compliance and patient/ clinician convenience. This is particularly relevant for paediatric patients suffering with chronic conditions which usually require regular dosing by the patient, parent or teacher during the day<sup>25</sup>.

Spacer devices can be used in conjunction with nebulized inhalers for delivery of paediatric formulations to the lung. Dry powder devices can usually be used for children aged four years and above, and some devices require very low inspiration flow rates (30 L min<sup>-1</sup>) e.g. Turbohalers, whereas children aged 10 years and above are, after appropriate training, usually able to use an inhaler.

Doses of parenterally delivered drugs can be tailored to a wide range of paediatric patients by adjusting dose volumes. However, this route of administration is still not community friendly, but the advent of hospital care in the community will facilitate greater uptake. Subcutaneous and intramuscular injections are the most widely used parenteral dosage forms in the community<sup>26</sup>. Rectal preparations (for example, suppositories) offer a relatively easy route of administration for certain conditions, for example, seizure control using rectal diazepam; however, compliance may be an issue due to parent or care giver distaste for this route of administration.

Dosing devices are intrinsic to the successful dosing of the paediatric medication; e.g. dosing spoons, syringes, etc. Finally, consideration needs to be given to different delivery systems (ICH E11 2000).

### Packaging/Dosing:

Pediatric products need to be appropriately packaged to guarantee chemical and physical stability, to protect from microbial and other types of contamination, and to make storage and handling easy for care givers. Child-resistant packaging is also required, even though the product is intended for children. In the case of liquid formulation, the use of appropriate dosing devices is important to support accurate dosing by volume. Dosing devices (droppers, measuring cups, graduated pipettes etc.) should be part of the pediatric product and provided by the manufacturer to avoid the use of household spoons and other inappropriate measuring devices<sup>27</sup>.

### CONCLUSION

The development of an appropriate pediatric formulation is a complex task that requires multiple considerations. Therefore, it is appropriate that drug developers consider possible pediatric formulations early in the drug development process. A natural point in time would be at the same time a solid oral form is being considered for adults. This will allow for an appropriate consideration of adolescents and pre-adolescents as potential users of such a solid oral form. It is also important to assess all the possible formulations that will be needed for the entire spectrum of the pediatric population. By developing appropriate pediatric formulations, we can make off-label use of drugs and use of extemporaneous formulations things of the past.

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