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From Paediatric Formulations Development to Access: Advances Made and Remaining Challenges

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Abstract

Developing suitable paediatric formulations and ensuring access to them by the greatest number of the 2.2 billion children worldwide are equally important to provide optimal pharmacotherapy. This review focuses on the progress made over the last two decades with paediatric oral formulations with respect to evidence for acceptability and dosing flexibility of liquid and solid oral dosage forms (SODFs). It also discusses the clinical needs for, and the access to, paediatric formulations for existing authorised medicines. A significant body of new knowledge now supports the acceptability of solid oral dosage forms (SODFs) in children, resulting in an increasing number of medicines commercialised as multiparticulates, including minitablets that are starting to be brought to market. However, there are gaps with these formulations that deserve more research. Even though efforts have been made to identify medicines in need of age-appropriate formulations, there is no common priority list shared internationally. Such prioritization would help to develop paediatric formulations with the greatest potential for providing a health benefit to children worldwide. In addition, available data highlight that paediatric formulation access is fragmented and unequal, with

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commercialisation of suitable paediatric formulations too often limited to some countries/regions. We propose actions to better align decisions during the development of paediatric formulations and promote a more globalized approach to facilitate registration pathways between different jurisdictions. Furthermore, discussions about alignment between approval, pricing, and reimbursement processes should also happen, leaving working in siloes behind us. It is time adults start thinking outside the box for children.

Introduction

The road from the development of paediatric formulations to children accessing them remains a very challenging one (1, 2). Every day all over the world, those caring for children have to struggle with the fact that many medicines administered to the youngest ones are not child-friendly, forcing them to use these products off-label outside their marketing authorisation. Pharmacists, nursing staff, and parents or caregivers must daily adapt commercialised adult pharmaceutical forms (e.g., splitting or crushing adult tablets) to overcome this barrier and to appropriately treat sick children (3). These adaptations can be done by pharmacists (compounding) or at the point of use by nurses or parents (manipulation). Although compounded and manipulated medicines serve an important unmet medical need for the paediatric population, they cannot be viewed as equivalent to commercial forms (4). When compared to manufacturing standards (Good Manufacturing Practices) required by regulatory agencies for commercial products, compounding/manipulation has multiple inherent limitations (Table 1) which can translate into sub-optimal adherence due to bad taste, exposure to unsafe ingredients, under dosing with therapeutic failure, or overdosing with unintended adverse events (5-7).Furthermore, the lack of bioavailability data for most compounded/manipulated medicines administered to children is rarely known to prescribers despite the fact that these manipulations can interfere with the integrity of the active

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pharmaceutical ingredient (API) and affect systemic drug exposure with therapeutic consequences. The potential impact of manipulation on drug bioavailability is well illustrated by a cross-over trial evaluating the pharmacokinetics of lopinavir/ritonavir tablets (Kaletra®) in human immunodeficiency virus (HIV)-infected children (8). This study showed a significantly reduced and highly variable lopinavir and ritonavir exposure with crushed tablets (mixed with pudding) compared with whole tablets (mean 40% decrease in area under the curve for both compounded medicines, ranging from 5 to 75% reduction, compared to whole tablets). Finally, physicians rarely consider a formulation issue as a potential cause for inefficacy or occurrence of an adverse event, as they are most of the time unaware whether or not the medicine they are prescribing is compounded. Furthermore, there are no universal standards for extemporaneous compounding or manipulation (3). All these deficiencies reinforce the need for suitable paediatric formulations to ensure the delivery of the intended dose, children's compliance to treatment and safe and effective pharmacotherapy in this population.

Over the last two decades, regulations and incentives have been implemented by the United States (US) (the Best Pharmaceutical for Children Act (BPCA) (2002) and the Pediatric Research Equity Act (PREA)(2003), both of which were permanently re-authorised under Title V of the 2012 Food and Drug Administration (FDA) Safety and Innovation Act (FDASIA)), and the European Union (EU) (EU Paediatric Regulation; EC No. 1901/2006). These initiatives aim to fill these gaps by promoting the development of paediatric medicines and age-appropriate formulations, recognizing the unique nature of children in many physiological processes as well as their limited capabilities in taking adult medicines. In order to raise awareness and accelerate action to meet the need for improved availability and access to child-specific medicines, in December 2007 the World Health Organization (WHO) launched its initiative "Make Medicines Child Size"(9). In parallel, a number of initiatives have been

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deployed to specifically ensure children have access to optimal formulations, including the BPCA Pediatric Formulation Initiative (2005)(10), the European Paediatric Formulation Initiative (EuPFI) (2007)(11), and the Global Accelerator for Paediatric Formulations (GAP-f)(2016)(12), all with the goal to connect formulation scientists, researchers, academia, pharmaceutical industry, and regulators to facilitate and expedite the development of age-appropriate paediatric formulations. As an example, the Safety and Toxicity of Excipients for Paediatrics (STEP) database is the product of a collaboration between the EU and US paediatric formulations initiatives launched in 2014, recognizing that when available, the data were often scattered, and that screening and careful selection of excipients is a critical step in paediatric formulation development (13, 14).

For a long time, liquid formulations were viewed by many as the "holy grail" for paediatric oral medicines, especially for the young ones (15). Since around 2008, there has been a paradigm shift led by the WHO and the European Medicines Agency (EMA), with experts in the field stating that flexible SODFs (e.g., multiparticulates, including minitablets, orodispersible tablets, soluble tablets) were likely to prove most suitable for children, although indicating the need for further research to determine their acceptability in different age groups from clinical and safety perspectives (16, 17). The WHO defined a flexible dosage form as one that can be administered in more than one manner, for example, dispersed in water or breast milk or taken orally as a whole (18).

The challenges of developing paediatric formulations have been described (19). This review focuses on the progress that has been achieved over the past years regarding the development and access of oral paediatric formulations with a threefold aim: 1) to summarize the evidence supporting acceptability and dosing flexibility of liquid and SODFs in the paediatric

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population, 2) to describe the clinical needs for oral formulations for existing authorised medicines, and 3) to discuss access to paediatric oral formulations. The overall goal of this paper is to identify elements at different points of the roadmap of paediatric formulations development and access that can be standardised, aligned, and shared across jurisdictions and countries to better serve children's needs. Age-appropriate paediatric formulations for routes of administration other than the oral route (intravenous, intramuscular, topical, rectal etc.) are beyond the scope of this review.

Paediatric oral dosage forms: where do we stand?

There is no ideal paediatric formulation and there is no single formulation that can address the needs across all age groups from birth to adulthood. This is well highlighted by two comprehensive reviews of commercially available paediatric formulations (20, 21). Overall, 138 commercially available paediatric formulations were identified for 107 medicines, with 21 different formulation types (Figure 1). A holistic approach taking into account both formulation-related factors alongside those of the intended population and therapeutic indication is needed to pharmaceutical drug product design in paediatrics (22, 23) .

The sought-after attributes of a paediatric oral formulation are listed in Table 2 (16, 24). Acceptability is defined as the overall ability and willingness of the patient to use and its caregiver to administer the medicine as intended (17). Both acceptability, including palatability, along with the ease for the caregiver to administer the medicine, contribute to whether or not the child will ultimately take the medicine (15). Dosing flexibility is also a critical aspect to consider as unit per weight directed dosing (e.g., mcg/kg or mg/kg) is the most commonly used approach in paediatric pharmacotherapy, and that weight can easily vary 140-fold (from a 500 g premature neonate to a 70 kg adolescent). Guaranteeing that dosing

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requirements of a specific medicine are met at all age and developmental stages for which the medicine is intended is pivotal.

Evidence for acceptability of liquid and SODFs in children is summarized below, although recognizing that there is a lack of standardisation in the available literature regarding study design as well as assessment methods used to evaluate acceptability of medicines in children (25). Clearly defined international criteria to determine whether or not a formulation is acceptable for children are unavailable. Manufacturing technologies and technical processes behind oral drug delivery platforms have been recently reviewed (26, 27) and will not be addressed in this paper.

Liquid oral dosage forms

From the child's perspective (i.e. what he/she will actually take), liquid formulations include ready-to-use liquids, liquid forms requiring some compounding or manipulation, and solid forms reconstituted into liquid forms. The latter reconstitution can be performed by pharmacists at dispensing (e.g., amoxicillin powder for oral suspension, Amoxil®) or by caregivers at the time of administration (e.g., tacrolimus granules for oral suspension (Modigraf®)). Altogether, liquids presented to children represent 60% (83/138) of formulations identified as suitable for paediatric use by two comprehensive reviews (20, 21), highlighting that oral medicines are still administered most frequently as liquids in children.

Liquid formulations stand out from solid forms by their excellent dosing flexibility, which best supports the unit per weight directed dosing often required in the younger ones. There is often minimal or no need for manipulation for the caregiver which makes liquid formulations attractive from an end-user perspective. They are also best suited for enteral tube

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administration. However, to ensure dosing accuracy and acceptability, special attention should be paid to final concentration(s) of liquids formulations to prevent instances where one would need to administer very large volumes (risk of underdosing if refusal to take) or very small ones (e.g. < 0.1 mL) (risk of over/underdosing). The maximum recommended single dosing volume proposed in a EMA draft guideline in 2011 was 5 mL for children aged below 4 years, and 10 mL for children aged between 4 and 12 years (28). As for the minimum recommended volume, there is no clear guidance but it depends on the accuracy of measuring devices, and factors such as dead space during administration (17). During a workshop organised by the EuPFI in 2018, many challenges associated with the correct oral dosing of small liquid volumes were identified along with potential solutions. (29).

For some medicines such as bitter-tasting medicines, one major drawback of liquid formulations is their inability to achieve an acceptable taste, limiting their acceptability in children. An unpleasant taste can affect the ease of administration and influence compliance, and as a consequence effectiveness (30). In addition, compared to solid forms, liquid formulations can be challenging in terms of stability with shorter shelf-life, refrigeration needs, and transportation complexity (weight and bulk). Moreover, liquids formulations are not suited for controlled release and some of their excipients (e.g., propylene glycol or ethanol) may be inappropriate for paediatric use, especially in neonates, with the potential for adverse effects (31). On the other hand, liquid formulations can be much cheaper than solid formulations, particularly dosage forms that need specialised manufacturing processes such as SODFs.

Taking into consideration their advantages and disadvantages, liquid formulations remain an acceptable option to treat paediatric conditions from birth until school-age, and many medicines can be successfully developed as child-friendly products using this approach.

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However, liquid formulations do fall short in a number of instances and their limitations outlined above have become a driving force for stakeholders to invest in the development of flexible SODFs for paediatric use.

Solid oral dosage forms

In recent years, there have been tremendous efforts to derive scientific data on the acceptability of SODFs in young children. To capture important and critical aspects of the current knowledge of this topic, a bibliographic search was conducted on PubMed (from inception to March 5, 2021) using the following key words in different combinations: "paediatric formulation", "pediatric formulation", "children", "acceptability", "minitablet", "granules", "pellets", "multiparticulates", "sprinkles", "orodispersible film", "orodispersible tablet", "orally disintegrating tablet", "chewable tablet", "dispersible tablet", "tablet", "scored tablet", and "capsule". In addition, the reference lists of full-text reviewed studies, systematic reviews (25, 32) and review articles (26, 27, 33) were hand-searched for potential citations. A total of 36 studies were reviewed and summarized in Tables 3, 4, 5, 6, 7 and 8 and are discussed in more details below. The unsystematic approach used in this review is a limitation.

Multiparticulates

Multiparticulates are small solid multiple-unit dosage forms including granules, pellets, beads, and minitablets, typically below 4 mm in diameter, with one dose made up of multiple particles (Figure 2). When a defined quantity of multiparticulates is intended to be given as a single dose, the multiparticulates are usually presented in capsules, sachets, or stick packs (unit-dose package). Alternatively, multiparticulates can be presented in a bottle or other container that contains multiple doses. Depending on the properties of the formulation, multiparticulates can be placed directly in the mouth or mixed with soft foods and beverages (34). The suitability of

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multiparticulates for taste-masking and controlled release with film-coating technologies for example (35) can translate into potential clinical benefits compared to liquid forms. Multiparticulates can be mixed with liquids or food (i.e. suspended in liquids or food) but are not intended to be dissolved in liquid (that is multiparticulates should not lose their form in liquid) for administration as this may affect palatability and pharmacokinetic profile profile. Minitablets made by compression or moulding of ingredients may also be considered as multiparticulates, but because of the extensive interest in minitablets, they are discussed separately.

Evidence supporting acceptability of multiparticulates in children is summarized in Table 3 (36-45). Although interest for multiparticulates has been increasing over the last decade, this pharmaceutical form is not new to the care of children, with the first study reporting on its use in the paediatric population dating back in the early 1990 (43). Since then, studies have involved outpatient children as young as 3 months of age receiving medicine-containing multiparticulates for conditions such as hypercholesterolemia (37), iron-deficiency anaemia (treatment or prophylaxis) (38-40), HIV (41), cystic fibrosis (42), and epilepsy (43-45). The duration of the studies ranged between 7 days up to 48 weeks. Acceptability defined as "preference", palatability, and/or ease of administration was assessed using questionnaires administered to caregivers and/or children (25).

Seven studies involving 1428 children, aged 3 months and over compared medicine-containing multiparticulates with a liquid form. Five of them showed a better acceptability of granules or "sprinkles" over syrup (43), solution (44, 45), and oral drops (39, 46), with a good safety profile (Table 3). In one study performed in HIV-infected children recruited from two clinics in Uganda (CHAPAS-2 trial), lopinavir/ritonavir pellets were compared to syrup and tablets after

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12 and 48 weeks (41, 47). For children less than 4 years, pellets were more acceptable than syrup at week 12 but not at week 48. Among caregivers preferring syrup despite its known unpleasant taste and need for refrigeration, key issues with pellets were their bitter taste, problems with masking this taste with food and food refusal, needing to sweeten food with sugar and honey (which is expensive), and concerns about not giving the whole dose. For children 4 years and above, tablets were more acceptable than pellets throughout the study, mainly because of the bitter taste of the pellets.

One study compared the acceptability of coated and uncoated placebo multiparticulates of different sizes in healthy children and adults (36). This trial concluded that multiparticulates could be used as a suitable formulation platform for the administration of medicines to children aged 4 years and above as well as adults, although palatability appeared as a potential barrier to patient acceptability due to gritty mouthfeel. Moreover, if these multiparticulates would have been administered in viscous and flavoursome vehicle such as apple sauce or yogurt, instead of water, palatability and ease of swallowing of particulates might have been improved and hence acceptability.

Data supporting the capacity of children less than 6 months of age as well as that of sick hospitalised children to take multiparticulates are scarce and warrant further investigation. Also, as multiparticulates are usually administered with soft foods and beverages, there is a need for compatibility studies using these various food vehicles, which can be challenging (34).

Dosing flexibility of multiparticulates can be achieved with success with the commercialisation of multiple strengths of unit-dose package, by rounding up dosing to the nearest strength available, or by prescribing according to weight-band dosing tables (48) instead of unit per

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weight dosing (e.g., mg/kg) if clinically appropriate and safe. For one dosing, the use of multiple sachets of the same strength or multiple sachets of different strengths may be required. The hydrocortisone granules (Alkindi ®) recently commercialised are available in 4 different strengths (0.5, 1, 2, and 5 mg granules in capsules for opening) to fulfil dosing requirements for replacement therapy for adrenal insufficiency from birth to <18 years of age (49). The VPA modified-release granules (Epilim Chronosphere MR®) are available in the United Kingdom in 6 different strengths (50, 100, 250, 500, 750, and 1000 mg sachet) to meet dosing requirements in epileptic children and adults (50).

The commercial availability of multiparticulates for use in children has been increasing over the last decade (Figure 1)(20, 21) and should continue to do so. As of mid-2018, there were at least 20 medicines marketed as multiparticulates for paediatric use. Since 2019, additional medicines have been approved as oral pellets for children, and in one instance in infants as young as 3 months of age (sofosbuvir (Sovaldi®)(51), ledipasvir and sofosbuvir (Harvoni®)(52), sofosbuvir and velpatasvir (Epclusa®)(53) and dabigatran etexilate (Pradaxa®)(48), cysteamine bitartrate oral granules (Procysbi®)(54), sprinkle powder in capsules or sachet (Peanut (Arachis hypogaea) Allergen Powder-dnfp (Palforzia™)(55), and odevixibat (Bylvay®) (56).

At present, the number of strengths and the number of sachets that is safe and practical to use for one single dose, without increasing the risk of dosing errors, remains to be determined. Gathering real world evidence from patients, caregivers, and health care professionals with experience with multiparticulates could provide a great deal of information regarding their acceptability and ease of administration in the paediatric population. This could also assist in

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knowledge transfer to end-users in order to transition to an era where both liquid and SODFs are viewed as safe and acceptable therapeutic options.

Minitablets

Minitablets have been proposed as a novel method of oral medicine delivery in children and are considered by some as the future of paediatric oral formulations (21). They are compressed tablets typically ranging between 1 to 3 mm in diameter (34, 57), although there are no strict regulatory guidelines that define minitablets (21, 58, 59) (Figure 2). They provide some advantages over liquid forms with regard to medicine stability, storage conditions, taste-masking, and controlled release capacity (26, 60). Although their manufacturing costs are usually low with the well-established tableting technology used to produce them, their packaging might be quite costly.

To date, seven prospective studies evaluated the acceptability and safety of placebo minitablets (2 to 4 mm in size) in the paediatric population (60-66) and one study investigated the palatability of medicine-containing minitablets in cystic fibrosis children (Pancrease MT, McNeil Consumer Health care, Ft Washington, PA)(67) (Table 4). A total of 1213 children aged between 2 days and 6 years, including 151 neonates, participated in these studies. Five trials dealt with the administration of a single minitablet either once (61-63, 66) or twice for one day (64) while three studies evaluated the acceptability of multiple minitablets per dosing (60, 65, 67).

As shown in Table 4, the definition of acceptability for minitablets in the four German studies performed by the same group of investigators was an aggregate of "everything swallowed without chewing" and "chewing with most of the tablet pieces swallowed" for children between

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6 months and 6 years of age (60, 62, 63) with a slight variation for their neonatal trial (66). Similar criteria were used by Kluk et al. while Thomson et al. defined acceptability as swallowing minitablet whole without chewing. With the available data, one can conclude that one medicine-free minitablet can be safely administered to term neonates, with an excellent and comparable acceptability to that of glucose syrup (66). In children from 6 months to 5 years of age, minitablets appear more acceptable and swallowable than glucose syrup (60), suspension, liquid and powder (64) with a good safety profile. The current evidence suggests that children 6 months of age and older are capable of taking multiple medicine-free minitablets in one dosing without choking or any adverse events (60, 67). Two studies collected parental views. In the study by Thomson et al, many parents stated a preference towards liquids while others commented that orally administered liquids were problematic, welcoming novel paediatric dosage forms, such as minitablets (61). In the study by van Riet-Nales (64), parents and children preferred the minitablet and syrup over the suspension, and the suspension over the powder (all p values < 0.05).

Although significant progress has been achieved regarding the acceptability of minitablets which should be applauded, there are gaps that need to be addressed. The handling of minitablets in children aged between one to six months is yet to be demonstrated. As the longest study was five days in duration, the long-term acceptability of repeated administration of one or multiple minitablets in children remains to be explored. For ethical reasons, only medicine-free minitablets were investigated, with the exception of the study involving pancrealipase. As a consequence, the capacity of minitablet to ensure palatability in children could not be appropriately tested nor the impact of the form on drug bioavailability. In five studies, chewing of minitablets prior to swallowing followed by partial or complete deglutition was considered acceptable, while this may be of concern in some situations. If a minitablet contains a bitter

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API, chewing can result in bad taste, with potential difficulties in administrating subsequent doses to the child. If a minitablet is designed for sustained release or is enterically coated, chewing will alter the pharmacokinetics and ultimately drug efficacy and safety. Even though underlying diagnoses and severity of illness were not specified in any study, enrolled children appeared relatively well, as indicated by some authors (63) and suggested by the fact that a certain number were outpatients, preventing any conclusion regarding the capacity of more severely ill children to handle minitablets. Furthermore, the generalisability of these results is limited to the studied populations which excluded children with known impairment of swallowing, either as part of a chronic illness (e.g., cerebral palsy) or as part of acute illness (e.g., gastroenteritis or respiratory tract infection, and those who had recently undergone surgical intervention) (62, 63).

Minitablets are often viewed as offering great dosing flexibility (26) but this deserves further thought. As the maximal amount of API that can be loaded on a minitablet is very small (≤ 2.0-2.5 mg of active medicine for a 2 mm minitablet) (57), the administration of several minitablets at a time must be considered if they are intended as a dose-adjustable formulation. The oral delivery of multiple minitablets per dosing can be achieved by packaging them in fixed dose strength sachet as for granules and pellets, with similar limitations regarding dosing flexibility. Another option is to rely on manual counting of minitablets by the caregiver, with the risk of counting errors and thus dosing errors (34). Devices to count minitablets are under development. Currently, the number of minitablets a caregiver could manually count safely is unknown. Given that a typical dose is provided by a small number of minitablets, miscounting is likely lead to significant dosing errors. In addition, the use of more than one minitablet strength per dosing may pose a risk. The results of the LENA trial (Labeling of Enalapril from Neonates to Adolescents) will bring some light on the feasibility and safety of such approach

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as enalapril orodispersible minitablets of two strengths (0.25 and 1.0 mg) are being studied (68). Interestingly, for the initial titration doses in very small children (2.5 to 7 kg), the research protocol has planned that minitablets may be dispersed in water to allow administration of smaller doses. If it had not been for its orodispersible design, such smaller doses could not have been possible, highlighting potential dosing rigidity for non-orodispersible minitablets when used in the youngest ones. To further complicate the matter, the method of administration of orodispersible minitablets, swallowed or dispersed, can affect bioavailablity, as shown for enalapril in healthy adults (69).

According to a recent review focusing on the US, European and Japanese markets, there was only one commercially available minitablet formulation for use in children as of mid-2018 (21) (Figure 1), levetiracetam minitablets (Desitrend®) indicated for children > 6 years. They are 2 mm in diameter with 5 mg levetiracetam per minitablet dispensed in fixed doses sachets of 250, 500, 750 and 1000 mg (70): (70): counting is not possible with this number of minitablets. For children under 6 years of age, the manufacturer recommends the use of commercial levetiracetam oral solution. The authors are aware of at least one other medicine now available as minitablets for paediatric use, namely melatonin 1 and 5 mg prolonged-release 3 mm minitablets (Slenyto®) in pink and yellow color, respectively (71). They are indicated for the treatment of insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome. The two strengths cover well the dosing requirements as the dose range is from 2 to 10 mg once a day, with a maximum of five minitablets per dosing (the 9 mg dose, 4 minitablets of 1 mg and one of 5 mg). Both strengths need to be used for four doses (6, 7, 8, and 9 mg). Of significance, the use of one minitablet per dose may not always be feasible as ensuring content uniformity for single minitablets may be challenging (34), thus affecting dosing delivery.

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Minitablets are a promising formulation platform for paediatric use, and as we start using them in the clinical setting, we should gain more insights into which medicine, patient, and disease characteristics they are best suited for, recognizing their shortcomings. Steroids, including prednisone, prednisolone, and dexamethasone, would be ideal candidates to consider for the minitablet technology as drug load is small, taste-masking is required, and dosing flexibility could be achieved with less than 10 minitablets of two different strengths (1 and 5 mg minitablets) for children under 6 years of age. From a paediatrician point of view, their administration are too often challenging as the available liquid formulations taste terrible (described as "metallic taste", most notably for prednisone), some formulations contain unsuitable excipients (ethanol), and their concentrations are such that large volumes are required for older children. Developing palatable steroid minitablets would address an unmet need for medicines that are frequently used in the paediatric population, both for common conditions such as asthma and laryngitis, and more complex ones such as organ transplantation and oncologic diseases.

Orodispersible films

Orodispersible films (ODFs) are postage stamp-like strips of thin polymeric films formulated to disintegrate or dissolve almost instantaneously when placed onto the tongue or cheek pouch, eliminating the need for water and swallowing (Figure 2). They are also referred to as oral soluble film and orally disintegrating film. They are packaged either in single-dose sachets or contained in multi-dose packs (72). Caution is required when manipulating ODFs as they can be easily damaged. They are also very sensitive to humidity (73). The amount of medicine that can be loaded is limited, typically < 60-70 mg (74). Taste-masking can be challenging and controlled release is not feasible. ODFs may be of particular interest for those with swallowing difficulties.

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The first study that evaluated the acceptability of ODFs in the paediatric population dates back to 2011 when vitamin D in a thin, rapidly adhering and dissolving strip given to healthy newborns was shown to be preferred by parents over vitamin D syrup with better adherence (75) (Table 5). However, concentrated liquid vitamin D preparations were not available at the time of the trial and as such no conclusion can be drawn regarding parental preference between the film and these concentrated preparations. The second study was published in 2017 and referred to as the STAMP study (Study into Thin orodispersible film Acceptability as Medicine for Preschool children) where placebo ODFs were investigated in infants and pre-school children (76). Approximately half of the patients were recruited from the outpatient department and half from the emergency department, representing both stable and acutely ill children, respectively (no specific diagnosis reported). One pre-administration questionnaire (caregiver) and three post-administration questionnaires (for children ≥ 3 years old, caregiver, and research nurse, respectively) were used to capture end-user perceptions. Overall, this study showed high degree of acceptability of ODF among young children, regardless of whether the assessment was made by the child, the caregiver or the nurse (Table 5). In children ≥ 3 years old, 72% reported a willingness to take ODF again. Issues regarding color, taste and shapes were raised. Some caregivers suggested elongated shapes for the ease of administration. The validity of the 5-item medication acceptance scale (MAS) used by caregivers and nurses to rate ODFs acceptability in children in this study can be questioned as it was designed and validated to assess acceptance of paediatric oral liquid medicines (77). In addition, the investigators arbitrarily chose a total score of 5 and above (over a maximum score of 10) to define acceptability, as the original description of MAS did not specify a threshold value for the definition of medicines acceptability. More recently, a non-inferiority trial performed in neonates and infants, both in- and outpatients, showed that the acceptability and swallowability of one placebo ODF were superior to that of glucose syrup (78). However, about one-third of

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the children under the age of 6 months did not chew the ODF but left a part sticking to the mother's breast or bottle; this may be a limitation for use of ODT in this age group. Palatability was also measured and considered by the authors in favor of ODF but as both ODF and glucose syrup were medicine-free, this result is of limited significance. The safety of ODF was reported in two of the three studies for a total of 193 patients, including neonates; there was no choking event (75, 78).

Dosing flexibility for ODFs is reported by many as being excellent or increased (26, 27, 79), although this remains a concept with no clinical proof thus far. The feasibility of achieving the desired dose by cutting films of the required size (for example, cutting at appropriate length using a tape-like supply) (72, 80) has never been demonstrated in real-life and comes with the risk of dosing errors. Furthermore, how the packaging allows for such manipulation and how damaging ODFs in the process can be prevented are still unclear.

As of 2018, ondansetron ODF (4 and 8 mg) was the first and only prescription film that has reached the market in the US, Europe, and Japan for paediatric use (prevention of nausea and vomiting associated with chemotherapy in children 4 to 18 years of age) (Figure 1) (21). Of concern, it was approved in 2010 in the US, but is no longer marketed. Manufacturing issues and poor revenue have been raised as potential factors behind market discontinuation of ODF products (81).

Orodispersible tablets

Orodispersible tablets (ODT), also known as orally disintegrating tablets, are solid oral forms containing API which disintegrates rapidly, usually within a matter of seconds (30 seconds or less), in saliva without the need for chewing, swallowing or drinking liquids to ingest the

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product (82). It may be taken by other means than intended on the label, with caregivers dispersing the ODT in a liquid prior to giving it to the child. As with liquid formulations, taste masking is challenging.

A total of 312 children aged between 2 and 15 years have completed three studies evaluating the acceptability of ODTs in children (Table 6) (83-85). One involved a single placebo ODT (83) and two tested medicine-containing ODTs, following a single dose of ondansetron ODT administered to children undergoing adenotonsillectomy (85) and after a 3 weeks administration of an oral lyophilisate formulation of desmopressin (MELT) in children with primary nocturnal enuresis (84). Acceptability was measured by observation and/or questionnaires administered to research staff, caregivers, and/or patients. Overall, acceptability of ODT was found to be good and no safety issues related to the pharmaceutical form was raised, although the number of patients studied remains small.

The dosing flexibility of ODT is limited by the available dosing strengths, along with the fragility of ODT formulations which usually contraindicates tablet splitting (81). Some had suggested that the use of orally dispersible minitablets, as developed for the LENA trial (68), could potentially attenuate these shortcomings by administrating multiple orodipersible minitablets per dosing to achieve dosing flexibility (26). However, dispensing the right amount of orodispersible minitablets to fulfill dosing requirements across age groups will remain as challenging as for minitablets, and the taste-masking advantage of minitablets will be lost, which could be a significant disadvantage for some medications.

As of today, the number of commercialised ODTs for paediatric use remains small, with fixed dosing for short-term use and usually for children of at least 4 years of age (20, 21) (Figure 1).

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More research is needed to evaluate the acceptability and safety of ODTs in children less than 2 years of age along with the long-term acceptability of medicine-containing ODTs in children.

Chewable tablets

Chewable tablets are intended to be chewed and then swallowed rather than swallowed whole (Figure 2). In many countries, they are available as over-the-counter and prescription medicines. The advantages of chewable tablets include stability, precise dosing, portability, and ease of delivery.

In 2002, there were already more than 60 chewable tablet formulations approved for paediatric use in the United States, encompassing mostly vitamins/dietary supplements (n=40) along with some medicines from other therapeutic classes (analgesic/cold preparations (n=16), anti-infectives (n=6), anticonvulsants (n=2), antacids (n=3), and anti-asthmatics (n=1)) (86). At that time, a review was conducted to investigate the safety of this pharmaceutical form in young children by retrieving the literature on choking. The available evidence suggested that chewable tablets were safe and well-tolerated in children 2 years of age and older, with aspiration injuries being extremely rare (86). Two case reports specifically related to chewable tablet formulations were identified, involving four children who aspirated chewable "baby aspirin", three of whom were aged less two years (9-month, 13-month, and 22-month-old) (87, 88). Two died and two suffered severe neurological deficits following successful resuscitation efforts.

More recently, the acceptability and safety of a single dose of mebendazole chewable tablet was assessed by three studies involving a total of 1067 children aged between 1 to 16 years (Table 7) (89-91). Overall, most children chewed the tablets before swallowing with few

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needing the tablet to be dispersed in water before swallowing. There were no serious adverse events reported, with one study clearly stating no instances of choking or vomiting (90). Unfortunately, none of these studies reported on the size of the tablets tested, even though in one trial the size of the chewable tablet was considered "too big" by some children (91). Further studies are needed to better define what is the acceptable and safe size range for chewable tablets and what is the youngest age at which they can be safely administered. As for dosing flexibility, this pharmaceutical form is somehow limited and may require multiple strengths to meet the clinical needs, depending on the medicine.

Dispersible tablets

Dispersible tablets, also referred to as soluble tablets, are uncoated tablets or film-coated tablets intended to be dispersed in water before administration (Figure 2), as opposed to orodispersible tablets that are intended to be placed in the mouth where they quickly disintegrate in contact with saliva. Dispersible tablets have some advantages over liquid formulations, most notably for use in developing countries. For example, dispersible tablets have a longer shelf-life, and are easier to distribute and store, less costly to produce, and easier for the caregiver to handle and keep track of the number of days given (92). They are also suitable for fixed-dose combination products, which is appealing for conditions such as tuberculosis or HIV (93). However, they do share one common drawback with liquid forms, namely their limited capacity for taste-masking with resulting palatability issues. Also, they require access to drinkable water, which can be of concern in some regions of the world.

Three studies have evaluated the acceptability of fixed-dose medicine-containing dispersible tablets for the treatment of malaria (94) and acute diarrhea (92, 95) in 897 children aged between 0 and 5 years living in developing countries (Table 7). Caregivers' opinion was

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obtained through questionnaire or follow-up interviews. A significant proportion of them reported that dispersible tablets were equally, or more, acceptable to their children than other formulations. Dispersible tablets appear to be most suitable for medicines for which the requirement of dosing flexibility is such than one or two strengths can provide the correct age-related dose over a wide age range. The development of scored dispersible tablet is a mean to increase the dosing flexibility of this form (e.g., ZinCfant®).

Conventional tablets, capsules, and scored tablets

Conventional tablets refer to individual SODFs that provide all of a single dose, generally designed for adults with variable shapes and sizes, usually ranging from 5 mm up to 22 mm in length (96) (Figure 2). They are easy to store and transport, with low manufacturing costs and simple packaging (30). However, their use in children is limited by three important considerations, namely whether or not children can take them safely without risk of choking or aspiration, whether an accurate dose can be delivered, and whether children will be willing to attempt to swallow them,

The age at which children can safely take tablets, or capsules, has been a matter of great debate for years. The perceived cut-off age at which young children are capable of swallowing conventional adult tablets is between 6 and 8 years. Such belief is supported by evidence-based data, with children 6 years of age and older capable of taking medium-sized tablets (5-9 mm) (Table 8) (97). Though it is worth mentioning that being capable of taking adult size tablet does not equal willingness to do so; as such, there are some children older than 6 years who still prefer to take liquids. The use of tablets of 5-10 mm with appropriate shape was proposed as being acceptable for children 6 of age and older by a EMA draft guideline in 2011 (28). As described below, this age threshold is a moving target and could well be lowered in coming

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years as evidence accumulates for acceptability of conventional tablets/capsules in younger children (Table 8)(97-101).

In a retrospective study evaluating the age at which 92 HIV-infected children converted from liquid formulations to solid formulations for five antiretroviral medicines (size of solid forms not specified), the overall age at conversion was 7.3 years (95%CI ranging from 6.3 to 8.2), with children as young as 3 years of age switching to solid forms for stavudine (102). In another trial involving HIV-infected children, most children were capable of switching from syrup to scored adult-dose tablets of combination antiretroviral medicines at about 3 years (103). Furthermore, there is accumulating evidence that some children aged 2 to 5 years can swallow tablets, and even capsules (98-100, 104) (Table 8). More recently, Bracken et al. have shown that tablets of 6 to 10 mm in size are potentially acceptable formulation for children aged 4 to 12 years. Most children aged 4 to 8 years who attempted to swallow tablets successfully did so (Table 8) (101). Another observation was that the younger children who successfully swallowed the 6 mm tablets were able to succeed in swallowing the 8 and 10 mm tablets, suggesting a learning effect. One limitation of this study is the small sample size of each age subset in the younger age group, with 5, 2 and 9 patients for the 4-, 5-, and 6-year-old groups, respectively.

Dosing flexibility is often difficult to achieve with tablets as the vast majority are designed to meet adult needs and the available strength(s) are not adapted for paediatric dosing in the young ones. Splitting or crushing tablets are most often contraindicated as neither the integrity of the API nor dosing accuracy and pharmacokinetics can be guaranteed. Such pitfalls can be partly addressed by the development of scored tablets. Examples of medicines commercialised for

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use in children as scored tablets include clobazam (Onfi®), hydroxyurea (Siklos®), rufinamide (Banzel®) and more recently nifurtimox (Lampit®) (21, 105).

Children's and parent's preferences over different dosage forms are of utmost importance. These were evaluated through age-adapted questionnaires, without children and adolescents required to swallow them (106, 107). Perceived preferences primarily differed based on age, health status, and prior experience. In one recent survey, the most selected dosage forms were conventional ones, i.e. liquid (35%), tablets (19%), and capsules (14%). Monolithic solid forms were mostly chosen by adolescents and children with chronic disease taking medicines frequently, while liquid was widely selected by children less than 12 years. As for multiparticulates (granules), they were not appreciated, particularly by adolescents. Finally, there was a clear lack of familiarity with more novel dosage forms (e.g., orodispersible films and granules) (107). These results stress the need to actively involve children and parents in the development of formulations at an early stage as well as educate them regarding SODFs to have their buy-in to use them.

In summary, a range of SODFs has been developed. Widespread use of these dosage forms will improve paediatric health care. Development of and access to these technologies could be enhanced by a globalized approach with standardisation of many areas involved in the medicine life cycle. These are further discussed below.

Paediatric formulation needs for existing authorised medicines

Although numerous efforts have been devoted to identify and prioritize paediatric needs for existing authorised medicines, there is no common priority list dedicated to paediatric formulations at the international level and shared by BPCA, EMA, and WHO.

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Since 2003, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICDH), under the 2002 BPCA legislation, has developed and prioritised a list of off-patent medicines updated regularly for which paediatric studies were most urgently needed. The 2020 BPCA priority list includes 16 medicines and two therapeutic classes, adolescent pharmacology and antiretrovirals, in need for age-appropriate formulations (Appendix 1) (108). All 16 medicines have been on the BPCA priority list at least since 2014.

During the same time period, EMA published an inventory of needs for paediatric medicines and child-friendly formulations, building on an earlier exercise to establish paediatric needs carried out by the former Paediatric Working Party between 2001 and 2007. The main objective of this list is to help medicinal-product developers identify opportunities. It also assists the EMA Paediatric Committee (PDCO) in their decisions and provides information to health care professionals and patients. Since 2005, lists have been published for 16 therapeutic classes, with most lists (N=13) adopted between 2005 and 2008 (109-129). Lists of only six classes have been updated since. A total of 192 medicines have been reported as requiring child-friendly formulations for oral administration (Appendix 1). The last revised priority list for studies on off-patent paediatric medicinal products adopted by the PDCO in 2013 identified 21 medicines in need of an age-appropriate oral formulations (130).

As for the WHO, the 2019 list of essential medicines for children (131) included 149 medicines for oral administration along with available formulation(s) for each medicine. A recent study has shown that around 50 % of the oral dosage forms were listed as authorised age-appropriate medicines by EMA and/or FDA (132), leaving at least half of the WHO essential medicines list for children in need of suitable oral formulations (Appendix 1).

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Altogether these lists add up to a significant number of needed paediatric formulations (N=239) with some overlap, although this figure is not exact as commercial availability is constantly changing and some of these lists were not updated recently. For example, paediatric oral solutions have been approved by FDA for 6-mercaptopurine in 2014 (Purixan®) (133), methotrexate in 2017 (Xatmep®)(134), baclofen (Ozobax®) in 2019 (135) and for levothyroxine in 2016 (Tisorint-sol®) (136) and 2021 (Thyquidity®) (137). Hydroxyurea (Siklos®), available in 2 strengths (including a triple-scored tablet for dosing flexibility), has also been approved for use in children 2 years of age or older in 2017 in the US (138) and more recently in Europe as 100 mg/mL oral solution (Xromi®) (139). It should be noted that sildenafil oral powder for suspension (Revatio®) is available in the US (140) but not approved for use in children despite approval for paediatric use in Europe (140). Two antiparasitic medicines, benznidazole and nifurtimox (Lampit®), that were not previously available for oral administration and which also appear on the WHO list of essential medicines, are now available as tablets approved for use in children (105, 141).

Access to paediatric formulations: how can we move forward?

Access has many dimensions. At the present time, it is extremely difficult to determine how many children benefit from suitable paediatric formulations. However, available data highlight that their access is fragmented and unequal. A recent study demonstrated that almost 50 % (n=28) of medicines frequently compounded at a tertiary Canadian paediatric hospital had suitable commercialised paediatric formulations either in the US and/or Europe (142). Among the top ten compounded medicines listed in 208 Japanese hospitals, the authors of this review identified that 60 % were commercially available outside of Japan (143). A similar trend exists regarding access of paediatric formulations which were granted a paediatric-use marketing authorisation (PUMA) by EMA.

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PUMA was established by Article 30 of the Paediatric Regulation in 2007 to stimulate research into existing approved medicines no longer covered by patents, and to help transform known paediatric off-label use into authorised use supported by evidence for safety and efficacy. It offers 10 years of data protection, including eight years of data exclusivity and two years of market protection. In 2014, to further stimulate industry interest, EMA clarified that a paediatric investigation plan (PIP) for a PUMA "does not have to necessarily address all age groups" (144).

To date, only six PUMAs have been authorised since 2007 (Table 9), with a median time between PIP initial submission and EMA approval of 46 months (ranging from 33 to 89 months). As shown in Table 9, most of these child-friendly formulations are not available yet in the US, Canada, Japan, and Australia, and may never be if not submitted by manufacturers. For those PUMA that were granted a market authorisation, it took up to 9 years after EMA approval for a medicine to be marketed in other jurisdictions. Only Hemangiol®/Hemangeol® is now approved in all five jurisdictions considered for this review. At this point, it seems unlikely that Sialanar®, a glycopyrrolate oral solution approved by EMA in 2016 for use in children 3 to 18 years of age, will be submitted in the US or Canada as Cuvposa®, another glycopyrrolate oral solution for paediatric use, has been approved in these countries since 2010 and 2017, respectively (Table 10). This case raises at least two questions. What can be done to facilitate moving products between jurisdictions? When is developing a similar product appropriate? More than one similar formulation may be unnecessary duplication or may allow resilience to problems in the supply chain.

During a consultation with manufacturers and regulators across Europe conducted by the European Commission 10 years after the Paediatric Regulation took effect, respondents

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concluded that PUMA was a disappointment. They pointed out that there is no guaranteed access to the market, which in fact depends on many non-regulatory factors such as inclusion of formulations in country-specific paediatric formularies along with pricing and reimbursement related hurdles. They also indicated that cheaper compounded medicines continue to be used after these PUMA paediatric formulations become available (145). Although their disappointment should not be attributed to PUMA itself and is a consequence of the complexity of post-regulatory steps leading to access, it calls for further thought on to whether some degree of alignment between regulatory approval and access to paediatric formulations should be sought, and if so how and in which instances (for example, in the case of paediatric formulations for old off-patent medicines).

All the above findings related to access are concerning. This is even more so considering that developing child-friendly products to provide treatment options for most age groups has remained problematic (146) and that the development of paediatric formulations is a costly and complex undertaking (146, 147). Two guiding principles should now prevail. First, stakeholders need to define a shared approach to the development of paediatric oral formulations that is rationalised internationally. Second, regulators need to recognise these shared standards to move from country or region-specific regulatory provisions to a more globalized approach to facilitate registration pathways between different jurisdictions. The WHO Paediatric Regulatory Network offers a global paediatric working platform for regulators and other interested stakeholders to support the availability of quality medical products for children through facilitation of communication, collaboration, training, and regulatory harmonisation across the life-cycle of paediatric medical products. In addition, the Global Accelerator for Paediatric Formulations (12), a WHO Network, aims to stimulate cross-sectoral collaborations to accelerate investigation, development, registration, and uptake of prioritized

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child-appropriate medicines. Table 11 summarises proposed actions to address some of the challenges/deficiencies related to access identified in this paper.

A shared approach to the development of formulations should include standards for assessment of acceptability for liquid and SODFs in children. This needs to be done by a global consortium of relevant stakeholders. Exemplars include EuPFI and the IQ consortium (148) or public private partnerships that facilitate programmes such as the Critical Path Institute or Innovative Medicines Initiative 2. A global consortium for standards relating to the development of paediatric oral formulations needs appropriate resources. In the absence of a global pharmaceutical regulator harmonised standards will promote aligned research programmes (such as shared paediatric investigation plans) and facilitate regulatory decision-making. A more globalised coordinated approach by regulators should decrease the burden and costs for manufacturers, streamline and expedite authorisation processes in both large and small to mid-size countries, increase the potential market size, and ultimately translate into improved access. Furthermore, although complex, time has come to explore the feasibility of some alignment between approval, pricing, and reimbursement processes.

Many aspects of developing formulations benefit from a "platform" approach to technological developments (26, 149). In fact, as described above, technology platforms have emerged in the form of flexible SODFs to cover developmental specificities of children of all age, ability, and size. Whether it is to formulate *de novo* new chemical entities or repurpose/reformulate an off-patent product, paediatric specific key attributes need to be identified to be appropriately included in a paediatric Quality Target Product Profile (pQTPP) (150) to plan and support paediatric-centric formulation design. More integrated collaboration between formulation experts and clinical colleagues, including healthcare professionals, is advocated.

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Similarly, rational development of formulations needs shared information about clinical needs and currently available formulations so that effort can be targeted efficiently. In addition, shared information about existing formulations would promote moving existing formulations across borders.

There is active surveillance of medicines in order to assess safety and efficacy. This surveillance needs to include formulations. Gathering information about use of formulations from clinical records (real-world data) or from specific surveys will allow insight into how formulations are used and when problems arise. Insights from these sources will inform developers and users of formulations.

The needs for paediatric oral formulations will be best served by integrating research standards, technological development, research design and delivery, and sharing information about needs for and experience with products. We call on the global formulations and paediatric communities to work together on this important topic.

Conclusion

Developing suitable paediatric formulations and ensuring access to them by the greatest number of the 2.2 billion children worldwide are equally important. Over the last two decades, the leadership of many stakeholders from the pharmaceutical industry, regulators, academia and the health care professional community, catalysed by organisations such as the EuPFI, the BPCA Pediatric Formulations Initiative, and the WHO, has resulted in advances in scientific, technological and regulatory issues associated with paediatric formulations development. Liquid formulations remain an acceptable option in many instances, but their limitations have prompted stakeholders to generate a significant body of new knowledge

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supporting the acceptability of flexible SODFs in children. We are now witnessing an increasing number of medicines becoming commercially available in these pharmaceutical forms. This is especially true for multiparticulates, including minitablets are starting to reach the paediatric market. However, gaps do remain with these formulations. Further research is needed to confirm the acceptability of minitablets in neonates and children younger than 6 months of age. The capacity of multiparticulates and minitablets in achieving the required dosing flexibility does not equate that of liquid formulations, and may be limited in some circumstances. Their dosing flexibility depends mostly on the number and the strengths of minitablets, or sachets of multiparticulates, that can be given safely for one dosing by caregivers outside the research environment; this still needs to be defined. Also, their performance for acute conditions in hospitalised children remains to be proven. As we expect their use to increase in the coming years, gathering real-world data will be of utmost importance if we want children to fully benefit from this solid platform technology.

In contrast to the major milestones that have been reached for the development of child-friendly medicines over the past years, children's access to these formulations still require additional efforts. Too often the commercialisation of suitable paediatric formulations is limited to some countries/regions, with at least two negative consequences. It forces the use of compounding with its inherent risks in those countries deprived of these forms, and can result in the development of paediatric formulations with similar attributes to those that already exist, without bringing additional benefit, that may not be a rational use of resources. In order to improve access, we propose working on global standards for the assessment of paediatric oral formulations to facilitate harmonisation of regulatory requirements across jurisdictions and sharing information about the needs for, availability of, and experience with, paediatric oral formulation. Although it is against the laws of market as we know them,

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discussions regarding some alignment between approval, pricing, and reimbursement processes should also happen, leaving working in siloes behind us. It is time adults start thinking outside the box for children.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and have no competing interests with the exception of Dr. Strickley who received an honorarium and travel expense as a speaker at Eupfi in 2019.

Contributors

CL, SB and EKL performed the literature review and collection and analysis of the data. CL and SB prepared the original draft of the manuscript. MT made substantial contributions to the intellectual content of the original draft. All authors critically revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Table 1. Limitations of compounding

Limited stability data
Taste issue with limited options available to mask bad-tasting APIs
Inaccurate dosing
Altered absorption
Lack of bioavailability data for compounded drugs
Lack of testing for purity, potency, content, or stability
Deficient environmental control with potential contamination of the compounded drugs
Exposure of HCPs and/or parents to toxic APIs
Lack of awareness of physicians
No or weak oversight by regulatory agencies

Abbreviations: API, active pharmaceutical ingredient; HCP, health care professional.

Table 2. Desirable attributes of a paediatric oral dosage form

Acceptable and palatable dosage form
Dose and dose volume/weight adjusted to the intended age group (dosing flexibility)
Convenient, reliable administration (accurate dose, suitable administration device)
Minimal manipulation by HCPs, parents, or caregivers prior to use
Minimal administration frequency
Minimal impact on life style
Minimum non-toxic excipients
Transportable and low bulk/weight
Easily produced and stable in a variety of climates
Affordable
Commercially viable

Abbreviations: HCP, health care professional.

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Table 3. Evidence regarding acceptability of multiparticulates in children (with the exception of minitablets discussed in Table 4)

Ref	Study design[1] and (duration)	N	Age (yrs)	Multiparticulates	Comparator	Acceptability
Drug-free (placebo)						
Lopez et al. (36) 2018	Randomised, single-blind (3 samples at 5-10 min interval)	71 with 213 occasions[5]	4-12[2]	Coated and uncoated pellets of 4 different sizes[3] (on a spoon)	None	92 % swallowed the complete dose. There were negative facial expressions on 72% of the occasions[4]. 60% of children had negative hedonic scores to grittiness perception[6]. Willingness to take the pellets everyday was reported in 31% of the occasions.
Drug-containing						
Cholestyramine resin[7]						
McCrindle et al. (37) 1997	Randomised, cross-over, two 8-week periods (16 wks)	38[8]	10-18	Powder[9] (in packet)	Tablets[10]	82% participants preferred the tablet form, and 16% participants preferred the powder form. Significantly greater compliance with tablet form compared to powder form was reported.
Iron						
Zlotkin et al. (46) 2001	Randomised (2 mths)	493[11]	6-18 mths	Sprinkles[12] (in sachet)	Oral drops[13]	74% of mothers in the drops group reported their children objected to taking the drops in some way while 16% in the sprinkles group reported having problems giving their children sprinkles.
Zlotkin et al. (39) 2003	Randomised, placebo-controlled 4 treatment groups (6 mths)	324[14]	8-20 mths	Sprinkles (iron) (in sachet)[15]	Sprinkles (iron + vit A) or iron oral drops or placebo sprinkles[15]	93% of children expressed a dislike for the drops while only 7% objected to take sprinkles.
Geltman et al. (40) 2009	Randomised (3 mths)	112[16]	5-7 mths	Sprinkles (in packet)[17]	Oral drops[17]	Adherence was generally poor with both formulations. Parents were significantly more likely to be concerned about using sprinkles as a new product (12% vs 0%) and about safety of sprinkles for children (14% vs 1%) than oral drops. In contrast, parents in the drops group were significantly more likely to

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						report difficulty in integrating administration supplementation into a daily routine compared to sprinkles (38% vs 17%).
Lopinavir/ritonavir						
Musiime et al. (47) 2014 Kekitiinwa et al. (41) 2016	Open, randomised phase 1, two period cross-over (48 weeks)	77	3 mths - <1 yr (N = 19) 1-<4 (N = 26) 4-<13 (N = 32)	Pellets (in capsule)[18]	Syrup Syrup Tablet	72% of caregivers preferred pellets at 12 weeks. 44% of caregivers preferred pellets at 48 weeks. 22% of children used pellet during last 4 weeks. 64% of caregivers preferred pellets at 12 weeks. 36% of caregivers preferred pellets at 48 weeks. 46% of children used pellet during last 4 weeks. 19% of caregivers preferred pellets at 12 weeks. 13% of caregivers preferred pellets at 48 weeks. 13% of children used pellet during last 4 weeks.
Pancreatic enzyme supplement						
Munck et al. (42) 2009	Multicenter, open, randomised, cross-over (4 wks)	39[19]	6-36 mths	Granules (in a glass container)[20]	Granules (in a capsule)[21]	51% of parents preferred the granules in the glass and 23% preferred the granules in the capsule; 26 % liked both preparations.
Valproic acid						
Cloyd et al. (43) 1992	Randomised, two-period cross-over, two 7-day regimens (14 days)	12	5-16	Sprinkles (in capsule)[22]	Syrup	75% of parents preferred sprinkles over syrup and 75% of children found sprinkles more palatable than syrup.
Motte et al. (44) 2005	Phase 4, multicenter (90 days)	302[23]	3-14	Prolonged-release microgranules[24]	Solution (N=199)[25]	Granules were well accepted (84% in 3-<5yrs, 78% ≥5 yrs), and significantly better accepted than solution (88% vs 34% in 3-<5yrs, 78% vs 43% ≥5 yrs). Parents experienced significantly less difficulties to administer the granules compared to the solution (19% vs 48%). In children in whom granules were difficult to administer, the main difficulty resided in their texture.

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Verrotti et al. (45) 2012	Multicenter[26]		108[27]	6.7 ± 3.6	Modified-release granules[28]	Solution	Palatability evaluated in 53 children older than 4 years. The overall palatability score of granules was significantly higher than the solution in children and parents; parents reported significantly fewer problems in giving granules to their children compared to solution. At 6-mth follow-up, all patients continued to use the granules.

Abbreviations: mths, months; N, number of patients who completed the study; ref, reference; VPA, valproic acid; vs, versus; yrs, years.

[1]All studies were prospective and single-center unless otherwise specified.

[2]Children participants included 14 children betwen 4 and 5 years, 37 children between 6 and 8 years, and 20 children between 9 and 12 years.

[3]The study was divided into two phases, with the first phase dedicated to the evaluation of the effect of particle size (200-355, 350-500, 500-710 and 700-1000 µm) and the second phase dedicated to the evaluation of the effect of coating. Each participant received three 500 mg samples of coated and/or uncoated microcrystalline cellulose pellets of different sizes administered with water at 5-10 min intervals.

[4]Rated by researchers.

[5]As children refused the sample in seven occasions, negative facial expresion, responses to hedonic ratings, and willingness to take the sample every day were calculated based on a total of 206 occasions instead of 213.

[6]Rated by participants.

[7]Questran ®.

[8]Of the 40 children enrolled, 38 completed the study.

[9]Two packets of powder (4g/packet) once a day.

[10]Eight tablets (1g tablet) once a day.

[11]557 children were randomised and 493 completed the final assessment.

[12]One sachet of microencapsulated ferrous fumarate (with ascorbic acid) added to the child's meat after it was cooked once daily.

[13]Ferrous sulfate drops provided in three equal doses per day.

[14]Of the 437 children enrolled, 324 completed the supplementation period.

[15]One sachet of microencapsulated ferrous fumarate (with or without vitamine A) or placebo sprinkles was added to the child's food once daily; iron drops were provided once daily on an empty stomach.

[16]Of the 150 children enrolled, 112 were included in the final assessment and 97 completed the exit survey.

[17]One packet of microencapsulated ferrous fumarate added to prepared food once daily; iron drops were provided once daily on an empty stomach.

[18]FDA gave tentative approval for the lopinavir/ritonavir (40/10 mg) pellets used in this study in May 2015 (its marketing status remains as of today a tentative approval (ref)

[19]Of the 40 children enrolled, 39 completed study.

[20]One spoon of Creon® for children with 100 mg granules (minimicrospheres) containing lipase 5000 Ph. Eur. Units, amylase 3600 Ph.Eur. Units, protease 300 Ph. Eur. Units.

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[21]Opening of one capsule of Creon® 10000 with 150 mg pancreatin labelled containing lipase 10000 Ph. Eur. Units, amylase 8000 Ph.Eur. Units, protease 600 Ph. Eur. Units).

[22]125 mg sprinkle capsules were opened and the contents mixed with one or two tablespoons of apple sauce.

[23]Of the 307 children enrolled, 302 children received the studied treatment and were included in final analysis.

[24]Micropakine®. Packaging and strenght were not specified.

[25]The authors compared the acceptability of VPA prolonged- release microgranules with that of VPA solution in those children already treated wih the solution at baseline (N=199).

[26]Abrupt switch from VPA solution to VPA modified-release granules at identical dosages, but regimems were changed from 3 or 4 daily doses to twice daily.

[27]112 subjects were recruited. Four participants discontinued VPA modified-release granules before the end of the study (child dislike for granules (n=2) and parent fear the complete dose was not ingested with the food (n=2). The final analysis was performed on 108 patients.

[28]Depakine® Chronosphere®. Packaging and strenght were not specified.

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Table 4. Evidence regarding the acceptability of minitablets in children

Ref	Study design[1]	N	Age (yrs)	Minitablets	Comparator	Acceptability
Drug-free (placebo)						
Thomson et al. (61) 2009	Exploratory descriptive	100	2-6	One uncoated 3 mm MT[2]	None	% who swallowed MT as a whole, without chewing: 2-3 yrs: 46%, 3-4 yrs: 53%, 4-5 yrs: 76%, and 5-6 yrs: 87%.
Spomer et al. (62) 2012	Open randomised two-way cross-over exploratory	60 (10 in each age group)	0.5-6	One uncoated 2 mm MT[3]	3 mL of glucose syrup 15%[4]	Overall acceptability[5] was 93% for MT compared to 78 % for syrup; overall swallowability[6] was 67% for MT and 73% for syrup.
Kingmann et al. (63) 2013	Open randomised cross-over	306 (51 in each age group)	0.5-6	One uncoated or coated 2 mm MT[3]	3 mL of glucose syrup 15%[4]	The acceptability[5] and swallowability[6] of uncoated and coated MT were significantly higher compared with glucose syrup. In each individual age group, point estimates for the acceptability of uncoated MT,coated MT, and syrup were 78-100%, 84-100%, and 65-90%, res pectively, and those of swallowability were 53-88%, 47-84%, and 39-73%, respectively
van Riet-Nales et al. (64) 2013	Multicenter, randomised cross-over trial[8]	148[7]	1-4	One 4 mm MT	Powder (1 sachet) Suspension (2.5 mL) Syrup (2.5 mL)	Estimate of the mean VAS score[9] was significantly higher for the MT than for the suspension. Estimate of the mean number of intakes fully swallowed was significantly higher for the MT than for the other formulations. Children and parents preferred the MT and syrup over suspension and the suspension over the powder. The data revealed a period/cross over effect.
Klingmann et al. (66) 2015	Open randomized cross-over	151[10]	2-28 days	One uncoated 2 mm MT[11]	0.5 mL of glucose syrup 15%[4]	Acceptability[12] was 100% for both MT and syrup. Swallowability[13] of MT was noninferior to syrup (82% MT, 72% syrup).
Kluk et al.	Open cross-over[14]	60	24-48 mths	5 or 10 coated 2 or 3 mm MT	None	MT were acceptable[16] in 83% of subjects (75% in

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(65) 2015				administered daily for up to 4 days[15]		24-36 mths (N = 32) and 93% in 37-48 mths. (N = 28)). 57% of children were capable of swallowing the MT without chewing (50% in 24-36 mths; and 64% in 37-48 mths).
Klingmann et al. (60) 2018	Open randomised 3-way, cross-over	372[17]	6-23 mths (N=186)	25 or 100 uncoated 2 mm MT once[18]	5 mL of glucose syrup 15% once[19]	Higher acceptability[5] for 25 and 100 MT compared to syrup (87%, 95%, and 79%, respectively). Higher swallowability[6] for 25 and 100 MT compared to syrup (81%, 74%, and 36%, respectively).
			2-5 (N=186)	100 or 400 uncoated 2 mm MT once[18]	10 mL of glucose syrup 15% once[19]	The acceptability[5] of 400 MT was noninferior to that of syrup (85 % and 83%, respectively). The swallowability[6] of 400 MT was inferior to that of syrup (16% and 31%, respectively). The acceptability[5] of 100 MT was inferior to that of syrup (73% and 83%, respectively). The swallowability[6] of 100 MT was noninferior to that of syrup (31% and 31%, respectively).
Drug-containing						
Van de Vijver et al. (67) 2011	Multicenter, phase II, randomised investigator-blinded parallel-group pilot	16 CF pts[20]	6-30 mths	Pancrealipase 2 mm enteric coated MT for a maximum of five doses per day for five days (4 different doses studied)[21]	None	Overall, mean palatability was scored as fair to good by parents

Abbreviations: CF pts, cystic fibrosis patients; mths, months; MT, minitablets; N, number of patients who completed the study; ref, reference; VAS, visual analogue scale; yrs, years.

[1]All studies were prospective and single-center unless otherwise specified.

[2]With water or a drink of the child's choice.

[3]With up to 3 mouthfuls of a drink of patient's choice.

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[4]Without additional liquid.

[5]Acceptability of MT defined as swallowed (no chewing during deglutition and no solid residuals found during oral inspection) or chewed (swallowed most of the MT pieces, but small residuals found during oral inspection), and acceptability of syrup defined as everything swallowed (no liquid residuals found during oral inspection) or small runlet (liquid rinse or flowing out off the mouth).

[6]Swallowability of MT defined as no chewing during deglutition and no solid residuals found during oral inspection, and swallowability of syrup defined as everything swallowed (no liquid trickling out of the mouth before and during deglutition).

[7]183 children were included and 148 were evaluated.

[8]Parents were asked to administer four oral placebo formulations (MT, powder, suspension, and syrup) to their child at home on four consecutive days. The formulations was given in a pre-defined, randomised order, and each formulation twice on day 1 only.

[9]Visual analogue scale score for child acceptability according to parents' observation (0 to 10 cm with 0 being very unpleasant/bothersome etc. and 10 being not at all).

[10]Including 11 preterm newborns with a median gestational age of 36+1 weeks.

[11]With a drink of the parent's choice.

[12]Acceptability defined as an aggregate of two categories, everything swallowed and partially swallowed.

[13]Swallowability defined as everything swallowed.

[14]The study design was such that on the 1st day five 2 mm MT were administered and if accepted, on the 2nd day, ten 2 mm MT were administered and if accepted on the 3rd day, five 3 mm MT were administered, and if accepted, on the 4th day, ten 3 mm MT were administered.

[15]Mixed on the spoon with a fruity jelly.

[16]Acceptability of MT defined as either smooth swallowing, swallowing with a choking reflex or cough, or biting or chewing followed by swallowing.

[17]374 children (187 in each age group) were enrolled, but 2 were excluded from analysis, leaving 372 patient for evaluation (186 in each age group).

[18]Given with soft food or a drink of the child's choice on a teaspoon.

[19]Given via a syringe without any food or drink.

[20]18 children were enrolled and 16 were evaluated.

[21]The number of MT were individualized based on patient's weight but the exact number was not specified. An unblinded research pharmacist prepared capsules containing the appropriate number of minitablets according to the subject's weight and the meal-specific dose required for each dose group. The capsule needed to be opened and MT placed on a spoon containing a small amount of applesauce, infant formula, or fruit puree and provided before the feed.

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Table 5. Evidence regarding the acceptability of orodispersible films in children

Ref	Study design[1]	N	Age (mths)	ODF	Comparator	Acceptabilty
Drug-free (placebo)						
Orlu et al. (76) 2017	Exploratory open label	110	6-71 (6 age groups)	One 3 cm x 2 cm slightly sweetened	None	Acceptability as per children[2] ≥ 3 yrs was 78%. Acceptability as per caregivers[3] and nurses[3] was 79% and 83% for children < 2 yrs, respectively, and 86% and 91% for children 2-5 yrs, respectively. Overall swallowability as per caregivers and nurses was 65% and 62%, respectively. In 15% of the children, a partial loss of administered ODF was observed by both.
Klingmann et al. (78) 2020	Open randomised two-way cross-over	150 (50 per age group)	2 days-12 mths	One 3 cm x 2 cm[4]	Glucose syrup[5] 2-28 days: 0.5 mL 1-5 mths: 3 mL 6-12 mths: 3 mL	Both the acceptability[6] and swallowability[7] of ODF were significantly superior to that of glucose syrup (95% vs 81%, and 70% vs 49%, respectively). Acceptability by age group: 2-28 days: ODF 100% vs syrup 82%; 1-5 mths: ODF 98% vs syrup 74%; 6-12 mths: ODF 88% vs syrup 86%. Swallowability by age group: 2-28 days: ODF 66% vs syrup 76%; 1-5 mths: ODF 86 % vs syrup 32%; 6-12 mths: ODF 58% vs syrup 38%.
Drug-containing						
Rodd et al. (75) 2011	Randomised two-phase cross-over	41[8]	0.5-1	Vitamin D filmstrip daily for 3 weeks (400 IU Vitamin D3)	Vitamin D 1 mL syrup daily for 3 weeks (400 IU Vitamin D3)	85% of parents preferred the filmstrip over the drop at the end of 6 weeks.

Abbreviations: mth, month; N, number of patients who completed the study; ODF, orodispersible film; ref, reference; vs, versus; yrs, years.

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[1]All studies were prospective and single-center unless otherwise specified.

[2]Acceptability defined as a score ≥ 3 on a five-point facial hedonic scale.

[3]Acceptability defined as a score ≥ 5 on the Medication Acceptance Scale (MAS) (a total score from 0 to 10 was possible).

[4]Divided into two halves, simultaneously placed in the child's right and left cheek pouch with a drink of choice.

[5]Glucose syrup was given without any additional liquid or food via a syringe, pipette or teaspoon.

[6]Acceptability defined as "everything swallowed or chewed/ partially swallowed" for ODF and "everything swallowed or partially swallowed" for glucose syrup.

[7]Swallowability defined as "everything swallowed" for both ODF and glucose syrup.

[8]43 children were recruited and 41 completed the study.

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Table 6. Evidence regarding the acceptability of orodispersible tablets in children

Ref	Study design[1]	N	Age (yrs)	ODT	Comparator	Acceptability
Drug-free (placebo)						
Wagner-Hattler et al. (83) 2021	Cross-sectional observational	40	2-10	One 5 mm ODT placed on the tongue or into the buccal cavity[2]	None	ODT palatability as assessed by research staff, parents, and older children (6-10yrs), was 93%, 93%, and 100%, respectively. 80% of older children reported they would agree to take a second pacebo ODT on another occasion.
Drug-containing						
Desmopressin						
Lottmann et al. (84) 2007	Randomised, open-label, multicenter, cross-over, two 3-week periods	210[3]	5-15	MELT (ODT) once daily[4]	Tablet once daily	Overall, 56% of subjects preferred the MELT compared with 44% who preferred the tablet. In children aged 5-11 yrs, there was a statistically significant preference of MELT over the tablet. Ease of use and compliance were high for both formulations.
Ondansetron						
Cohen et al. (85) 2005	Randomised, double-blind, placebo-controlled	62[5]	5-11	One 4 mg ODT	One placebo ODT	100% of subjects accepted ODT but a significantly larger proportion of subjects found ODT not to be as "good" tasting as compared with the placebo group (39% vs 16%). 94% of the subjects (87%, ondansetron ODT; 100% placebo ODT) stated that they would be willing to take the ODT in the future.

Abbreviations: MELT, oral lyophilisate formulation of desmopressin; mths, months; N, number of patients who completed the study; ODT, orodispersible tablet; ref, reference; yrs, years.

[1]All studies were prospective and single-center unless otherwise specified.

[2]Flavour functionalized calcium carbonate (insoluble carrier material)-based ODT.

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[3]221 patients were randomised and the overall intention-to-treat population with evaluable data consisted of 210 patients.

[4]Sublingual, oral lyophilisate formulation of desmopressin, Minirin®.

[5]62 patients were included for assessment of study drug acceptability and safety, though 3 were not included in the evaluation of the primary outcome (vomiting) because of protocol violations.

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Table 7. Evidence regarding the acceptability of chewable and dispersible tablets in children

Ref	Study design[1]	N	Age (yrs)	Tablet form	Comparator	Acceptability
Drug-containing chewable tablet						
Mebendazole						
Friedman et al. (89) 2012	Open-label, single arm, phase 3	396	2-10 2-5 (N = 271) 6-10 (N = 125)	One 500 mg chewable tablet	None	98% (N = 390) of children chewed the tablet and swallowed; in 2 children, tablet was dispersed in water to facilitate swallowing while in the remaining 4, the drug was not taken at all. 49% of children (73%, 2-5 yrs; 27%, 6-10 yrs) took the study drug with water and 8% of children had to take tablet once broken down into half or quarters.
Silber et al. (90) 2017	Multicenter, phase 3, randomised, double-blind placebo-controlled	278[2]	1-16	One rapidly disintegrating 500 mg chewable tablet[3]	Placebo chewable tablet	91% of children chewed the tablets, and 9% received the study drug with water in a spoon. They were no instances of choking or vomiting. There were 5 instances of gagging (n = 3) or difficulty in swallowing (n = 2), all in pts <3 yrs old.
Palmeirim et al. (91) 2020	Randomised, superiority multi-sites	393[4]	3-12[5]	One chewable 500 mg tablet (strawberry taste)[6]	One solid 500 mg tablet of similar size (no taste)[7]	Both chewable and solid tablets were taken without difficulty in 99% and 97% of children, respectively. After receiving the chewable tablet, 87% of children said they would like some water and 95% reported to have liked its taste. More children in the chewable arm, compared to the solid arm, said they were reluctant to take this tablet again (36 vs 26%).
Drug-containing dispersible tablet						

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Artemether-lumefantrine						
Ogutu et al. (94) 2014	Randomised, open-label,	448[8]	6-59 mths	Arthemether-lumefantrine DT (six doses/three days)[9,10]	Dihydroartemisinin-piperaquine paediatric DT (three doses/three days)[10,11]	Caregivers reported DTs to be "simple" or "very simple" to use in 82% (AL) and 67% (DP) of children, with good palatability in 72% (AL) and 56% (DP). In general, caregivers preferred DTs as compared to a syrup formulation (77% (AL) vs 17% (syrup), 62% (DP) vs 30% (syrup).
Zinc						
Nasrin et al. (92) 2005	Cohort, community-based multi-sites	303[12]	3-59 mths	One 20 mg DT daily for 10 days[13]	None	93% of caregivers thought that zinc DTs were equally or even more acceptable to their children than other medicines; there were no observed age-group differences in acceptability. Most (84%) caretakers were willing to use zinc DTs for their children in the future.
Winch et al. (95) 2006	Part of the pilot phase of a multicenter study	123	0-60 mths[14]	1/2 of a 20 mg DT (<6 mths) and one 20 mg DT(≥6 mths) daily for 14 days[13]	None	7% of caregivers reported problems with zinc administration, either vomiting or refusal to take the tablets. Adherence to the full 14-day regimen was 64%.

Abbreviations: AL, arthemether-lumefantrine dispersible tablet; DP, dihydroartemisinin-piperaquine dispersible tablet; DT, dispersible tablet; mths, months; N, number of patients who completed the study, ODT, orodispersible tablet; ref, reference; vs, versus; yrs, years.

[1]All studies were prospective and single-center unless otherwise specified.

[2]295 children were enrolled for randomisation, and 278 completed the study.

[3]For children 1 year to < 3 years of age, the tablet was placed in a teaspoon and bottled potable drinking water was poured into the remaining volume of the teaspoon (2-3 ml). The tablet quickly absorbed the water, converting into a soft semisolid mass, which was then easily administered to the patient. Patients older than 3 years of age chewed the tablet without mixing with water.

[4]397 children were randomised with 393 included in the analysis and 365 contributing to the evaluation of acceptability of the two formulations.

[5]Only 17 children were in the 3-5 years age range.

[6]All children were to chew the tablet and swallow it without water. After chewing the tablet, children were asked whether they would like some water. The size of tablet was not specified.

[7]Children aged 3-5 years were given a crushed tablet mixed with a small amount of water while 6-12 years old children were given the whole tablet and asked to swallow it with a glass. of water.

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The size of the tablet was not specified.

[8]454 patients were randomised and 448 completed the study.

[9]Patients with body weight 5-14 kg received one dispersible tablet (20 mg artemether, lumefantrine 120 mg) per dose, and 15-24 kg received two tablets per dose.

[10]Both drugs were dispersed in a small amount of water or milk and administered by the caregivers under the observation of the study personnel.

[11]Patients received the standard dosage of 2.25 mg/kg and 18 mg/kg per dose of dihydroartemisinin and piperaquine, respectively, rounded up to the nearest half tablet.

[12]320 children were enrolled in study, and 303 were included in subsequent analysis.

[13]Supplied in blister packages.

[14]Almost half of the children (47%) were 12-23 months of age.

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Table 8. Evidence regarding the acceptability of conventional tablet/capsule in children

Ref	Study design[1]	N	Age (yrs)	Medicine	Size (mm)	Proportion of children who swallowed conventional tablet/capsule
Kokki et al. (98) 2000	Longitudinal, open	555[2]	1-9	Ketoprofen	7	80%[3]
Patchell et al. (99) 2002	Multicenter, randomised, open cross-over	54[4]	3-17	Pancrease Creon® 10 000[5]	Size 2 capsule (≈ 17.5-18 mm)[6]	100%
				Pandrease Creon® 8000[7]	Capsule twice bigger[6]	94%
Meltzer et al. (97) 2006	Observational, cohort	124	6-11	Placebo	7	91% using an ordinary cup or patented pill cup, with or without training
Kreeftmeijer-Vegter et al. (100) 2013	Multicenter, double-blind, placebo-controlled randomised	100	2-18	Levamisole	5-8	100%[8]
Bracken et al. (101) 2020	Multicenter, feasability	55	4-12	Placebo	6-10	4-8-year-old group (n=30): 67% swallowed the 6 mm tablet 91% swallowed the 8 mm tablet[9] 95% swallowed the 10 mm tablet[10] 9-12-year-old group (n=25): 100% swallowed the 6 mm tablet 100% swallowed the 8 mm tablet 96% swallowed the 10 mm tablet

Abbreviations: N, number of patients who completed the study; ref, reference; yrs, years.

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[1]All studies were prospective and single-center unless otherwise specified.

[2]611 children were studied, 555 were included in final analysis.

[3]Main problems in administering ketoprofen tablets to children were difficulty in swallowing and unpleasant taste of the tablet. These problems were three times common in children under 48 months compared to older children.

[4]59 children were randomised, and 54 completed study.

[5]Creon® 10 000 minimicrospheres.

[6]Exact size in mm not indicated .

[7]Creon® 8000 microspheres.

[8]Almost half (46%) of the patients were aged 2-5 years, 50% were aged 6-11 years, and only 4 % were older. The 5 mm tablets were given only to 3% of the patients , while 26% received 6 mm tablets, 28% received 7 mm tablets, and 43% received 8 mm tablets. More than 20 000 levamisole tablets were swallowed without any difficulties, choking or aspiration.

[9]7 children refused to attempt swallowing the tablet.

[10]9 children refused to attempt swallowing the tablet.

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Table 9. Authorisation in various jurisdictions of paediatric formulations which were granted a PUMA by EMA

				Jurisdiction				
Medecine (Commercial name)	**Formulation**	**Concentration (Strength)**	**Age group**	**Europe**	**US**	**Canada**	**Japan**	**Australia**
Midazolam (Buccolam®)[1]	Oromucosal solution	5 mg/mL (2.5, 5.0, 7.5 and 10 mg prefilled syringes)	3 mths-18 yrs	MA: 09-2011 PIP IS: 10-2008	-	-	MA: 09-2020	-
Propranolol (Hemangiol® /Hemangeol®)[2]	Oral solution	3.75 mg/mL	5 wks-5 mths	MA: 04-2014 PIP IS: 02-2009	MA: 03-2014	MA: 09-2016	MA: 07-2016	MA: 06-2015
Glycopyrrolate (Sialanar®)[3]	Oral solution	320 mcg/mL	≥ 3 yrs	MA: 07-2016 PIP IS: 10-2012	-	-	-	-
Hydrocortisone (Alkindi®)[4]	Granules in capsule	0.5, 1, 2 and 5 mg	0-18 yrs	MA: 02-2018 PIP IS: 04-2012	MA:09-2020	-	-	MA:08-2020
Melatonine (Slenyto®)[5]	3 mm prolonged-release tablet	1 and 5 mg	2-18 yrs	MA: 09-2018 PIP IS: 04-2011	-	-	-	MA: 05-2020
Vigabatrin (Kigabec®)[6]	Soluble tablet	100 and 500 mg	1 mth-7 yrs	MA: 09-2018 PIP IS: 11-2013	-	-	-	-

Abbreviations: EMA, European medicines agency; MA, market autorisation (month- year); mth(s), month(s); PIP IS, paediatric investigation plan initial submission (month-year); PUMA, paediatric-use marketing autorisation; US, United States; yrs, years.

[1]Indication: treatment of prolonged, acute, convulsive seizures in children from 3 months to < 18 years.

[2]Indication: treatment of proliferating infantile haemangioma requiring systemic therapy in children 5 weeks to 5 months.

[3]Glycopyrrolate: symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.

[4]Indication: replacement therapy of adrenal insufficiency in infants, children, and adolescents (from birth to < 18 years old).

[5]Indication: treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and/or Smith-Magenis syndrome.

[6]Indication: treatment in monotherapy of infantile spasms (West's syndrome) and in combination with other antiepileptic medicinal products for patients with

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resistant partial epilepsyfor infants and children from 1 month to less than 7 years of age.

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Table 10. Comparison between formulations of glycopyrrolate currently marketed by two different manufacturers for paediatric use

	Sianalar®	**Cuvposa®**
Market authorisation (month-year)	EU (07-2016)	US (02-2010), Canada (11-2017)
Manufacturer	Proveca	Merz
Form	Oral solution	Oral solution
Concentration	320 mcg/mL	1 mg/5mL (200 mcg/mL)
Age group	3-18 yrs	3-16 yrs
Indication	Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders	To reduce chronic severe drooling in patients aged 3-16 years with neurologic conditions associated with problem drooling (e.g., cerebral palsy)
Administration via NG tube mentioned in label	Yes	No
Taste	Rasberry flavouring	Cherry-flavored
Excipients	Sodium benzoate, raspberry flavouring (containing propylene glycol), sucralose, citric acid, purified water	Citric acid, glycerin, natural and artificial cherry flavor, methylparaben, propylene glycol, propyl-paraben, saccharin sodium, sodium citrate, sorbitol solution, and purified water
Price	£320.00 for a 250 mL bottle	$625 (CDN) for a 473 mL bottle
Cost by mg/mL	£4,0 per mg[1]	$6,60 (CDN) per mg[2], equivalent to £3,5 per mg[3]

Abbreviations: CDN, Canadian; EU, Europe; INESSS, Institut National d'Excellence en Santé et Services Sociaux (Quebec, Canada); NG, nasogastric tube; NICE, National Institute for Health and Care Excellence (United Kingdom); US, United States; yrs, years.
[1]Cost estimated by NICE.
[2]Cost estimated by INESSS.
[3]Based on currency conversion on April 16, 2021.

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Table 11. Proposed actions to improve some dimensions of access of appropriate paediatric oral formulations

Area	Proposed actions	Who could do this?
Development of formulations	Establish international standards for: - Assessing acceptability and palatability of medicines in the paediatric population - Technical design and evaluation of oral and enteral dosing devices (e.g. syringes) and global harmonisation of oral syringes with the establishment of an ISO standard - Compatibility testing based on food physicochemical attributes (e.g., pH, buffer capacity, free water), to enable a sufficiently broad range of soft foods/liquids to be included in the product label, while ensuring the effectiveness of the medicine and children's safety - Reporting of results, e.g. every paediatric study performed using SODFs should report on the dimensions(s) of the dosage form tested Involve actively children and caregivers in the early stage of development	Pre-competitive organisations with appropriate representation (professional, patient and public involvement, industry, regulatory). For example, EuPFI, IQ consortium or public private partnerships
Research	Improve the liquid and SODFs platforms for developing paediatric formulations For multiparticulates and minitablets, further explore the safety and ease of administration of using multiple sachets of the same strenght or multiple sachets of different strenghts per dosing to ensure their dosing flexibility Generate more evidence on the acceptability of multiparticulates and minitablets in children less than 6 months of age Explore the long-term acceptability of repeated administration of one or multiple SODFs in children	Public and professions to lobby funders (public, philanthropy, and industry) Funders to identify need and opportunities Researchers to bid for funding and complete research, with appropriate knowledge transfer and full involvement of children, young people, parents, and families. For example, EuPFI etc... Information from specific studies about these topics by clinicians, academics, and industry). Information gathered before licensing / marketing authorisation (clinicians, academics, industry, and when appropriate regulators)

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	Better define the capacity of SODFs to ensure palatability in children	Information gathered after licensing / marketing authorisation (using real world data when possible as well as specific studies)
	Gather qualitative and quantitative evidence regarding the use of paediatric oral formulations outside of a research environment as SODFs hit the market by: 1) capturing real-world evidence about the use, acceptabilty, palatability, and safety of SODFs in sick children, and 2) obtaining feedback from healthcare professionals, caregivers, and patients	
	Evaluate the generalisability of existing acceptability and safety results regarding SODFs across medical conditions	
Clinical needs	Develop standards for extemporaneous compounding	The International Pharmaceutical Organisation (FIP) Pediatric Formulations Focus Group strives to achieve global harmonisation of oral extemporaneous pediatric compounding practices and will conduct a survey to support this goal.
	Establish at the international level an inventory specific to paediatric formulation needs with regular updates and prioritisation	Pharmacist professional groups with other stakeholders
	Educate patients, caregivers, and health care professionals regarding SODFs	
Regulations	Promote a globalized approach for paediatric formulation regulatory requirements based on shared standards to facilitate moving paediatric formulations across jurisdictions	International Conference for Harmonisation (ICH)
	Establish a requirement for the pharmaceutical industry to include in the product monograph the size of the SODFs (e.g., in most instances, the size of tablet, capsule, minitablets, granules or pellets is not stated on the product label)	

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Commercialisation	Establish an inventory of which formulations are commercialised per country with regular updates	Pharmacist professional groups with other stakeholders
	Explore the feasibility of some alignment between approval, pricing, and reimbursement processes	A pre-competitive organisation with appropriate representation (professional, patient and public involvement, industry, regulatory)

Abbreviations: EuPFI, European Paediatric Formulation Initiative; SO, International Organisation for Standardisation; SODFs, solid oral dosage forms.

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Figure 1. Trends in commercial availability of paediatric oral formulations during two time periods: up to 2007 (in the United States) and from 2007 until mid-2018 (in the United States, Europe, and Japan).

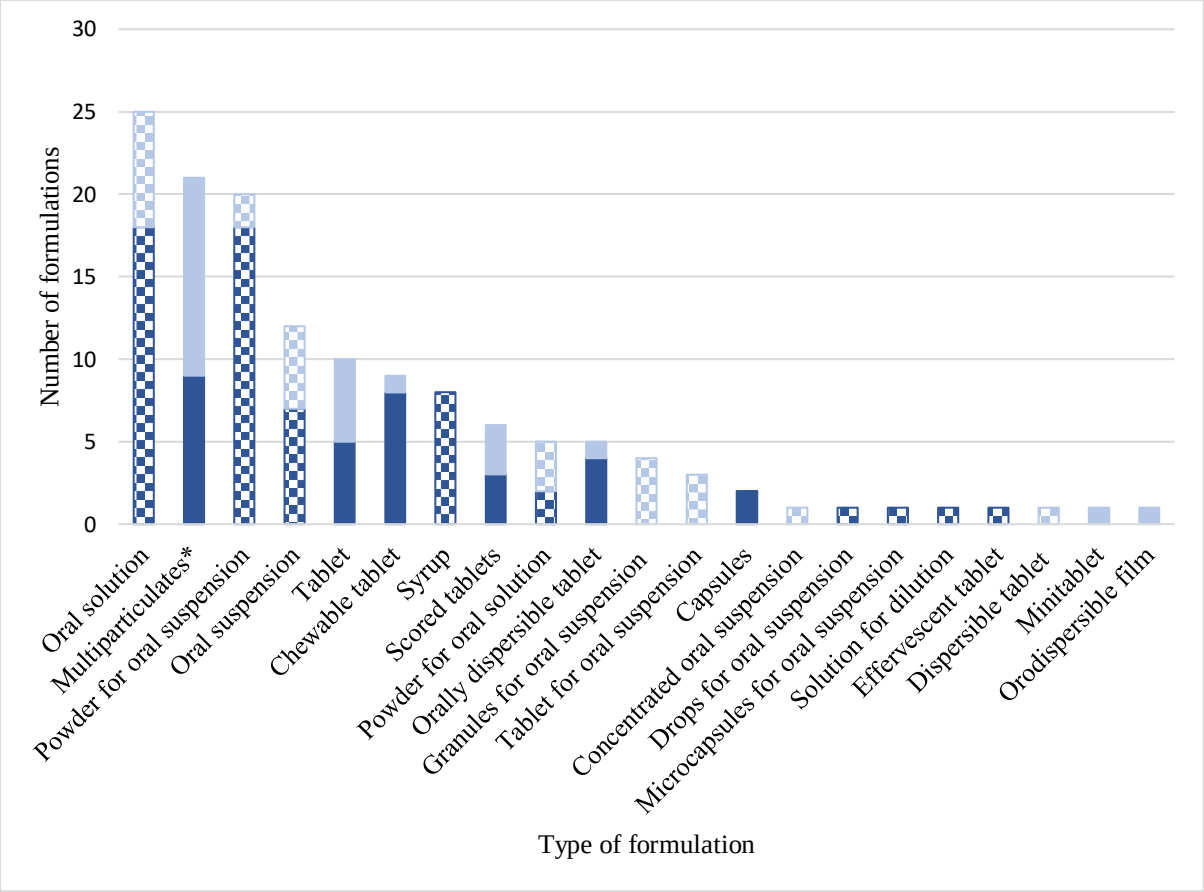

Figure 1: This figure was constructed by combining raw data from two comprehensive reviews from the same group of authors (20, 21). Data are presented according to types of formulations from the manufacturer's perspective as well as from the patient's perspective (i.e. taken either as liquid or as solid by the child). Six medicines included in the original articles (benazepril, defasarisox, imatinib, losartan (x 2), and mefloquine) were excluded as formulations deemed child-friendly were in fact medicines for which the drug monograph included recipes for compounding. Tablet (w/wo scored) were re-categorised into tablet and scored tablet. *Multiparticulates included sprinkle capsules, oral powders, oral granules, and manipulated minitablet known as oral granules. Formulations taken as liquid by the child (up to 2007) , taken as solid by the child (up to 2007) , taken as liquid by the child (from 2007 until mid-2018) , and taken as solid by the child (from 2007 until mid-2018) .

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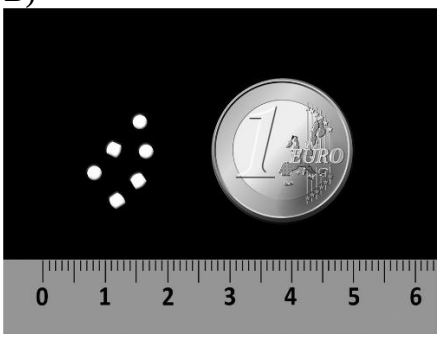
Figure 2. Pictures of SODFs for children.

A)

B)



C)

D)

E)

F)

G)

H)

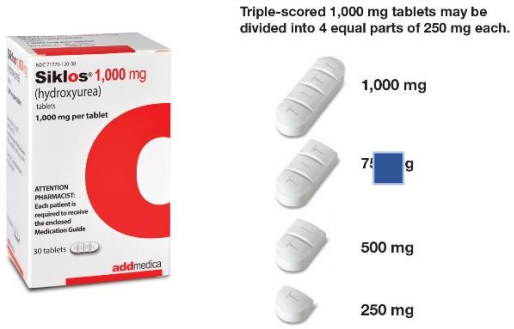


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Figure 2: A) Alkindi® oral granules (hydrocortisone) supplied in 0,5 mg, 1 mg, 2 mg, and 5 mg capsules (49, 151); B) Six uncoated minitablets in relation to a 1 Euro coin (66); C) Orodispersible films (21); D) Orodispersible tablet, Zofran® ODT (ondansetron) (152) ; E) Chewable tablets for pediatric use, Isentress® (raltegravir) (153). F) Dispersible tablet containing fixed dose combination of isoniazid, rifapentine, and rifampin for the treatment of tuberculosis in children dissolved in water (154) G) Conventional tablets, Viread® (tenofovir disoproxil fumarate) (21); H) Scored tablets for paediatric use, Siklos® (hyroxyurea) 1000 mg triple-scored tablet and (21, 155).

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Appendix 1. Existing authorised medicines in need of oral paediatric formulations: comparison of priority lists of EMA and BPCA, and WHO model list of essential medicines for children

Therapeutic Area(s)	Medicine	EMA inventory	Revised EMA priority list (2013)	BPCA priority list (2020)	WHO ELMc (2019)[1]
Anesthesiology	ketamine	x			
Anesthesiology, Pain, Psychiatry	chloral hydrate	x			
Anesthesiology, Neurology, Psychiatry	midazolam	x			
Cardiology	amiodarone	x			
Cardiology	aspirin	x			x
Cardiology	bisoprolol	x			
Cardiology	bosentan	x			
Cardiology	carvedilol	x			
Cardiology	chlorothiazide	x	x		
Cardiology	clopidogrel	x			
Cardiology	colesevelam	x			
Cardiology	enoximone	x			
Cardiology	flecainide	x			
Cardiology	labetalol	x			
Cardiology	prazosin	x			
Cardiology	sildenafil	x		x	
Cardiology	sotalol	x			
Cardiology	atorvastatin	x			
Cardiology	fluvastatin	x			
Cardiology	simvastatin	x			
Cardiology	warfarin	x			
Cardiology, Nephro-urology	captopril	x			
Cardiology, Nephro-urology	ramipril	x			
Cardiology, Nephro-urology	enalapril	x			
Cardiology, Nephro-urology	hydrochlorothiazide	x			x
Cardiology, Nephro-urology	lisinopril	x		x	
Cardiology, Nephro-urology	nifedipine	x			
Cardiology, Nephro-urology	verapamil	x			
Cardiology, Nephro-urology	nicardipine	x			
Cardiology, Nephro-urology	irbesartan	x			
Cardiology, Nephro-urology	valsartan	x			
Cardiology, Nephro-urology	candesartan	x			
Cardiology, Nephro-urology	telmisartan	x			
Cardiology, Nephro-urology	spironolactone	x			x
Cardiology, Neurology	metoprolol	x			
Cardiology, Neurology	propranolol (migraine)	x			
Cardiology, Pain	clonidine	x	x		
Endocrinology	cholestyramine	x	x		
Endocrinology	ethinyl estradiol	x			
Endocrinology	levothyroxin			x	
Endocrinology	propylthiouracil				x
GI	alginic acid	x			
GI	aprepitant	x			
GI	bisacodyl	x	x		
GI	docusate sodium				x
GI	pancreatic enzymes	x			

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GI	esomeprazole	x			
GI	lansoprazole	x			
GI	pantoprazole	x			
GI	raberprazole	x			
GI	ranitidine	x			
GI	famotidine	x			
GI	nizatidine	x			
GI, Anesthesiology, Oncology	tropisetron	x			
GI, Immunology, Nephro-urology, Oncology, Rheumatology	cyclophosphamide	x			x
GI, Immunology, Nephro-urology, Rheumatology	azathioprine	x	x		x
GI, Immunology, Rheumatology	cyclosporin, cyclosoprin A	x			
GI, Immuology, Nephro-urology	sirolimus	x			
GI, Oncology, Rheumatology	methotrexate	x		x	
Immunology	everolimus	x			
Immunology	hydrocortisone	x			
Immunology	mycophenolate sodium ~~mofetil~~	x			
Immunology	nilotinib				x
Immunology	prednisone	x		x	
Infectious disease	albendazole	x		x	x
Infectious disease	amantadine	x			
Infectious disease	amodiaquine				x
Infectious disease	ampicillin	x			
Infectious disease	artesunate				x
Infectious disease	arthemeter/lumefantrine	x			
Infectious disease	atazanavir	x			
Infectious disease	benznidazole	x		x	x
Infectious disease	boceprevir	x			
Infectious disease	brivudine	x			
Infectious disease	caspofugin	x			
Infectious disease	chloramphenicol				x
Infectious disease	chloroquine	x			x
Infectious disease	chlorproguanil-dapsone			x	
Infectious disease	clindamycin	x			
Infectious disease	clofazimine				x
Infectious disease	cloxacillin	x			
Infectious disease	cobicistat	x			
Infectious disease	cycloserine				x
Infectious disease	dapsone				x
Infectious disease	darunavir	x			
Infectious disease	delamanid				x
Infectious disease	diethylcarbamazine	x			x
Infectious disease	dihydroartemisinine/piperaquine	x			
Infectious disease	diloxamide				x
Infectious disease	dolutegravir	x			x
Infectious disease	dolutegravir/abacavir/lamivudine	x			
Infectious disease	efaviranz				x
Infectious disease	eflornithine	x			
Infectious disease	entacavir	x			
Infectious disease	ethambutol	x	x		x
Infectious disease	ethionamide				x

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Infectious disease	etravirine	x			
Infectious disease	famciclovir	x			
Infectious disease	fexinidazole				x
Infectious disease	flucloxacillin	x			
Infectious disease	flucytosine				x
Infectious disease	ganciclovir	x	x		
Infectious disease	griseofulvin	x			
Infectious disease	isoniazid	x	x	x	
Infectious disease	itraconazole	x			
Infectious disease	ivermectin	x			x
Infectious disease	ketoconazole	x			
Infectious disease	lopinavir	x			
Infectious disease	lopinavir/ritonavir	x			
Infectious disease	maraviroc	x			
Infectious disease	maribavir	x			
Infectious disease	mefloquine	x		x	x
Infectious disease	miltefosine	x			x
Infectious disease	moxifloxacin				x
Infectious disease	nevirapine	x			
Infectious disease	niclosamide				x
Infectious disease	nifurtimox	x		x	x
Infectious disease	oseltamavir	x			
Infectious disease	oxamniquine				x
Infectious disease	p-aminosalicylic acid				x
Infectious disease	praziquantel	x			x
Infectious disease	primaquine				x
Infectious disease	proguanil				x
Infectious disease	proguanil/atovaquon, proguanil/chloroquine	x			
Infectious disease	pyrazinamide	x	x		x
Infectious disease	pyrimethamine				x
Infectious disease	pyronaridine tetraphosphate				x
Infectious disease	quinine				x
Infectious disease	raltegravir	x			
Infectious disease	ribavirine	x			
Infectious disease	rifampicin	x	x		
Infectious disease	rifapentine				x
Infectious disease	sulfadiazine				x
Infectious disease	sulfadozine-pyremethamine			x	
Infectious disease	simeprevir	x			
Infectious disease	tenofovir	x			
Infectious disease	tenofovir/emtricitabine/rilpivirine	x			
Infectious disease	triclabendazole	x			x
Infectious disease	valaciclovir	x			
Infectious disease	valganciclovir	x			
Infectious disease	vancomycin	x			
Infectious disease	vicriviroc	x			
Infectious disease	voriconazole	x			
Nephro-urology	amiloride		x		
Nephro-urology	amlodipine	x	x		
Nephro-urology	Aquaretics (tolvaptan)	x			
Nephro-urology	bendroflumethiazide	x			
Nephro-urology	bisphosphonates	x			
Nephro-urology	cinacalet	x			

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Nephro-urology	levamisole	x			x
Nephro-urology	losartan	x			
Nephro-urology	mesna				x
Nephro-urology	metolazone	x			
Nephro-urology	phosphate	x			
Nephro-urology	potassium chloride	x			
Nephro-urology	pyridoxine	x			
Nephro-urology	sodium bicarbonate	x			
Nephro-urology	sodium chloride	x			
Nephro-urology	solifenacin	x			
Nephro-urology	tacrolimus	x			
Nephro-urology	tiopronine	x			
Nephro-urology	trospium	x			
Neurology	baclofen			x	
Neurology, Epilepsy	clobazam	x	x		
Neurology, Epilepsy	clonazepam	x			
Neurology, Epilepsy	diazepam	x			
Neurology, Epilepsy	gabapentin	x			
Neurology, Epilepsy	lorazepam	x			
Neurology, Epilepsy	oxcarbazepine	x			
Neurology, Epilepsy	phenobarbital	x			x
Neurology	phenobarbitone	x			
Neurology, Epilepsy	phenytoin	x			
Neurology	sultiam	x	x		
Neurology	naratriptan	x			
Neurology	almotriptan	x			
Neurology	eletriptan	x			
Neurology	frovatriptan	x			
Neurology	valproate, valproic acid	x			
Neurology	vigabatrin	x			
Neurology	zonisamide	x			
Neurology, Epilepsy, Psychiatry	carbamazepine	x			
Neurology, Epilepsy	topiramate	x	x		
Obstructive lung disease	zafirlukast	x			
Oncology	allopurinol	x			x
Oncology	chlorambucil	x			
Oncology	crizotinib	x			
Oncology	etoposide (etopophos)	x	x		x
Oncology	hydroxicarbamide, hydroxyurea			x	x
Oncology	imatinib	x			x
Oncology	irinotecan		x		
Oncology	isotretinoin	x		x	
Oncology	lomustine	x			
Oncology	melphalan	x			
Oncology	mercaptopurine	x		x	
Oncology	mitoxantrone[2]	x			
Oncology	pilocarpine	x			
Oncology	procarbazine	x			
Oncology	sorafenib	x			
Oncology	sunitinib	x			
Oncology	temozolomide	x			
Oncology	thioguanine, tioguanine	x	x		x
Oncology	topotecan	x			

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Oncology	tretionin (retinoic acid)	x			
Oncology	vinblastine		x		
Oncology	vincristine[2]	x			
Oncology	vinorelbine	x	x		
Other	ascorbic acid				x
Other	calcium gluconate				x
Other	cyclizine				x
Other	fludrocortisone				x
Other	methylprednisolone				x
Other	neostigmine				x
Other	potassium iodide				x
Other	retinol				x
Other	riboflavine				x
Other	succimer				x
Other	thiamine				x
Other	zinc sulfate				x
Pain	diclofenac	x			
Pain	fentanyl	x			
Pain	morphine	x			
Psychiatry	amisulpride	x			
Psychiatry	aripiprazole	x			
Psychiatry	chlorpromazine	x			
Psychiatry	clozapine	x			
Psychiatry	fluvoxamine	x			
Psychiatry	lithium	x			
Psychiatry	melatonin	x			
Psychiatry	olanzapine	x			
Psychiatry	pregabaline	x			
Psychiatry	quetiapine	x			
Psychiatry	sertraline	x			
Psychiatry	ziprazidone	x			
Respiratory	montelukast	x			
Rheumatology	cox-2 inhibitors (not otherwise specified)	x			
Rheumatology	hydroxychloroquine	x	x		x
Rheumatology	indomethacin	x			
Rheumatology	meloxicam	x			
Rheumatology	sulfasalazine	x			
Total count	239	192	21	16	65

Abbreviations: BPCA, Best Pharmaceutical Children Act,; ELMc, Model list of essential medicines for children; EMA, European Medicine Agency; WHO,

World Health Organization;

[1] Of the 149 medicines on the 2019 WHO ELMc, 84 had an age-appropriate formulation available in the US/Europe according to delMorale-Sanchez et al. (132).

leaving 65 medicines in need of an oral paediatric formulation.

[2]Unclear whether an oral form is needed.

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