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REVIEW

Opportunities for enteral drug delivery for neonates, infants, and toddlers: a critical exploration

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ABSTRACT

Introduction: The field of neonatal, infant and toddler pharmaceutical development is constantly improving, however a lag still remains in comparison to older children and adults. Their rapid anatomical, physiological and behavioral developmental rates pose extra challenges in diagnosing, treating, or preventing their disease. In turn, this brings complexity in formulating truly age-appropriate medicinal products that suit this heterogeneous pediatric subset. Progress in the availability of such products has ensued following the introduction of the 2007 European Union Pediatric Regulation, and in recent years, oral multiparticulate and dispersible solid formulations have gained interest alongside liquid formulations. However, the need is still great for dosage forms that do not compromise on pharmaceutical efficacy, safety and global accessibility in those aged under 2.

Areas covered: This article highlights some of the formulation challenges correlated with this age group and critically explores recent solid age-appropriate formulations and their administration devices for enteral drug delivery.

Expert opinion: There are many formulation requirements to consider when formulating drug products for children aged under 2. Efforts are required into understanding acceptability in this age group and of their carers, and whether innovation or optimization is required, to help guide formulators toward optimal approaches without impacting access.

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Neonate; infant; toddler; pediatric formulation; age-appropriate; acceptability; dose flexibility; oral/enteral solids; administration device; nasogastric; rectal drug delivery; low-middle income countries

1. Introduction

The 2007 European Union (EU) Pediatric Regulation has improved the research for developing children's medicines, increased the quality of information concerning their safety, efficacy and dosing but also the availability of pediatric medicines designed with the age and capability of the unwell children in mind. With the regulation came the mandatory Pediatric Investigation Plan (PIP) scrutinized by the European Medicines Agency Pediatric Committee (EMA PDCO); safeguarding a pharmaceutical company's consideration for the entire pediatric population for a new indication, a new route of administration or a new age-appropriate dosage form [1] at early stages of development. The ICH E11 guideline on clinical investigation of medicinal products [2] sets out the pediatric subsets to consider as shown below, based on developmental biology and pharmacology, for clinical study design:

- Preterm and term new-born infants (up to 27 days after birth)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 16–18 years)

Article 10 and 11 of the regulation also allows for the application of 'deferrals' and 'waivers' The deferral provision allows pediatric research to occur when it is ethical and safe to do so by permitting a delay in commencement and/or completion of all or some PIP measures; its purpose is to prevent the delay of the adult product's marketing authorization. However, it does elongate the time for pediatric formulations to be authorized and available. A waiver can be sought if the disease/condition indication does not occur in part of/the entire pediatric population or if it has likelihood for insignificant therapeutic benefit, effectiveness or safety over standard of care. This waiver could be a reason of the lack of advancement in certain pediatric therapies [3]. However, there is also a provision in the EU regulation for off-label (OL) or off-patent (OP) medicines to be reformulated appropriately for children, with a 10-year Pediatric Use Marketing Authorization (PUMA) in return. Unfortunately, only 6 PUMAs have been approved and completed so far [3], [a detailed table can be found in [4]]. Thus, many older formulations commonly expose to risk of inappropriate dosing especially in under 2s, namely neonates [5]. Balan et al., 2018 reviewed 101 studies [1996–2016] and showed that up to 99.5% of patients in neonatal intensive care units (NICU) were prescribed at least one medicine OL, with administered drug dose and age commonly associated with this OL prescribing [6]. To quote Tomasi et al., 2017, '*children are not small adults and neonates are not small children*' [1].

'Key binding elements' in PIP decisions [7] aid understanding of formulation quality requirements in early stages of its development. They revolve around developing product characteristics and of its delivery that foster patient 'acceptability' to ensure the formulation can achieve

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Article highlights

- Further understanding into neonatal, infant and toddler therapeutic and pharmaceutical requirements, and advancement in their pharmacotherapy is still required to stop fuelling off-label/off-patent/unlicensed drug use and sub-optimal treatment.
- Age-appropriate medicines for the under 2's should encompass good acceptability for them and their carers without affecting pharmaceutical quality, safety and accessibility.
- Oral solid multiparticulates such as minitablets and sprinkle formulations (granules, pellets, powders) as well as monolithic dispersible formulations, and their administration devices have shown good acceptability in children aged under 2 as an alternative to commonly used liquid formulations.
- Rectal formulations provide an alternative to patients who cannot take oral medicines; without need for a palatable product or enteral feeding tube administration and can provide fast systemic effects, for emergency use or use in pre-referral treatment in LMICs.
- Deeper investigation is required into the acceptability of formulations and how it is understood and evaluated in order to produce more globally accepted age-appropriate medicines.
- Efforts are required to understand how perception of non-favoured administration routes/dosage forms in different geographical locations can be overcome to shift convention and welcome newly developed formulation trends.
- Understanding is required to identify when innovation or optimisation of existing platforms is needed to ensure access is not affected.

This box summarizes key points contained in the article.

optimal patient adherence and thus treatment effectiveness. For example, the requirement of a particular pharmaceutical form, formulation, dose strength, administration route, possible excipient issues [e.g. level of exposure, type of excipient], administration device [e.g. syringe, nasogastric tube (NGT)], product manipulation (if any) to be detailed in the Summary of Product Characteristics (SmPC) [e.g. mix with food/drink], and palatability [7,8]. Regulations in the USA contain similarities to EU regulations. A comparison is detailed in [9].

Ten years post-EU regulation implementation, the EMA reported that the research, development, and supply of pediatric medicinal products had increased but also that gaps remained, particularly in developing age-appropriate dosage forms (only 43 approved between 2007 and 2016 in EU [1]), as seen in Figure 1 [3].

Noticeably, neonates (term/preterm), infants, and toddlers fill the largest portion of this gap [2] Hence this article is explicitly targeted toward providing a holistic awareness and update of the current standpoint on their dosing with appropriate formulations, to help inform on advancements made and existing limitations.

1.1. Neonate, infant, and toddler ontogenesis considerations

The lack of appropriate dosage forms is profoundly linked to their sharp dynamic increase in growth and maturation rate: not only visible height/weight changes but also organ maturation, body composition, developmental and behavioral changes during these two first years of life. This deepens the complexity to treat this subset as disease diagnosis can be blurred due to overlap in symptomatic presentation, and also since it creates a moving target product profile for formulation scientists.

The Infant and Toddler Forum proposes 5 key stages categories [Birth-1 month, 1–3 months, 3–6 months, 6–12 months, and 12 months-2 years] encompassing developmental transformations including cognitive understanding, recognition, (oral)motor functions, language, feeding changes from liquids to semi-solids, teething, and declination of gag reflex. Behavioral changes such as sleeping times, nappy habits, attitudes, taste/texture preferences, and teething discomfort could also have effects on medicine administration [10]. Plausibly, children <2 years cannot proactively partake in their treatment to any extent, unlike older children, with complete dependence on their caregivers. Therefore, consideration

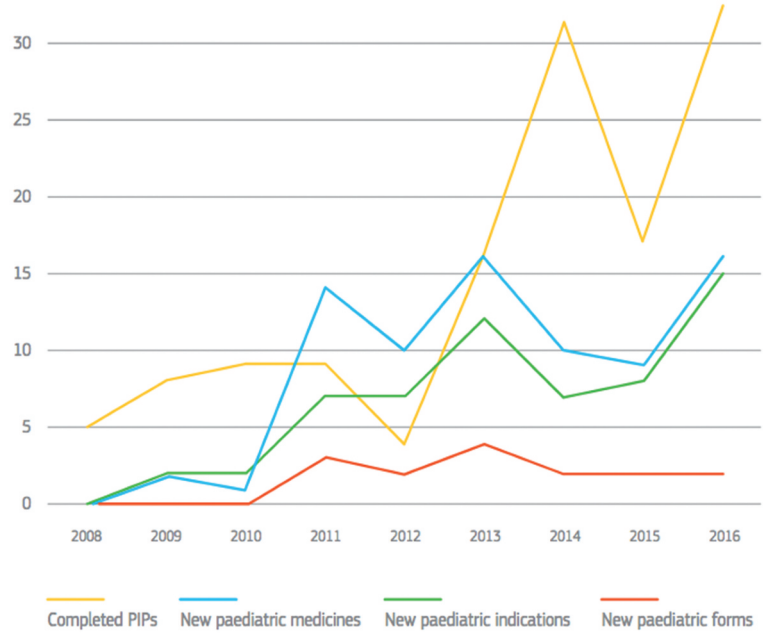


Figure 1. Trends from completed PIPs for medicines authorized for the pediatric population between 2008–2016. from EMA 2017 10-year report [3].

weighs even more heavily toward ease of administration of the dosage form by the caregiver [11].

There are still many knowledge gaps on the physiology of the pediatric gastrointestinal system relevant to the absorption of enterally administered medicines; how this system develops from birth, how it differs to adults, and how it changes with disease. Key physiological parameters of the gastrointestinal system relevant to the design of age-appropriate enteral drug products are discussed in [12,13]. Regarding pharmacokinetics, in the first two years of life, drug Absorption, Distribution, Metabolism and Excretion (ADME) profiles are greatly affected [14–16]. Some of these physiological parameters such as, increased gastric pH, gastric emptying time, decreased absorption capacity, microbiome status, intestinal fluid composition, and diet are known to affect drug absorption (more so in preterm/term neonates) [14,15,17]. These factors can show inter-individual variation, especially of the different developmental stages within these first two years; resulting in inter-individual drug absorption and exposure. The European Network on Understanding Gastrointestinal Absorption-related Processes (UNGAP) recognize this and use physiologically based pharmacokinetic modeling (PBPK) as a method to investigate formulation approaches closer during the drug development stages to reduce this pharmacokinetic variability [17]. Drug distribution can also be affected due to lower plasma protein concentrations, higher body water content, and lower blood volumes. From birth, immaturity in metabolic processes and lower body fat content can result in reduced drug clearance and increased drug half-life. Immaturity in glomerular filtration, tubular secretion, and reabsorption can also cause a reduction in renal drug excretion [14,15]. Unlike in older children, these factors mature and change rapidly at different rates between birth and the second birthday, creating a need for dosing regimens to be adapted. Figure 2 shows the sharp increase in weight [approximately triples] from term birth to two years relative to the rest of the pediatric population. But for preterm neonates, their weight may increase threefold over several weeks when receiving postnatal care [18]. Hence, dose adjustment constantly required brings constant concern/risk of misdosing, possibly even more to emotional parents returning home with their child from the hospital. Complex medicine regimes, polypharmacy, and difficulty in administration introduce dosing error risks and cause much anxiety as it is likely to cause significant effects the more vulnerable the patient is e.g. discharged babies form NICU. The PADDINGToN study [19] shows that supporting medicine administration with technology such as a phone application or QR codes on packaging could help provide easy access to information and advice when required by parents.

Flexible and acceptable (swallowable, palatable, easy to administer) dosage forms are therefore desired to allow for safe dose adjustment and optimal medical treatment, without impairing the quality, performance, and commercial viability of the pharmaceutical product, principally when considering (preterm)neonates [14,16,18].

1.2. Neonate, infant, and toddler excipient safety and administration considerations

Excipients generally recognized as safe for adults and possibly for older children/adolescents can be unsafe when dosed in under 2s due to their immaturity in ADME [11,18]. Those in intensive care are often polymedicated, leading to cumulative effects, drug interactions, and exacerbated adverse reactions, especially for preterm babies, with excipients in their treatment regime potentially exceeding the adult accepted daily intake. Therefore, when formulating suitable dosage forms for this group, the need for, type, and quantity of excipient used that does not deter its quality nor the bioavailability of the active pharmaceutical ingredient (API)

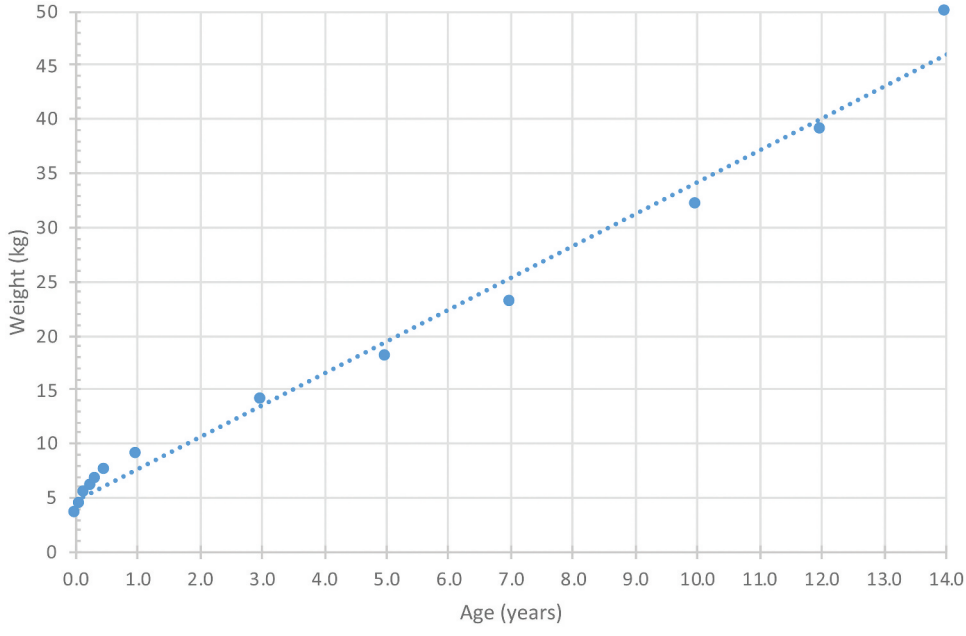


Figure 2. **Body weight as a function of age of children aged between term birth to 14 years**. Data obtained from 2009 UK-World Health Organization (WHO) growth charts and 1990 UK standard centile charts as per the British National Formulary [20].

should be considered [2,18,21]. Recent papers [22,23] highlight excipient concerns and mention studies such as ▣Safe Excipient Exposure in Neonates and Small Children (SEEN) and ▣European Study on Neonatal Exposure to Excipients (ESNEE) and their generation of an 'excipients of interest list' that demonstrate the achievability of progress in this area. The safety, tolerability, and exposure of excipients remain an underlying core consideration but will not be central to this review as it has been extensively detailed elsewhere [Walsh, *et al*., 2021 give an overview [4]].

1.3. Enteral feeding tubes

It is a norm for patients <2 years in ICU, or even preterm neonates returning home to have nutrition and treatment administered through enteral feeding tubes. Currently, many medicines given require unlicensed (UL) manipulation for this administration. Not only is there risk of incompatibility with enteral tubes and affecting the pharmaceutical quality and efficacy of the drug product but also these unstandardized manipulations introduce a true mis-dosing risk with possible significant side effects. This is the case especially for potent drugs given in small volumes. Liquids are more easily dosed through enteral tubes, however where solid formulations are concerned detailed guidance on suitable manipulation methods in SmPCs should be provided. Whether solid or liquid, future age-appropriate formulations should consider safe and efficacious administration (to the product's best ability) through enteral tubes by undertaking feasibility studies [24] if relevant to the condition treated.

1.4. Preferences toward route of drug delivery

Currently, treating children under 2 is skewed toward parenteral drug delivery, responding to a clinical need for fast and acute treatment of the seriously ill. For perspective, the European Union Clinical Trials Register (EudraCT) records 760 clinical trials conducted in children <2 since it began in 2004, of which ~72% were parenteral products [25]. However, oral drug delivery remains highly desirable, as suggested by O'Brien et al, 2019 [11], as it is better suited to long-term treatments, can be administered (or via enteral tubes) at home, and off-sets parenteral route limitations: punctuation and pain, risk of phlebitis, infection, electrolyte imbalance, fluid overload, incorrect dose volume measurement, and limited/difficult intravenous access [2,18,26]. There is prospect for the rectal route of administration as it bypasses these limitations and those associated with oral delivery for fast treatment, but there is an attached stigma to this route.

Prior to the regulation enforcement, the 2006 EMA reflection paper was first to propose a matrix to evaluate 'applicability' (i.e. age suitability) and 'preferability' of oral dosage forms for children but only based on general opinion of a few healthcare workers and carers. Figure 3 outlines the variability in responses for preterm, term neonates, infants, and toddlers.

Tablets, capsules, and chewable tablets were equally considered 'not applicable' for all age groups but, with all other formulations becoming more 'applicable' and 'preferable' with age. Interestingly, multiparticulate and monolithic formulations (powders, orodispersible) likewise were 'not deemed applicable' at all for preterm neonates and just slightly more 'applicable' yet still problematic for term neonates, infants, and toddlers. Liquids were deemed to have the greatest 'applicability' and 'preferability' across all the age groups, the assumption being a lower aspiration/choking risk [28] and that they can accommodate different age/weight-based doses via volumetric measurement (syringe, cup, and spoon). This highlights the deeper drug delivery gap for neonates. Although this study shows useful comparison between dosage forms, it is slightly outdated and shows how there is a lack of available and recent evidence that can be reflected upon to gain a more

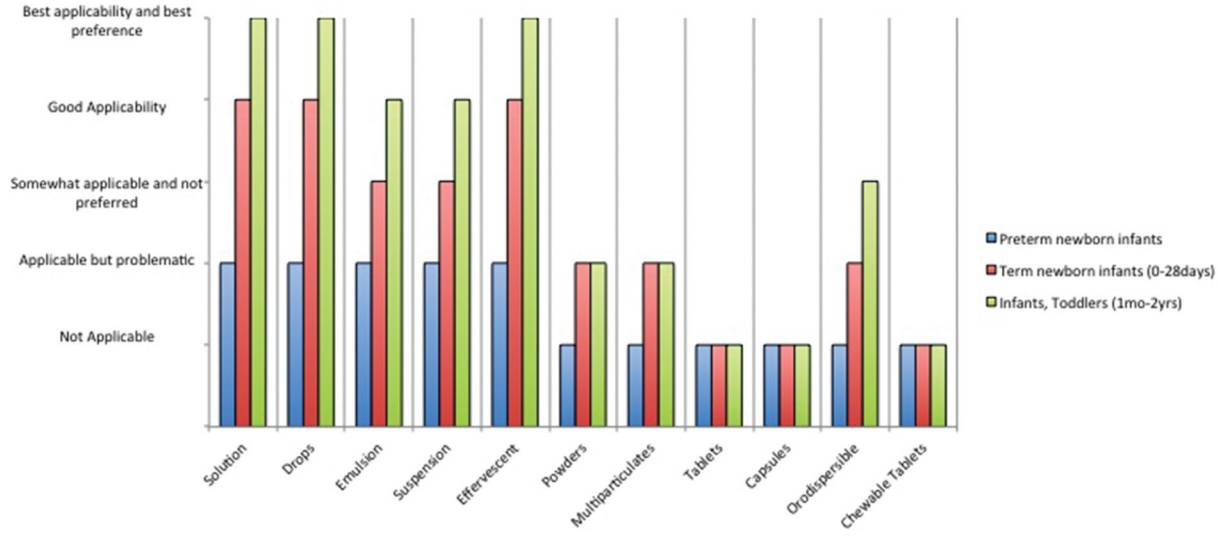


Figure 3. **Healthcare worker and carer (N = 40) opinion on the 'applicability' of various oral dosage forms to preterm and term neonates, infants and toddlers**. Adapted from EMA 2006 reflection paper [27].

current perspective, which may include other types of dosage forms for alternative administration routes, e.g. the rectal route.

Liquid oral drug delivery has been the gold standard for pediatric dosing, but is it the golden standard? As part of this, the 2007 WHO 'Make medicines child size' initiative has raised awareness and shifted the paradigm from liquids toward *flexible solid dosage forms: orodispersible tablets (ODT), dispersible/soluble tablets (DT) used to form a liquid preparation upon administration or smaller solids (i.e. multiparticulate) that may be mixed into a vehicle such as food, breastmilk to aid dosing particularly for <6 years* [29]. Recent publications such as Mfoafo et al., 2021 [30], consider them as a future trend to oral drug delivery. Hence, this review will not explore liquid, tablet, and chewable formulations but will present the advancement, trends, age-suitability, and an evidence-based analysis of these novel dosage forms for neonates, infants, and toddlers in order to assess if they could offer new innovation-fits-all approaches. The rectal route of administration and its associated barriers will also be explored.

2. Criteria to assess the age-appropriateness of dosage forms and evidence available

Acceptability of dosage forms is a concept that has emerged in the past decade. The 2013 EMA document 'Guideline on pharmaceutical development of medicines for paediatric use' formally defines 'acceptability' as *'The overall ability and willingness of the patient to use and its caregiver to administer the medicine as intended'* [31]. It indirectly encompasses factors such as illness status, treatment duration, mood, cultural influence, and general habits [27].

Table 1 shows the framework that will be used for the purposes of this review, to consider the added values and limitations of commercially available enteral formulations for children under 2.

As mentioned, there has been a shift away from oral liquids for children <2 years. Although advantageous in many regards, especially swallowability, oral liquids carry a higher risk of unsafe excipients and dosing error that oral solids can overcome. Illustrated by Table 2, in the past decade, there has been a surge of placebo clinical studies designed to generate evidence around acceptability of multiparticulates, DTs, ODTs, and orodispersible films (ODFs). More studies were found for multiparticulates, less so for ODFs, and none for (O)DTs, but it should be noted that this does not sway particular favorability toward multiparticulates.

These studies of children physically ingesting the dosage forms revealed that against general consensus, flexible solid dosage forms were acceptable, carrying less (if any) administration safety issues than expected, i.e. no significant cases of aspiration/choking. However, longer term usage, multiple (daily) administration and API inclusion were not explored, meaning palatability was not considered despite being a key limiting factor.

The driver for the switch to these flexible solid dosage forms is based on increased chemical and physical stability, fewer problematic excipients in comparison to liquids [28], potential for more efficient taste masking, smaller administration volumes and no swallowability issues. Section 3.0 of this article details currently licensed solid oral multiparticulate and monolithic formulations for children <2 years. No systematic search strategy was used; products were found in the literature as a starting point and then refined using electronic sources such as the Electronic Medicines Compendium.

3. Oral solid dosage forms

3.1. Multiparticulate dosage forms

There is potential for flexible dosing of multiparticulates, providing a suitable device or unit-dose packaging is integrated into product development and/or available; a field that has developed quickly in parallel [41].

Table 3 lists multiparticulate formulations (including two of the six PUMAs approved) for use in the under 2s grouped by their therapeutic indications.

It is to be noted that Table 3 may not be exhaustive as there is no official, easily searchable database that lists all currently licensed pediatric medicines globally. It should be noted that although more commercially available multiparticulate formulations have been sourced, this does not show favorability bias toward this dosage from type compared to the others. Moreover, most limitations listed are from the authors' interpretation and opinion as there is little public reports available.

3.1.1 – Minitablet Formulations

They are generally regarded as tablets measuring less than 4 mm in diameter [42,43], with similar low production costs but with enhanced swallowability. They can offer dose flexibility, but where smaller doses/counts are needed for younger/lighter children this can result in higher or significant risk of dosing error if

Table 1. **Consideration criteria involved in assessing the age-appropriateness of a dosage form**. Adapted from [28,29,31].

ACCEPTABILITY	Dosing	Sub-dividing of formulation for dosing flexibility without affecting safety or efficacy, directions, volume, number of tablets, frequency
	Preparation	Requirement to measure or manipulate formulation, device use, directions
	Ingestion ease	Swallowability, palatability (smell/taste/aftertaste/mouthfeel), size, shape, quantity, volume, discomfort level
SAFETY	Tolerability	No adverse effects/toxicity due to excipients
	Mis-dosing risk	Incorrect handling, measurement or administration, use of device
ACCESS	Stability	Shelf-life, in-use stability
	Manufacturability	Complexity, packaging, use of specialized processes
	Supply chain	Storage, transportability
	Cost	Cost of dosage form, device, API

Table 2. Recent placebo studies showing the shift and increase in acceptability toward solid formulations in children, participants including <2 years.

Study	Main Conclusion
MULTIPARTICULATE FORMULATIONS	
Minitablets	
Spomer et al., 2012 [32]	6 months–6 years: one 2 mm uncoated minitablet placed on tongue and swallowed with 3 or less mouthfuls of chosen drink. Better or equal acceptance compared to 3 ml of 15% glucose syrup. For 6–12 months, swallowability of tablet to syrup was higher. For 12–24 months, swallowability of tablet to syrup was higher, only 10% refused the tablet compared to 40% for the syrup.
Klingmann et al., 2013 [33,34]	6 months-5 years: one 2 mm coated/uncoated minitablet placed on tongue (swallowed with 3 or less mouthfuls of drink). For 6 months-2 years Acceptability and swallowability significantly higher for coated/uncoated minitablets than 3 ml 15% glucose syrup. No significant difference between acceptability/swallowability of uncoated/coated.
Van Riet-Nales et al., 2013 [35]	1–4 years: one 4 mm uncoated minitablet given twice on one day (method decided by parents). Better acceptability than syrup, granules, and suspension, good preference by child and parent for minitablets reported across all ages.
Klingmann et al., 2015 [34,36]	Neonate 2–28 days (11 preterm): one 2 mm uncoated minitablet placed in cheek pouch with neonate lying on side (swallowed with drink) showed better swallowability than 0.5 ml 15% glucose syrup
Van Riet-Nales et al., 2015 [37]	1–4 years: one 4 mm uncoated minitablet administered twice in one day. For 12–23 months: Good visual analogue scale score regarding administering the tablet directly or mixed with food.
Klingmann et al., 2018 [38]	6 months-5 years: For 6 months–2 years: 25 or 100 minitablets given with drink. Swallowability more superior than 5 ml 15% glucose syrup
Granules/Sprinkles	
Van Riet-Nales et al., 2013 [35]	1–4 years: one sachet administered twice in one day (method decided by parents). Good visual analogue scale score.
Van Riet-Nales et al., 2015 [37]	1–4 years: one sachet administered twice in one day. For 12–23 months: Good visual analogue scale score regarding administering the granules directly, with little food/drink and larger quantity food/drink. Score highest when given with large quantity food/drink.
MONOLITHIC FORMULATIONS	
Orodispersible film (ODF)	
Orlu et al, 2017 [39]	6 months-–5 years: one ODF (2x3cm) given. 79% of the caregivers with an infant <2 years gave a score of 5 or more on the medicine acceptability scale *(5 or more was regarded as acceptable)* 83% of infants <2 years were given a score of 5 or more by nurses.
Klingmann et al. 2020 [40]	2 days–12 months: one ODF (2x3cm) split in half. One half placed in both left and right cheek pouch concurrently and given with a chosen drink (max. 4 mouthfuls) Vs. glucose syrup (0.5 ml for 2–28day old group, 3 ml for 29 days–5 months and 6–12 months group). Overall acceptability of ODF: 95.3% of participants Overall acceptability of syrup: 80.7% of participants (Acceptability of ODF versus syrup 100% in neonates.) Overall palatability and swallowability assessment favoring toward ODF.

NB. Other papers detailing placebo acceptability studies are available but are not included in Table 2 *as they involved children >2 years, and so will be discussed in the text.*

counted inaccurately, leading to dosing devices or packaging considerations being central to this application. Additionally, the number of minitablets for higher doses should not reach uncomfortable levels for the child to swallow [34,42].

Whilst there are more formulations of the granule/sprinkle type compared to minitablets approved for use in the under 2s, there are more placebo acceptability studies present for minitablets. The primary study conducted by Thomson et al. in 2009 [44] with participants 2–6 years, paved the way for further studies in younger children. These showed excellent acceptability and swallowability of at least 1 minitablet administered with <3 mouthfuls of drink in children as young as 2 days (including preterm neonates), with as many as 100 minitablets administered with a drink in infants as young as 6 months. When compared to the acceptability and swallowability of 15% glucose (0.5 ml in neonates; 3–5 ml in infants and toddlers), minitablets were always superior with parents being in their favor. Acceptability/swallowability of coated and uncoated minitablets were not significantly different. As these studies showed promising swallowability and ease of administration in neonates as young as 2 days, including preterm neonates, more licensed minitablets for under 2s might emerge in the coming years or as evidenced in some recent studies mentioned below.

To demystify concerns about swallowability safety in young infants, the concept of orodispersible minitablets has been pondered, e.g. Stoltenberg et al. 2011 [45]. Before the age of 5 months, infants only swallow liquids safely due to an extrusion reflex. From 6 months they should be able to swallow soft foods. Thus, combining the benefits of a minitablet with properties of disintegration in a small amount of saliva seems a way forward to dose the youngest of patients.

Other minitablets are marketed for slightly older children: Slenyto (melatonin) ~3 mm diameter minitablet [>2 years for insomnia treatment [46]] and Pancrease^{TM} HL Capsules containing ~2 mm enteric coated minitablets [>15 years for cystic fibrosis exocrine insufficiency [47]].

Merck & Co. addressed in a recent study [43] unpleasant minitablet palatability (taste, texture) containing amorphous solid dispersion APIs (*undisclosed*), when administered with semi-solids i.e. applesauce *(type unspecified)*. Their aim was to investigate a coating that prevented early API release to provide a pragmatic timeframe for administration whilst avoiding palatability issues that may deter the child from future dosing/feeding sessions.

3.1.2 – Granule, pellet, powder, sprinkle formulations

Granules are nonuniform in shape with a broad size distribution. Two placebo studies [35,37] (Table 2), showed good scores and suitability in children 1–4 years when administering granules with/without food or drink.

Table 3 lists 21 formulations of which the majority are granules and only 1 pellet and 1 powder formulation. 12 are packaged in unit-dose sachets, 9 in unit-dose capsules and only one product (Creon® Micro Pancreatin 60.12 mg Gastro-resistant Granules, 2004) is in a multi-dose bottle with a dosing scoop. As mentioned earlier, there is a larger gap in drug development for neonates. This is evidenced in Table 3 with only 7 licensed products for neonatal use: Lopimune® (lopinavir/ritonavir) and Co formulated lopinavir+ritonavir, Episenta® (sodium valproate) and Epilim Chronosphere® (sodium valproate/valproic acid), Alkindi® (hydrocortisone), Tamiflu® (oseltamivir phosphate) and Xuriden® (uridine triacetate). The other 14 are licensed for use in infants onwards.

Analyzing the SmPC's shows some disparity/clarity of information provided for carers which may affect administration ease, for example, unspecifying the type or volume of dosing vehicle required. Too little may result in unpalatable taste/texture, with too much meaning incomplete dose ingestion. This may also become an issue when extra food/liquid needs to be added to mixing containers to disperse remaining product. Vague terms such as to mix with 'food' 'liquid' or 'drink' are used. This could pose incompatibility risks of reduced drug efficacy/taste masking if administered with certain foods/drinks, especially if a coating is disrupted.

Some additional information can make administration guidance clearer such as: recommendations to not administer via a feeding bottle as blockage may occur hindering accurate dosing, explicitly saying bottles may be used, stating no mixing with liquids due to effects on taste masking as well as ability to administer a full dose, recommending certain vehicle types e.g. acidic (fruit juice/sauce), fat-containing media or even avoidance of a food type (e.g. grapefruit). Epilim® Chronosphere (sodium valproate/valproic acid) seems to be the only example from Table 3 making a clear statement in the SmPC that its drug PK is not altered when mixed with food. It should be noted that dosing vehicles to aid swallowing or taste can help to increase acceptability and adherence to the medicine (particularly for chronic use) and so, where warnings are provided in SmPCs such as those for Alkindi® (hydrocortisone) (i.e. no mixing with liquids), unless there is clear clinical evidence of significant negative effects, stating so should be carefully considered [37].

14 of the 21 formulations have a coating. To note on palatability, 6 of the 21 formulations contain flavors including: strawberry, orange-vanilla, apricot, and natural orange juice and 7 of the 21 formulations contain sweeteners and/or polyols: sucrose, mannitol, glucose, aspartame, sucralose, and acesulfame potassium.

The CHAPAS-2 study for Lopimune® (lopinavir/ritonavir) illustrates the importance of palatability for children under 2. Uncoated granules dissolved in a small quantity of breast milk were administered to unweaned infants with a spoon or placed directly on the tongue before breastfeeding. For weaned infants/toddlers, unspecified amounts were mixed into porridge, with recommendations to add honey/sugar to enhance palatability. Although swallowability of granules was superior compared to the syrup equivalent in children aged between 3 months and 4 years, parents reported poor taste resulted in the child struggling to eat or perhaps later refusing feedings. There were concerns on how much honey/sugar may be required to make Lopimune® (lopinavir/ritonavir) more acceptable; especially for higher doses, with added concerns around extra expense, and that perhaps the syrup equivalent would ensure more dose ingestion [48]. The LOLIPOP trial for Quadrimune® (abacavir/lamivudine/lopinavir/ritonavir) is underway with granules coated with strawberry flavor hopefully offering better taste. It should be noted that other palatability characteristics (texture: hardness, roughness, cohesiveness and fracturability/shape) as well as dose volume are concomitantly important for multiparticulate acceptability [49,50].

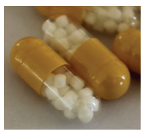
Although NGTs may be used as a method of drug administration, it cannot be expected that all formulations may be suited to this form of drug delivery. Only 4 products [Desitrend® (levetiracetam), Nexium® (esomeprazole), Vistogard® (uridine triacetate), Prevacid® (lansoprazole)] in Table 3 mention that an NGT may be used. All four give instructions on its use but are not necessarily clear on details such as flush volume, composition/frequency of flushing, tube lumen diameter, compatibility data of the prepared formulation with the tube material or blockage issues. Dose/flush volumes listed may also seem unsuitably high for the target age especially if fluid restricted [Desitrend® (levetiracetam) and Vistogard® (uridine triacetate)].

A recent Q&A on the quality of medicines by the EMA [24] outlines what data is required to show a formulation's feasibility to be administered optimally via NGT as well as what should be included in the SmPC and patient information leaflet (PIL). For the former, feasibility studies should encompass how modifying the drug product may affect bioavailability or risk of tube blockage: fine dispersal/complete dissolving of the solid dosage form is required and particle size, dispersion medium/volume/viscosity, tube lumen diameter/material and data on dose recovery (>90% is acceptable), and minimum flush volumes (a consideration for fluid restricted patients).

3.2 – Monolithic dosage forms

Although monolithic formulations [DT and orodispersible dosage forms (ODT, ODF)] may be administered flexibly to a young child (e.g. ODT/ODF can be predispersed or swallowed whole), they are not necessarily as dose flexible as multiparticulate formulations since they may require manipulation e.g. splitting. They would require multiple dose strengths to be fully flexible [11,87]. Compared to conventional tablets however, they do not require crushing associated with potential dosing error and altered biopharmaceutical properties [49]. Their stability is also regarded as being more challenging than conventional tablets due to their reactivity with moisture, yet are still more stable than liquid formulations [28]. Overall, they offer another option to dose the <2 years. Table 4 summarizes relevant

Table 3. Commercially available solid multiparticulate formulations for neonates, infants, and toddlers.

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
GRANULES, PELLETS, SPRINKLES, POWDERS									
HIV									
Lopimune, FDA approved 2015 (Cipla Pharmaceuticals) [20,48,51–54] 	Lopinavir/ Ritonavir fixed-dose combination (LPV/r), heat stable, Sprinkle (pellet) capsules, for sprinkling	40 mg/10 mg unit-dose capsules (for sprinkling) in bottle of 120 capsules	From 14 days old (term) weight-based dosing: twice daily regimen (morning/evening 5 < 6 kg *(~2–3 months) 2 capsules Up to >35 kg *(>10 years) 10 capsules *Dose adjustment required for co-administration with other anti-retroviral /tuberculosis therapies*	Capsule contents to be sprinkled onto sweetened porridge/ expressed breastmilk on a spoon and mixed.	n/a No data for administration via Nasogastric tubes (NGT)	Yellow-clear capsules uncoated pellet size unknown,	<30°C 24 months For immediate ingestion, No in-use stability times/data	▣Children 3 months-13 years with HIV in Africa Pharmacokinetics and Adherence of Simple Anti-retroviral regimens study (CHAPAS-2) 2012 [48,54] LIVING trial in infants and young children 3 < 25 kg in Kenya and Uganda [55,56]	**Reported Limitations**: • Poor taste – porridge sweetening with honey/sugar not very effective. Differences in taste/ mouthfeel for capsules sprinkled in breastmilk for neonates and infants. • Higher capsule number use as child's weight increases **Author Identified Limitations**: • A child of minimum 5 kg (of normal healthy weight) is typically ~2 months. This therefore does not account for treating neonates of 14 days. [20]
▣Co-formulated lopinavir + ritonavir, tentative FDA approval 2018 (Mylan Laboratories) [20,51,55]	Lopinavir/ Ritonavir fixed-dose combination (LPV/r), heat-stable, Sprinkle (granule) sachets	40 mg/10 mg unit-dose sachets	From 14 days old (term), Weight-based dosing: twice daily regimen (morning/evening) 5 < 6 kg * (~2-3 months) 2 sachets Up to >35 kg *(>10 years) 10 sachets *Dose adjustment required for co-administration with other anti-retroviral /tuberculosis therapies*	Sachets contents sprinkled and mixed with liquid/ semi-solid food For liquid: ~ ▣1 teaspoon (tsp) liquid for 2 sachets; -2 tsp for 3–8 sachets; -3 tsp or 1 tablespoon (tbsp) for 10 sachets	n/a No data for administration via NGT tube	uncoated granules size unknown	<30°C 24 months To be administered within 2 hours of preparation	Based on LIVING trial conducted for Lopimune	**Author Identified Limitations**: • Poor taste • Similar limitations to Lopimune • Granules may remain in sachet, full dose not achieved • A child of minimum 5 kg (of normal healthy weight) is typically ~2 months. This therefore does not account for treating neonates of 14 days. [20]

(*Continued*)

Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
Quadrimune, Under FDA review (Cipla Pharmaceuticals) [57,58] Mylan Laboratories to submit generic formulation of ABC/3TC/LPV/r granules for approval in 2020 [59]	Abacavir/ Lamivudine/ Lopinavir/ Ritonavir (ABC/ 3TC/LPV/r) fixed-dose combination, Sprinkle (granule) capsules	30 mg/15 mg/ 40 mg/10 mg unit-dose capsules	From 4 weeks old (term) Weight-based dosing twice daily regimen, Weight-based dosing: 3 < 6 kg *(term neonate – ~3 months): 2 capsules Up to 20 < 25 kg * (~6-8 years): 6 capsules	Capsule contents sprinkled and mixed into food/ water/milk	n/a	Granules size unknown, Coated and with strawberry taste masking	Data not available	LOLIPOP Phase I/II Trail in Uganda (NCT03836833), infants and young children 3 < 25 kg, still underway and unpublished [58]	**Author Identified Limitations**: • Higher capsule number use as child's weight increases • minimum volume of liquid not specified • type of milk unspecified
Reyataz, 2014 (Bristol-Myers Squibb) [60]	Atazanavir sulfate Oral powder	50 mg unit dose sachet (1.5 g powder) Each carton containing 30 sachets	From 3 months, >5 kg Weight-based dosing once daily dosing 5 < 15 kg *(3 months–~5 years): 200 mg (4 packets) 15 < 25 kg *(~5 years–8 years): 250 mg (5 packets) 5 < 10 kg who do not tolerate 4 packets, may take 3	Must be taken with 80 mg ritonavir (oral solution) and food For infants who can drink from a cup/ eat semi-solids: Mix with soft food (min. 1tbsp) e.g. apple sauce, yogurt. Add another tbsp food if required. Or infant formula, milk, water (min. 30 ml). Add 15 ml more for residual mixture left For infants who cannot drink from a cup/eat semi-solids: mix with 10 ml formula and administer via syringe into inner cheek area. Use another 10 ml of formula to rinse syringe and then re-administer this to child with syringe Do not use infant bottles as child may not receive full dose	Syringe	Orange-vanilla flavor, sucrose, aspartame	20–30°C For immediate ingestion within an hour of preparation	Two PK and virologic response studies in children in 3 months-6 years, 3 months-11 years Safety profile studies showing similarity to adults	**Reported Limitations**: Do not use infant bottles as full dose may not be achieved **Author Identified Limitations**: • Product may remain in/block syringe

(*Continued*)

Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
MALARIA									
Pyramax, Positive opinion from EMA 2015 and on WHO Essential medicines list 2017, submitted to EMA for regulatory approval (Shin Poong Pharmaceutical Co. Ltd.) [61–63] 	Pyronaridine-artesunate fixed-dose combination, Granules For treatment of uncomplicated malaria (*P. falciparum and P.vivax)*	60 mg/20 mg unit-dose sachets. Available in pack size of 90 sachets	For infants-children weighing 5–20 kg Once daily dosing for 3-day therapy 5 < 8 kg *(~2–9 months) 1 sachet 8 < 15 kg * (~9 months-4 years) 2 sachets 15 < 20 kg *(~4 years–6 years) 3 sachets	Empty contents of sachet into a cup containing ~10 ml (2tsp) of drinking water and stir until there is even suspension of granules (*should not dissolve*). Continue to add 2tsp water to the cup, stir and ingest until no remaining granules.	n/a	Orange colored granules, Coated Mannitol, acesulfame potassium	<30°C, 2 years For immediate ingestion. With/without food	West African Network for Clinical Trials of Antimalarial Drugs (WANECAM) phase IIIb/IV study in Africa In infants >6 months, >5 kg (safety, efficacy, PK) [62,63]	**Reported Limitations**: • No studies present on compatibility with feeding tubes • Only drinking water may be used in the preparation **Author Identified Limitations**: • Possibility of granulated mouthfeel

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Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
EPILEPSY									
Desitrend, 2012 approved, (Desitin Pharma) [49,64–66]  	Levetiracetam, granules	Available in 250 mg, 500 mg and 1000 mg unit-dose sachets. Pack sizes of: 20, 30, 50, 60, 100, 200 sachets	From 1 month-23 months: Twice daily dosing (morning/evening) as an add-on adjunctive therapy. Recommended for doses >250 mg and that which are multiples of 250 mg for ease of sachet use. Dose determined by doctor based on age and weight i.e. 20 mg/kg (However, Levetiracetam granules not adapted for use in children <6 years or weighing <25 kg. There is no safety and efficacy data on use of Levetiracetam in children <16 years). Dose adjustments required for renally impaired patients.	Sachets contents can be emptied directly into mouth and swallowed with required volume of liquid, with/without food. Suspend granules in minimum 10 ml water and shake for 2 minutes for NGT administration. Twice rinsing of tube with 10 ml water required after each administration.	NGT tube	White, ~2 mm diameter round granules, coated	Room Temperature, 5 years Immediate use following suspension preparation	Most studies are PK analysis in comparison to Desitrend oral solution Acceptability study survey found only performed in adults in Germany regarding general acceptance, satisfaction, swallowability or preference compared to larger conventional tablets. [66]	**Reported Limitations**: • Chewing of the coated granules by an infant/toddler may introduce bitter taste • Levetiracetam oral solution is still the recommended dosage form for doses <250 mg/not a multiple of 250 to achieve accurate dosing • Available strengths not suitable for those <25 kg for initial treatment **Author Identified Limitations**: • Granules may remain in sachet, full dose not achieved • Rinsing of feeding tubes with water post administration undesirable if patient is fluid restricted. • Incorrect rinsing of NGT tubes, may result in blockage

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Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
Episenta+, 2006, (Desitin Pharma) [67,68]	Sodium valproate granules (prolonged-release)	Available in 500 mg, 1000 mg unit-dose sachets. Pack sizes of 50, 100, 200 sachets Excipient known to have effect: sodium 69 mg (per 500 mg Episenta sachet)	Neonate-17 years According to BNFc: 1–2 daily doses Neonate: 20 mg/kg once daily initially. For maintenance 10 mg/kg twice daily 1 months-11 years: 10–15 mg/kg daily initially across 1–2 doses (max. for each dose 600 mg). For maintenance 25–30 mg/kg daily across 2 doses Up to 60 mg/kg daily can be used for infantile spasms (across 2 doses) According to SmPC: Weight-based dosing Children <20 kg *(<5–7 years): 20 mg/kg once daily (severe cases, 40 mg/kg/day) Children >20 kg *(>5–7 years): initially 300 mg/day max. going by 20–30 mg/kg (can be increased to 35 mg/kg/day) (sodium levels in max. dose within limits of max. recommended daily intake of sodium for neonates of <0.4 g, for 1–3 years of <0.8 g)	Granules should be mixed with plenty of drink/ amount of soft food that is room temp. or cold. Rinse with liquid if granules remain and ingest as well.	n/a	White/off-white round granules, Coated (Ethyl cellulose, dibutyl sebacate, oleic acid) No taste	<30°C, 36 months Immediate ingestion following preparation	PK/PD studies Study showing effects (palatability/ease of use) of switching from solution formulation to prolonged-release granules [69]	**Reported Limitations:** • Cannot be crushed/ chewed • From PK studies, infants <2 months, prolonged half-life of up to 60 hours. • Do not give to children in a bottle as blockage of the teat can occur **Author Identified Limitations**: • Full dose may not be achieved as granules may remain in preparation container • Dosing error may occur since required doses do not match unit-dose sachets. • No stability data available for when sachet is opened

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Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
Epilim Chronosphere, 2006[+], (Sanofi) [68,70]	Sodium valproate/ valproic acid granules (modified-release)	Unit-dose sachets containing sodium valproate/valproic acid in various amounts that equivalate to the active sodium valproate at doses of 50 mg, 100 mg, 250 mg, 500 mg, 750 mg, 1000 mg e.g. 152 mg sachet contains sodium valproate 33.33 mg/ valproic acid 14.51 mg, which is equivalent to 50 mg of the active Sodium Valproate Pack sizes of 30, 50 sachets	Neonate-11 years According to BNFc: 1–2 daily doses Neonate: 20 mg/kg once daily initially. For maintenance 10 mg/kg twice daily 1 months-11 years: 10–15 mg/kg daily initially across 1–2 doses (max. for each dose 600 mg). For maintenance 25–30 mg/kg daily across 2 doses Up to 60 mg/kg daily can be used for infantile spasms (across 2 doses) According to SmPC: Weight-based Children <20 kg *(<5–7 years): 20 mg/kg once daily (can be increased but only if levels of valproic acid can be monitored) – to the nearest whole 50 mg sachet Children >20 kg *(>5–7 years): initially 400 mg/day (regardless of weight) and then increased gradually to gain seizure control, going by 20–30 mg/kg (can be increased to 35 mg/kg/day) – to the nearest whole 50 mg sachet	Granules should be mixed with drink/small amount soft food that is room temp. or cold (not with hot food/drink) Rinse with liquid if granules remain and ingest as well. Granules may be directly emptied in mouth followed by a drink	n/a	Small white/off-white to slight yellow waxy microgranules Coated	<25°C, do not freeze/ refrigerate 24 months Immediate ingestion following preparation	PK/PD studies (Drug PK not affected by mixing with food)	**Reported Limitations**: • Cannot be crushed/ chewed • Cannot be administered with hot food/ drink • PK studies report half-life is shorter in children than adults • Cannot store partially used sachets • Do not give to children in a bottle as blockage of the teat can occur

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Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
ACUTE DIARRHEA									
Hidrasec, 2011, (Bioproject Europe Ltd.) [71]	Racecadotril, Granules	Available in 10 mg and 30 mg unit-dose sachets Pack sizes of 10, 16, 20, 30, 50, 100 (100 only for hospital usage)	From 3 months onwards, weight-based dosing (1.5 mg/kg per dose) 3 times daily regimen at appropriate intervals. Treatment to not exceed 7 days. -10 mg sachet suited to weights <13 kg -30 mg sachet suited to weights >13 kg <9 kg one 10 mg sachet 3 times daily 9–13 kg two 10 mg sachets 3 times daily	Sachet Granules can be dispersed into food or drink or feeding bottles.	n/a No data for administration via NGT tube	uncoated granules Appearance of white powder, apricot odor and flavor, sucrose	2 years For immediate administration.	Lack of dosage form acceptability studies. Majority in regard to Racecadotril versus placebo	**Author Identified Limitations**: • Available sachet strengths not suitable for infants <13 kg – dose splitting may result in inaccurate dosing • Volume of liquid/ food not specified • Granules may be left behind in bottle teat

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Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
CYSTIC FIBROSIS									
Creon Micro+, 2004 approved, (Mylan Products Ltd.) [72–75]  	Pancreatin Granules (gastro-resistant) For pancreatic exocrine insufficiency treatment (due to cystic fibrosis)	60.12 mg Pancreatin (per 100 mg scoop). Packaged in glass bottle with LDPE stopper containing 20 g granules.	From 1 month onwards Taken with each feed/ meal One 100 mg scoop	Granules to be mixed with apple juice (required volume). Administered on a spoon before a feed. Weaned infants and toddlers to take with undiluted acidic liquids or semi solids (e.g. fruit juice, fruit sauce) Alternatively, mixed with milk on a spoon. Must not be mixed in drink bottle	scoop No data for administration via NGT tube	Round, light brown granules Enteric Coated (Hypromellose phthalate)	<30°C, 2 years 12 weeks after opening For immediate administration Mixing with food with pH>5.5 will disrupt the enteric coating	Dosage form acceptability study part of 2012 safety and efficacy clinical trial in Russia, infants and toddlers <2 years and children 2–3 years. [74,75] 2004 French parent preferability study of Creon Micro versus Creon capsules, 6–36 months [76]	**Reported Limitations:** • Accidental chewing of the granules would disrupt the enteric gastro-resistant coating • Disruption of enteric coating causes early release of enzymes, thus reducing efficacy, causes oral irritation. • Product remaining in mouth may cause irritation • Must not be mixed in drink bottle **Author Identified Limitations:** • If contents are prepared in a separate container and then administered via a spoon, product may remain unadministered • Accurate weight of 100 mg may not be achieved with scoop due to ± of granules • Milk is pH6.5–6.7 (greater than recommended) • Type of milk unspecified

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Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
Kalydeco, 2015 approved, (Vertex Pharmaceuticals) [41,77–79]	Ivacaftor, Oral Granules	Available in 25 mg, 50 mg, 75 mg unit-dose sachets. Pack sizes contain 4 wallet cards, each wallet card has 14 sachets. (Total of 56 sachets – 1 month supply)	For ages 4 months-6 years, 5 < 25 kg Twice daily dosing (every 12hrs), to be taken just before or after consumption of food containing fat. 4 < 6 months, >5 kg: one 25 mg sachet 6 months–6 years – dosing is weight based: 5 < 7 kg one 25 mg sachet 7 < 14 kg one 50 mg sachet >14 kg one 75 mg sachet	Contents of each sachet to be mixed with 1 tsp (5 ml) of fat containing liquid/semi-solid food at room temperature or below. Avoid grapefruit. Through use of spoon/ syringe. Not to be given with bottle. Video aid available for patients for demonstration.	Optional use of syringe for administration No data for administration via NGT tube	White, ~2 mm diameter, Enteric coated (Hypromellose acetate succinate) Sucralose, mannitol	Room temp. 3 years, To be administered within 1 hour of preparation	Safety study of Kalydeco in infants 4 – <6 months and 6 months – <1 years and toddlers 1- <2 years Proved similar safety profile to Kalydeco use in children >2 years and adults. [78,79]	**Reported Limitations**: • Avoid administering with grapefruit **Author Identified Limitations**: • Minitablets may remain in sachet, full dose not achieved • Some of the pre-pared dose may remain in syringe

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Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
ADRENAL INSUFFICIENCY									
Alkindi, 2018 approved, (Diurnal Europe B.V.) [80] PUMA  	Hydrocortisone, Oral granules in capsules	Available in 0.5 mg, 1 mg, 2 mg, 5 mg unit-dose capsules. In bottles of 50 capsules with a polypropylene closure and integrated desiccant.	From term neonate-18 years Dosage to be individualized depending on clinical response (lowest possible dose to be used) Recommended: • Patients with adrenal insufficiency alone: 8–10 mg/m^2/day • Patients with congenital adrenal hyperplasia: 10–15 mg/m^2/day (given in ¾ doses) • Patients with some endogenous cortisol production: lower dose may suffice • Patients with excessive physical/mental stress: may require increased dose (particularly in afternoon/evening)	Capsule to be opened and granules poured directly on child's tongue or via a spoon. Alternatively, may be mixed with a spoonful of cold/room temp. semi-solid food. Not to be mixed with liquid as full dose may not be achieved and effect on taste masking Granules not to be chewed. Drink is recommended after administration to ensure all granules are swallowed.	Administration via NGT tube not recommended due to possibility of blockage	White/off-white granules, colorless transparent capsule Coated (Ethylcellulose taste masking)	<30°C, 3 years, 60 days after opening To be administered within 5 minutes of preparation (if mixed with food)	Swallowability and Palatability assessment using 5-item Likert scale and questionnaire, children aged birth-28 days, 28 days-2 years, 2–6 years [80]	**Reported Limitations:** • NGT tube not recommended • Preparation with liquid not recommended due to effect on taste masking • Not to be mixed with liquid as full dose may not be achieved and effect on taste masking • Do not chew granules, affects taste masking **Author Identified Limitations:** • Instructions for: Capsule to be held with printed side at top and tapped to ensure all granules are at bottom half of capsule. Bottom half of capsule to be squeezed and then top half twisted off. • (Package leaflet contains detailed pictograms) – however, may be done incorrectly, spilling some product. • In-use stability when prepared with soft-food is very short (5 mins)

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Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age*, *Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
TUBERCULOSIS									
Granupas, 2014 (Eurocept International BV) [81]	Para-aminosalicylate, Granules (gastro-resistant)	Available in 4 g sachets in pack sizes of 30	From >28 days, Uncertain optimal dose regimen, Weight-based dosing: 150 mg/kg per day over two intakes	Granules to be added to orange/tomato juice/ apple sauce/yogurt. Will not dissolve, add more liquid to any granules left	Dosing spoon to measure doses under 4 g	White/light-brown granules, ~1.5 mm diameter Enteric coated (Methacrylic acid – Ethyl acrylate copolymer)	<25°C 2 years, 24 hours after opening at 25°C For immediate administration	Limited PK data notes similarity between children and adult	**Reported Limitations**: • Granules may sink to the bottom of liquid preparation. Constant stirring is required to resuspend them • Chewing of granules disrupts gastro-resistant coating • Swelling to the sachet or discolouration of granules to dark-brown/purple color can occur – should then not be used **Author Identified Limitations**: • Volume of liquid/ food not specified

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Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
GASTROESOPHAGEAL REFLUX									
Nexium, 2007 (AstraZeneca) [41,82]	Esomeprazole (as magnesium trihydrate) Gastro-resistant delayed-release granules	20 mg, 50 mg unit dose sprinkle capsules provided in bottles Or as 10 mg, 20 mg, 40 mg sachets (cartons containing 28 or 30 sachets)	From 1–11 years, >10 kg: Weight-based dosing Once daily dose 10 < 20 kg: 10 mg for 8 weeks >20 kg: 10 mg or 20 mg for 8 weeks	Add to applesauce For children with NGT/ gastric tube (using sachets): For 10 mg dose, add to 15 ml water For 20 mg dose, add to 30 ml water Leave for a few minutes to thicken Inject via syringe into enteric tube (French size 6 or larger) Refill syringe with same initial quantity of liquid used to flush. Discard unused suspension	Suspension for NGT tube administration	Capsule granules: room temp, White/pale brown granules Sachet granules: room temp, pale yellow granules, some brown granules may be present Enteric coated Sugar spheres (sucrose, maize starch), glucose	3 years Sachet granules: use within 30 mins of preparation	Safety profile studies show similarity to adults PD Placebo studies in children between 0–11 years	**Reported Limitations**: • Sachets: Esomeprazole unstable in acidic media. Unsuitable therefore for apple sauce recommended • Doses over 1 mg/kg/ day have not been studied well • Interaction with other drugs not studied in children, only adults **Author Identified Limitations**: • Volume of apple-sauce not specified. • Extra strep of rinsing enteric tube would add extra fluid to fluid restricted patients • Short in-use stability time.
Aciphex, 2013 (Eisai) [83]	Rabeprazole Sprinkle granule capsules delayed-release	5 mg, 10 mg Supplied in bottles of 30, 90 capsules Or blisters of 100	From 1–11 years: Weight-based dosing Once daily dosing (up to 12 weeks) <15 kg *(~<5 years): 5 mg (can be increased to 10 mg) >15 kg *(~>5 years): 10 mg	Contents to be mixed with spoonful of soft foods e.g. apple sauce, yogurt, vegetable-based baby food, or liquids: formula, apple juice or pediatric electrolyte solution in a small container. Administered via spoon or syringe To be taken 30 mins before meals	syringe	Light yellow granules 5 mg capsule: transparent blue, opaque white capsule 10 mg capsule: transparent yellow, opaque white capsule Enteric coated Flavors, mannitol	Room temp Within 15 mins of preparation	Adverse reaction and efficacy studies in children 1–11 years PK studies in 1–11 years: total exposure of 10 mg dose equivalent to 10 mg tablet in adults	**Reported Limitations**: • Unstable in acidic media (meaning it would be unstable when mixed with recommended foods • Do not chew/crush granules **Author Identified Limitations**: • Product may remain in/block syringe • Short in-use stability time.

(*Continued*)

Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
Prevacid+, 1995 (Takeda Pharmaceuticals) [84] (Generic available by Sandoz) 	Lansoprazole (Delayed-release sprinkle granule capsules)	15 mg, 30 mg 15 mg packaged as 30,100 or 1000 capsules 30 mg packaged as 100 or 1000 capsules	From 1–11 years Weight-based dosing: <30 kg *(~<10 years): 15 mg/day for 12 weeks >30 kg: 30 mg/day for 12 weeks	Swallow whole. For those with swallowing difficulty: Open capsule and sprinkle on one tablespoon of applesauce, ENSURE pudding, cottage cheese, yogurt or strained pears Alternatively, sprinkle in small volume of apple/ orange/tomato juice (~60 ml), mix, swallow immediately. Then rinse glass with two more volumes of juice and administer. NGT administration: Mix granules in 40 ml of apple juice only and inject through NGT into stomach (size 16Fr or larger). Flush with additional apple juice.	NGT	Opaque hard gelatine capsules 15 mg: pink and green 30 mg: pink and black Enteric coated Sugar sphere, sucrose	20–25°C Sprinkled with food/drink: for immediate ingestion Dispersed in water for NGT administration: 15 mins	PK studies in neonates <28 days and infants 1–11 months (higher exposure compared to adults found) PK studies, 1–11 years, 12–17 years	**Reported Limitations**: • Studies on use of other foods not done so administer with recommended foods/drink only. **Author Identified Limitations**: • Administration with juice – volumes too large for infants • Apple juice volume for NGT administration too large for infants • NGT tube size too large for infants • Flush volume for NGT administration not given
ANTIVIRAL									
Sustiva+, 1999 (Bristol-Myers Squibb) [41]	Efazirenz Sprinkle capsules	50 mg, 100 mg, 200 mg Hard sprinkle capsules	From 3 months-17 years, >3.5 kg Weight based dosing 3.5 < 5 kg: 100 mg 5 < 7.5 kg * (~<6 months): 150 mg 7.5 < 15 kg: * (~<5 years): 200 mg Up to >40 kg *(~>14 years): 600 mg	Swallowed whole, but if cannot swallow: Open capsules and add contents to 1–2 tsp soft food e.g. apple sauce, jelly, yogurt and administered with a spoon. Add 2 tsp more food to container to disperse remaining product No administration of food for up to 2 hours after administration of Sustiva		n/a	50 mg capsule: dark yellow and white 100 mg capsule: white 200 mg capsule: yellow	3 years (for bottles) 2 years (for blisters) 30 mins after preparation with food	Drug interaction studies only performed in adults Adverse reaction studies: similarity to adults, except the frequency and severity of rash PK/PD studies **Reported Limitations**: • Capsule contents may disperse into the air if not opened carefully **Author Identified Limitations**: • Short in-use stability time.

(*Continued*)

Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
Tamiflu, 2007, (Gilead Sciences)	Oseltamivir phosphate Treatment of influenza virus Sprinkle capsule	30 mg, 45 mg, 75 mg	From birth: Weight based dosing: Birth to 1 year: 3–10 kg and above: For treating flu: 3 mg/kg twice daily for 5 days For weak immune systems: 3 mg/kg twice daily for 10 days For preventing flu: 3 mg/kg/day for 10 days 1–12 years: For treating flu: 10–15 kg * (~1-5 years): 30 mg/kg twice daily for 5 days Up to >40 kg: 75 mg/kg twice daily for 5 days For weak immune systems: 10–15 kg * (~1-5 years): 30 mg/kg twice daily for 10 days Up to >40 kg: 75 mg/kg twice daily for 10 days For preventing flu: 10–15 kg * (~1-5 years):30 mg/kg/day for 10 days Up to >40 kg: 75 mg/kg/day for 5 days	Contents can be mixed with a spoonful of sweet liquids e.g. chocolate syrup, corn syrup, caramel topping, light brown sugar dissolved in water in a container Alternative method for children <1 year: take a 75 mg capsule and use 12.5 ml water additionally to sweet liquid to dilute the mixture. Use a syringe to draw up certain volume of liquid depending on child weight: ~3 kg: 1.5 ml ~3.5 kg: 1.8 ml Up to ~ >10 kg: 5 ml If the child is >1 and using this method: ~ <15 kg: 5 ml Up to 23–40 kg: 10 ml		Syringe (for <1 year)	n/a	<25°C	n/a **Author Identified Limitations**: • Dosing error may occur via syringe method, especially if incorrect syringe size used. • Product may remain in/block syringe

(*Continued*)

Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
BILE ACID SYNTHESIS DISORDER									
Cholbam, 2015 (Manchester Pharmaceutical) [41] 	Cholic acid (sprinkle capsule)	50 mg, 250 mg Bottles of 90 capsules	From children >3 weeks weighing >4 kg onwards Weight based dosing 10–15 mg/kg Once daily dose or divided into 2 doses 4–6 kg: 50 mg 7–10 kg: 100 mg 11–15 kg: 150 mg 16–20 kg: 200 mg Up to 76–80 kg: 800 mg	To mask unpleasant taste, can be mixed with 15–30 ml formula/breast milk or soft food e.g. mashed potato/apple sauce		n/a	50 mg capsule: orange 250 mg capsule: white White-off-white powder	20–25°C	Clinical trials for adverse reaction and effectiveness (3 weeks – 36 years) n/a
HEREDITARY OROTIC ACIDURIA/OVERDOSE OF FLUOROURACIL OR CAPECITABINE									
Vistogard, 2015  (Wellstat Therapeutics Corporation) [41,85]	Uridine triacetate Oral granules Indication: Overdose of fluorouracil or capecitabine, hereditary orotic aciduria	10 g per packet Carton of 4 or 20 sachets	Dose on body surface area 4 daily doses 6.2 g/m^2 every 6 hours for 20 hours Minimum dosing age: 0.34–0.44 m^2 * (~6–8.5 kg/~3–9 months)	Weigh accurately via scale (accurate to 0.1 g) or graduated tsp. (accurate to ¼ tsp) administer with 3–4 ounces soft food e.g. apple sauce, yogurt, pudding or liquid e.g. formula, milk Discard unused granules For NG tube administration: Crush granules to fine powder and add to ~100 ml of a food starch-based thickening product that has been dissolved in water. After administration, flush tube		Scale for accurate measurement to nearest 0.1 g Or graduated tsp (accurate to ¼ tsp) NG tube	White/off-white granules Enteric Coated (Opadry®) Natural orange juice flavor	Room temp Within 30 mins of preparation	Clinical study for use in pediatric patients: 6 subjects (age range 1–16 years) **Reported Limitations**: • Do not chew granules **Author Identified Limitations**: • Dosing error may occur from inaccurate measurement • NG tube may become blocked • No details given on liquid used/ volume required to flush NG tube • Short in-use stability time

(*Continued*)

Table 3. (Continued).

Product name/ Pharmaceutical Company	Drug/Formulation Type	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
Xuriden, 2015 (Wellstat Therapeutics Corporation) [41,86] 	Uridine triacetate Oral granules	2 g per packet Available as 30 packets per carton	Weight-based dosing: Once daily dose 60–120 mg/kg (do not exceed 8 g) Minimum dosing age: 0.4 g on weights up to 5 kg * (~0-2 months)	Weigh accurately via scale (accurate to 0.1 g) or graduated tsp. (accurate to ¼ tsp) administer with 3–4 ounces soft food e.g. apple sauce, yogurt, pudding or formula, milk for patients receiving up to 2 g Xuriden pour 5 ml of it into 30 ml cup. Draw into syringe and then with syringe tip facing upwards draw air into syringe until the 10 ml mark. Place cap on tip. Face the syringe tip downwards again and remove the plunger. Add granules. Reinsert plunger (do not push). Swirl syringe to mix. Turn syringe so tip faces upwards and push plunger until 5 ml mark to remove air. Administer to child between cheek and gum at the back of mouth. Use 5 ml milk or formula to rinse remaining Xuriden, and then administer. Can be followed by bottled milk/ formula Discard unused granules		Scale for accurate measurement to nearest 0.1 g Or graduated tsp syringe	White/off-white granules Enteric Coated (Opadry®) Natural orange juice flavor	Room temp Within 30 mins of preparation	Safety trials in 4 patients aged between 3–19 years Pediatric use studies (2 months-12 years) **Author Identified Limitations**: • Syringe method for administration can seem lengthy and complicated. Incorrect following of steps may result in dosing error (from spillage of the mixture) • Do not chew granules • Short in-use stability time

**Where dosing regimens are weight-based, an approximate corresponding age has been given based upon the 2009 UK-WHO growth charts and 1990 UK standard centile charts as per the British National Formulary. (tablespoon = tbsp, teaspoon = tsp). +Products licensed with older 2006 EMA guidance. Discrimination between API or dosage form interaction with foods/drinks has not been made for drug products listed.*

key information on monolithic DT, ODT and ODF licensed currently for ages <2 years. In total, 11 products were retrieved; much less than for multiparticulates (Table 3), most being licensed after 2007. 1 of the 6 PUMAs approved to date is a DT [Kigabeq® (Vigabatrin)]. Only 4 of the 11 products, are licensed for use in neonates, with the other 7 for use from infancy. Like for Table 3, Table 4 may not be a comprehensive inventory of all licensed DT, ODT, and ODF for under 2s, and should be noted that there is no favorability bias toward any one dosage from type based upon how many commercially available products have been sourced for each.

3.2.1. – Dispersible tablets

The majority (8 out of the 13) of products are in Table 4 are DT's, with detailed methods of administration. However, instructions are not always clear, e.g. perhaps not specifying the volume of water required for dispersal which could affect acceptability.

5 of the 10 DT are flavored (strawberry, tutti frutti and orange). 7 of the 10 DT contain polyols and/or intense sweetener excipients (isomalt, sorbitol, sucralose, aspartame, sodium saccharin and acesulfame potassium).

3 formulations can also be administered via a device: i.e. syringe/NGT but a lack of details in the SmPC and PIL on administration through NGT is noticeable. The issue also presents that if tablet splitting is required, it is not clear if a lesser dispersion volume of water is required. Consider Ucedane® and Carbaglu® (carglumic acid), they are licensed for use from birth and are given across 2–4 daily doses using a volume of water in each administration appropriate for a whole tablet. This may be considered too high cumulatively, especially in fluid restricted patients. However, the 2013 EMA guideline [31] advises against taking a portion of liquid prepared from a tablet that has been dispersed, suspended, or dissolved to form a flexible age-appropriate medicine for a pediatric patient; as risk of dosing error is increased with such multistep procedures, unless it can be verified that the preparation is easily prepared, has homogeneity and the correct volume can be measured [31].

With no placebo studies or insufficient acceptability studies, it is difficult to inform with evidence common limitations that may be present for DTs intended for under 2s, but others may include: product being left behind in the drinking glass/syringe during preparation, which can lead to significant dosing error if small dispersal volumes (5–10 ml) are used or drugs have a narrow therapeutic index (NTI), NGT blockages and poor palatability which may interfere with subsequent feedings.

Developments for more DT for the under 2s is underway. Eurartesim® DT for treatment of Malaria, is not currently licensed, with studies ongoing. It is a fixed-dose combination of Dihydroartemisinin-piperaquine phosphate. The tablet dispersed in 10 ml of water has the advantage of not requiring food to increase absorption, easy administration, better palatability compared to the crushed film-coated tablet (flavors and sweeteners included) and increased compliance [88,89].

3.2.2. – Orodispersible tablets/films

ODTs and ODFs are formulated to disintegrate in situ in the saliva to be swallowed [87]. They can be useful for the delivery of larger drug doses in comparison to solutions and suspensions formed from DTs that can be higher in volume. Their rapid disintegration within the oral cavity and lack of requirement for solid/fluid vehicles also makes it easier (no extra steps) upon administration [90]. However, incorporating high drug loads into these dosage forms can be problematic from a manufacturing perspective and may compromise on dosage form size. Therefore inclusion of more potent drugs are favored [87]. Low drug loads per unit may also result in multiple administrations [91]. There is still a large absence on studies examining acceptable sizes of ODT/ODF for young children, but generally they are larger than regular tablets [50].

No placebo studies for ODT were found but two recent placebo studies looked at ODFs in children as young as 2 days showing good acceptability, with participant palatability and swallowability assessment favoring ODFs when compared to glucose syrup. Despite parents being unfamiliar with the dosage form, it was not a barrier in its administration, with children less likely to spit it out. The majority found 6cm^2 film size manageable but stated that flavors (e.g. strawberry commonly suggested) and colors should be included, although that was deliberately avoided in the placebo study to avoid preference bias [39]. Klingmann et al. 2020 [40] did not intend to investigate administration of ODF without a dosing vehicle (milk, water, fruit juice, tea, and 15% maltodextrin solution); 80% of caregivers preferring milk. This reiterates milk, a substantial part of neonatal, infant and toddler diets as an obvious and practical vehicle. Further studies would be required to discern palatability issues as well as ODF size and appearance, which govern ingestion ease (Table 1) in the acceptability of medicines. The importance of explicitly detailing in the SmPC precise instructions on the ODF's correct administration seems paramount: the ODF in this study [40] was intended to be orodispersible but not mucoadhesive and hence there were cases of the film not sufficient sticking to the cheek pouch, particularly in children <6 months, where part of it was retained on the feeding bottle/mother's breast. Therefore, ODF adhesive property analysis is important during development, although there are no standardized approaches [91].

Only two ODTs and one ODF were found to be licensed for children under 2 (Table 4). Only Prevacid® allows for alternative administration methods: syringe/NGT use and there are details in its SmPC on tube size and flush volume. These type formulations usually contain intense sweeteners, with both listed ODTs containing strawberry flavor; imperative taste masking aspects to cover poor API taste upon dispersal. It is to be noted that disintegration time would also carry an important acceptability aspect for the youngest of infants and children due to concerns of palatability and possible choking/aspiration hazards. Although sizes for Zofran melt® and Prevacid® (lansoprazole) could not be identified in the SmPC, it is intuitive that for under

Table 4. Commercially available solid monolithic formulations: dispersible/orodispersible tablet/orodispersible film available for neonates, infants, and toddlers.

Product name/ Pharmaceutical Company	Drug	Available doses/ packaging	Dosing: *Minimum age*, *Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
DISPERSIBLE TABLETS									
EPILEPSY									
Kigabeq, 2018, (Veriton Pharma Limited) [94] PUMA	Vigabatrin	Available doses of 100 mg and 500 mg Bottle of 50 tablets	1 month<7 years, Weight-based dosing Monotherapy for West's Syndrome: Starting dose of 50 mg/kg/day Can be increased by 25 mg/kg/day every 3 days up to a max. 150 mg/kg/day Resistant partial epilepsy: Starting dose 40 mg/kg/day Maintenance dose: 10–15 kg (~1–3 years) 0.5–1 g/day 15–30 kg: 1–1.5 g/day	Can be taken before or after meals Preparation into oral solution by dissolving required number of tablets in ~5 or 10 ml water in a glass and drink or withdraw in syringe Dissolving takes <1 min Rinse glass with ~5 or 10 ml water and administered to child accordingly Dissolve tablet in 5 ml or 10 ml water for NGT administration, following rinsing of tube with 10 ml water. (no stability studies for other liquids)	NGT tube capability for those who cannot swallow Syringe use for those not able to drink from glass	White, oval shape, 9.4x5.3 mm (100 mg tablet) 16x9mm (500 mg tablet) With a score line Resulting solution is white and cloudy due to insoluble excipients insoluble No sweeteners or flavors	No special storage conditions 4 years, 100 days once opened, Immediate ingestion once prepared	PK/PD studies in neonates and infants (15 days-22 months)	**Author Identified Limitations**: • Product may remain in glass/ syringe if undissolved • Tablet splitting would be required, could lead to inaccurate dosing

(*Continued*)

Table 4. (Continued).

Product name/ Pharmaceutical Company	Drug	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
MALARIA									
SPAQ-CO™/SUPYRA, 2012 (Guilin a Fosum Pharma Company) [95–98]	Sulfadoxine/ pyrimethamine (SP) + amodiaquine (AQ) (taste-masked)	500 mg/ 25 mg +150 mg 250 mg/ 12.5 mg + 76.5 mg Monthly dose per blister, 25 or 50 blisters per carton.	3–59 months, Monthly cycle (up to four cycles per year max.) during malaria seasons of: Amodiaquine once daily for 3 days and one day of Sulfadoxine-pyrimethamine (given on first day at same time as AQ dose) 3–11 months: using half of 150 mg AQ tablet and half of 500 mg/25 mg SP tablet or use whole 76.5 AQ tablet and whole 250 mg/12.5 mg tablet 12–59 months: use whole 76.5 AQ tablet and whole 250 mg/12.5 mg tablet	Put tablet in cup with ~10 ml water. Stir gently until an even suspension is achieved and administer to child within 5 minutes. Rinse cup with ~10 ml water and administer to child immediately. If child vomits within 30 mins, administer another tablet.	n/a	AQ: Pale yellow/ yellow, Mottled-circular, biconvex shape, score line on one side, uncoated orange, sucralose SP: White/off-white, flat beveled edge, Score line on one side Uncoated, Isomalt, sucralose	24 months, Administer suspension within 5 mins.	Placebo studies in children <5 years,	**Author Identified Limitations**: • Product may remain in cup

(*Continued*)

Table 4. (Continued).

Product name/ Pharmaceutical Company	Drug	Available doses/ packaging	Dosing: *Minimum age*, *Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
BACTERIAL INFECTION									
Amoxicillin, 2016 (Sigma Pharmaceuticals PLC) [99]	Amoxicillin trihydrate	1000 mg Packaged in blisters of 3, 6, 10, 12, 14, 16, 20, 24, 30, 100, 1000 tablets	Weight-based dosing: Children ≤40 kg For acute bacterial sinusitis, acute otitis media, community acquired pneumonia, acute cystitis, acute pyelonephritis and dental abscess with spreading cellulitis: 20–90 mg/kg/day in divided doses For acute streptococcal tonsillitis and pharyngitis: 40–90 mg/kg/day in divided doses For typhoid and paratyphoid fever: 100 mg/kg/day in 3 divided doses For prophylaxis of endocarditis: 50 mg/kg orally 30–60 mins prior to procedure For Lyme disease: early stage – 25-50 mg/kg/day in 3 divided doses for 10–21 days Late stage – 100 mg/kg/day in 3 divided doses for 10–30 days For pre-term neonates and neonates in the first week of life – should not exceed twice daily dosing due to immaturity of renal elimination pathway	If cannot be swallowed whole, can be suspended in water.	n/a	White/off-white, oblong shaped, 22x10mm tablet, Middle score line Strawberry flavor, Aspartame	<25°C 24 months	n/a	**Reported Limitations**: • Score line is for tablet breaking to make swallowing easier (for older patients who can swallow) and NOT for dose dividing **Author Identified Limitations**: • Tablet splitting must be undertaken to achieve suitable doses, and so may lead to dosing error • Recommendation for minimum volume of water to disperse tablet in is not given • Small volumes of water may be used by parents for infants and thus full dissolving of Solvazinc may not occur leading to product left in container

(*Continued*)

Table 4. (Continued).

Product name/ Pharmaceutical Company	Drug	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
HIV									
Abacavir/lamivudine dispersible tablets, 2014 (Mylan Pharmaceuticals Inc.) [100,101]	Abacavir/ Lamivudine Unit-dose tablets	120 mg/ 60 mg Bottle of 30 tablets	From 6 weeks, weight-based dosing Once/twice daily doing If taking twice daily, split once daily dose across 2 doses (~12 hours apart) 3–5.9 kg *(~term neonate-3 months): 1 tablet 6–9.9 kg *(~3 months-2 years): 1.5 tablets 10–13.9 kg * (~2-3 years): 2 tablets 14–19.9 kg *(~3–6 years): 2.5 tablets 20–24.9 kg * (~6-10 years): 3 tablets	Children unable to swallow: Disperse the required number of tablets in 10 ml water (2tsp) in a container, swirl until tablet disappears. Administer Rinse container with 10 ml water and administer	n/a	White/off-white, biconvex, Criss-cross score on both sides Strawberry Flavor Aspartame,	<30°C, 24 months	Adverse reaction and efficacy clinical trials	**Author Identified Limitations**: • Product may remain in container
TUBERCULOSIS									
Rifampicin/Isoniazid/ Pyrazinamide (intensive phase) & Rifampicin/Isoniazid (continuation phase) dispersible tablets (Macleods Pharmaceuticals Ltd) [102,103]	▣Rifampicin/ Isoniazid/ Pyrazinamide (intensive phase) Rifampicin/ Isoniazid (continuation phase) Unit-dose tablets	75 mg/ 50 mg/ 150 mg 75 mg/ 50 mg	Weight-based dosing: Intensive phase/ Continuation phase 4–7 kg * (~1-6 months): 1 tablet 8–11 kg *(~1–2 years): 2 tablets 12–15 kg * (~3-4 years): 3 tablets 16–24 kg * (~4-8 years): 4 tablets >25 kg: adult dosage	Disperse in water Disintegration time within 3 minutes	n/a	Brick red, mottled, circular, biconvex, Deep score one side, uncoated strawberry flavor, aspartame	n/a	Bioavailability studies	n/a

(*Continued*)

Table 4. (Continued).

Product name/ Pharmaceutical Company	Drug	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
HYPERTENSION									
Tracleer+, 2001 (Actelion Pharmaceuticals) [104] 	Bosentan	32 mg Supplied in blister packs of 56 tablets (4 strips of 14 tablets)	From 1 year, >4 kg: Weight-based dosing 2 mg/kg twice daily (morning and evening doses)	Disperse in minimal amount of water	n/a	Pale yellow/ off-white tablet, Clover shaped Quadrisected score lines Tutti Frutti flavor, aspartame acesulfame potassium	20–25°C Divided tablet pieces to store in blister packs and discard after 7 days Preparation to be ingested immediately	Placebo and open-label studies in adult patients only Efficacy studies in pediatric patients (3–15 years) PK/PD studies	**Author Identified Limitations**: • Not many details provided i.e. minimum volume water required/ best method to disperse • Small volumes of water may be used by parents for infants and thus full dissolving of Solvazinc may not occur leading to product left in container
HYPERAMMONAEMIA									
Ucedane, 2017 (Eurocept International) [105]	Carglumic acid	200 mg Blister pack sizes of 12 or 60 tablets	From birth Weight-based dosing Given across 2–4 daily doses Initial dose: 100 mg/ kg/day (up to 250 mg/kg/day maximum) Long term: may not be required to increase the dose as per weight if metabolic control is achieved, therefore doses can range 10–100 mg/ kg/day	Disperse tablets in 5–10 ml water Give before meals/feedings	NG tube using a syringe	White, biconvex, rod shaped, 3 score lines on both sides no flavors; no intense sweeteners.	36 months For immediate ingestion or fast push through NGT using a syringe	PK/PD studies Pre-clinical safety studies	**Author Identified Limitations**: • Tablet splitting may cause dosing error • No indication of flush volumes for NG administration/ tube size • Blocking of NG tube may occur • Volume of water may be considered high for oral administration to young children / via NGT esp. if fluid restricted

(*Continued*)

Table 4. (Continued).

Product name/ Pharmaceutical Company	Drug	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
Carbaglu[+], 2003 (Recordati Rare Diseases Inc.) [106] 	Carglumic acid	200 mg Tablets supplied in a bottle of 5, 15, 60	Weight-based dosing 100–250 mg/kg/day given across 2–4 doses	Add minimum 5–10 ml water per tablet in a small cup, stir and drink directly from cup or administer via NG tube using a syringe Give before meals/feedings	NG tube	White, elongated tablet Triple scored tablet no flavors; no intense sweeteners.	<30°C, keep in refrigerator 2–8°C before opening, 36 months After opening container: Do not refrigerate, 3 months For immediate ingestion or fast push through NGT using a syringe	Safety pre-clinical studies	**Reported Limitations**: • Carbaglu has slightly acidic taste **Author Identified Limitations**: • Acidic taste may reduce adherence • Tablet splitting may cause dosing error • No indication of flush volumes for NG administration/ tube size • Blocking of NG tube may occur • Product may remain in cup • Volume of water may be considered high for oral administration to young children / via NGT esp. if fluid restricted

(*Continued*)

Table 4. (Continued).

Product name/ Pharmaceutical Company	Drug	Available doses/ packaging	Dosing: *Minimum age*, *Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
ORODISPERSIBLE TABLETS									
CHEMOTHERAPY INDUCED NAUSEA/VOMITING									
Zofran melt®, 1998 (Novartis) [107] Generics available  	Ondansetron Nausea and vomiting induced by chemotherapy	4 mg, 8 mg Blister strips of 10 tablets	6 months-17 years, Body surface area-based dosing, Not to exceed 32 mg in a day (Weight-based dosing can be given, but results in higher total daily doses) To be administered 12 hours after chemotherapy for up to 5 days (every 12 hours) Body surface area-based dosing <0.6 $m^{2:}$ (only 2 mg syrup formulation is suitable) 0.6 m^2 < 1.2 m^2: 4 mg >1.2 m^2: 8 mg Weight-based dosing ≤10 kg *(~ <3 years): (only 2 mg syrup formulation is suitable) >10 kg: 4 mg	Place the tablet on the tongue which will disperse in seconds. Swallow.	n/a	White, round, plano-convex, freeze dried, fast disintegrating oral lyophilisate Strawberry flavor, aspartame	<30°C, 3 years	Double-blind efficacy studies in pediatric patients (IV/oral/ placebo ondansetron) (1–18 years) Double-blind placebo study in 1–17 years, 2–12 years Efficacy study of ondansetron for prevention of post-operative nausea (1–24 months) PK studies (1–44 years) (shows drug clearance longer in 1–4 months due to higher body water content and higher volume of distribution of water-soluble drugs)	**Reported Limitations**: • Do not push Zofran melt through the lidding foil of blister strip. Peel back. **Author Identified Limitations**: • Pushing Zofran melt through the lidding foil may damage the tablet, resulting in dosing error.

(*Continued*)

Table 4. (Continued).

Product name/ Pharmaceutical Company	Drug	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
GASTROESOPHAGEAL REFLUX									
Prevacid+, 1995 (Takeda Pharmaceuticals) [84] (Generic available by Sandoz) 	Lansoprazole (Delayed-release ODT)	15 mg, 30 mg Packaged as 100 tablets	From 1–11 years Weight-based dosing: <30 kg *(~<10 years): 15 mg/day for 12 weeks >30 kg: 30 mg/day for 12 weeks	Place tablet on tongue, allow to disintegrate (<1 min). Water may be used if desired. Alternatively, for those who have swallowing difficulty: Syringe administration: Place 15 mg in syringe and draw up 4 ml water (or 10 ml for 30 mg tablet). Shake to disperse. Administer within 15 mins. Refill the syringe with 2 ml water (5 ml for 30 mg tablet), shake, and then administer any remaining product NGT administration: Place 15 mg in syringe and draw up 4 ml water (or 10 ml for 30 mg tablet). Shake to disperse. Inject through NGT (size 8Fr or larger) into stomach within 15 mins. Refill syringe with 5 ml water, shake and then flush NGT.	Syringe, NGT	Yellow-white with orange-brown speckles Tablets are uncoated And contain enteric coated granule formulation of lansoprazole Artificial strawberry flavor, aspartame,	20–25°C Dispersed in water for syringe or NGT administration: 15 mins	PK studies in neonates <28 days and infants 1–11 months (higher exposure compared to adults found) PK studies, 1–11 years, 12–17 years	n/a

(*Continued*)

Table 4. (Continued).

Product name/ Pharmaceutical Company	Drug	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device/ NGT	Size/Shape/ Color/ Coating/ Flavor/ Polyol/ Sweetener	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
ORODISPERSIBLE FILMS									
CHEMOTHERAPY INDUCED NAUSEA/VOMITING									
Setofilm, 2010, (Norgine Limited) [108] 	Ondansetron	4 mg, 8 mg Packed in individual sachets Pack sizes of 2, 4, 6, 10, 30, 50 sachets	6 months-17 years, Body surface area-based dosing, Not to exceed 32 mg in a day (Weight-based dosing can be given, but results in higher total daily doses) To be administered 12 hours after chemotherapy for up to 5 days (every 12 hours) Body surface area-based dosing <0.6 m^2: 2 mg ≥0.6 m^2: 4 mg Weight-based dosing ≤10 kg *(~ <3 years): 2 mg (from day 2) >10 kg: 4 mg (from day 2)	Place film on tongue. Will disintegrate in seconds without water. Swallow. Patient's mouth should be empty, and fingers dry prior to placing on tongue	n/a	White, Rectangular (3 cm^2) Acesulfame potassium, levomenthol	3 years	Efficacy studies (1–18 years), (6–48 months), (1–24 months) PK studies (1 month-44 years) (shows drug clearance longer in 1–4 months due to higher body water content and higher volume of distribution of water-soluble drugs)	**Reported Limitations**: • Film cannot be divided for 2 mg dose **Author Identified Limitations**: • Accidental tearing of film may result when removing from individual sachets/not opened via tear tag • For 2 mg dose, film may be divided inaccurately against SmPC recommendations or oral syrup must be given instead

**Where dosing regimens are weight-based, an approximate corresponding age has been given based upon the 2009 UK-WHO growth charts and 1990 UK standard centile charts as per the British National Formulary. +Products licensed with older 2006 EMA guidance*

2s, a suitable size for their oral cavity that can be retained safely and long enough for disintegration is required. Such aspects require further investigation. Concern of size is why ODminitablets (see 3.1) have been established to include advantages of both dosage forms [49]. A 2019 paper illustrates ongoing Phase II/III clinical trials for a novel 2 mm ODminitablet of enalapril, currently used OL in children. Acceptability and palatability will be assessed in children with congenital heart disease (0 < 6 years) and dilated cardiomyopathy (1 month<12 years). These results can inform other product developments of this dosage form [92].

Palatability (taste/mouthfeel) of ODT/ODF has been scarcely studied in adults let alone in the under 2's [50]. A 2015 study by Kimura et al [93] investigated this and found that gritty mouthfeel was improved by incorporating core granules (<244 um) into an ODT rather than ingesting them alone, along with adjusting particle size, incorporating a suitable coating and necessary additives. Albeit an adult study, such considerations would be more important in under 2s who are likely to be more sensitized to aversive sensations.

4. Technologies to aid administration

As evident from previous discussion, although the various mentioned examples of commercialized multiparticulate and dispersible monolithic formulations bring innovation to drug delivery for the under 2's, complexities still exist. There have been recent technological advances and approaches to minimize this impact and aid more compliant drug delivery in a greater number of patients <2 years.

4.1. Dosing vehicles as a swallowing aid and palatability enhancer

Administering medicines with a dosing vehicle effectively aids swallowing [37] but can often help with palatability also (taste, smell, mouthfeel). In Japan, swallowing aid Jellies are available for children that have been weaned onto semi-solids (Ryukakusan Co. Ltd [109]). The product, available in a variety of flavors and multi-dose/unit-dose sachets, has means to taste mask whilst primarily easing swallowing of minitablets, pellets and granular formulations. With no sugar, artificial preservatives or colorings and the simplicity and convenience of carers being able to pour the jelly directly onto a spoon, swallowing aids provide a more standardized alternative to semi-solid foods [28,109]. Similar products are available outside Japan (Gloup® [110]) but seems more common for elderly patients. However, it relies on the ability and willingness of the carer to purchase them in adjunction to the main treatment which may reduce the viability of the formulation. Ideally an all in one product would be better, minimizing the steps required for administration. This is what the proprietary platform 'Parvulet™' offers [111].

Breast milk or infant formula are the sole source of nourishment for a neonate/infant in their first 6 months of life and still forms a large part of their diet once solid foods are introduced. After the age of 1, whole cows' milk can be given instead. Hence, it could be viable for milk to be seen as a practical dosing vehicle, universally.

Interestingly, recent papers [112,113] depicted the possibility of utilizing infant formula based lipid formulations to enhance drug solubility, with the applicable idea of lipid-fortified infant formula powders as a way to modify the degree of drug solubilization desired; (other milk faces quality/regulatory and component variability issues as an excipient). They also investigated how the products of milk/formula digestion may enhance the solubility and therefore bioavailability of co-administered drugs. Bennett et al, 2012 [114] explore the use of fat within milk (milk as a dosing vehicle) as means to reduce the poor palatability elicited by APIs. Since milk has such potentials, it therefore seems important to explore and clarify within SmPCs which, if at all, milk type may be of greater benefit for medicine administration.

Innovative technologies exist utilizing milk feeding to aid with medicine administration. The Medibottle™ [115] appears as a regular milk bottle with attached nipple and a syringe dispenser on the other end so during feeding, the syringe plunger can be pressed to dispense a little medicine near the bottle nipple at a time. There have been several studies concerning the nipple shield device. A recent study Maier et al., 2019 [116] proposes the superiority of delivering API through a liquid-core sodium alginate hydrogel dosage form in comparison to previously investigated rapidly disintegrating tablets and non-woven fiber dosage forms.

4.2. Devices to aid dose measurement and technologies to aid administration

The 2013 EMA 'List of criteria for screening PIPs with regard to paediatric specific quality issues' outlines a key binding element that 'appropriate dispensing devices' be developed for film-coated minitablets, pellets, granules [117].

Since minitablets offer high dose flexibility due to their low drug loading per minitablet, they need simply be counted (if stored in multi-dose containers) to adjust to the desired dose and hence for high doses a measuring device can accurately do so. Currently, the few available devices provide concerns of high cost, breakage, misplacement, or are unhygienic to use [49]. The smart mini tablet dispenser (sMTS) by Balda and dispenser commercialized by Philips-Medsize in 2020 [41,49] are both reusable and can fit to standard pharmaceutical bottles. It enables up to 10 and 20 minitablets respectively to be counted and lined up precisely before being dispensed together, minimizing miscounting dosing errors.

Sympfiny™ by hs-design, yet to be commercialized, furthers this with its syringe multiparticulate dispensing system that offers precise and controlled dosing of dry powders and microsphere formulations directly into the oral cavity. The system which promises one handed usage, easy cleaning, clog proof and chew resistant shell with spill proof interlocking design to guarantee full dose administration [118] consists of a bulk container that houses the multiparticulates, connecting to a bottle adaptor of which interlocks with the tip of a reusable syringe (with variable dose settings). Sympfiny™ may also help address syringe administration issues for formulation

such as Reyataz® (atazanavir sulfate), Kalydeco® (Ivacaftor), Aciphex® (Rabeprazole) and Tamiflu® (oseltamivir phosphate) (Table 3), but high cost may hinder its use in LMICs.

The X-straw® from DS Technology [119] works by containing a unit dose of pellets or granules within a straw structure whereby a filter pushes the medicine up the straw toward the mouth in response to the sipping drinker. Beneficially, the straw may be dipped into a beverage of choice; however, the application of this device may only be appropriate for use in older toddlers since it requires capability/understanding to drink from a straw. Moreover, unlike Sympfiny™, the X-straw® does not offer full dose flexibility as several different strengths would be required.

Parvulet™ technology is an unconventional technology for dispersible tablets. It allows for a DT or even a powder to be quickly dispersed (~30 s) with very minimal water (few mL) upon a spoon to form a semi-solid gel consistency, which can be administered directly [49]. This very simplistic method of preparation/combined administration has possibilities to reduce dosing error which is of particular importance for NTI drugs. The good texture (similar to applesauce) allows for easy swallowing, and thus increases treatment adherence without the need for a food-based vehicle [111]. Combination with taste masking and controlled release elements, with allowances for high drug loading is also conceivable [111].

Although these technologies improve DT administration, their applications to neonates would still be in question. It has been found that children can develop oral motor skills for feeding from around 2 weeks-9 months allowing them to open their mouth for a spoon, and at around 2 months be able to move food from a spoon to the back of the oral cavity. Neonatal diets are composed solely of milk/formula until weaned at the infant age of 6 months. Although the introduction of semi-solid food is not until this age, the gels from these technologies do not involve food and so could be pondered as a means for neonatal dosing. However, the presence of the gag reflex from birth protects against unfamiliar substances and textures (e.g. lumpy food) from being ingested and it may be that such semi-solid gels may initiate this reflex, despite being smooth [10].

4.3. 3D printing opportunities

3D printing has great potential in offering a more patient-centric approach to medicine delivery for a variety of dosage forms and may enable custom on-demand production within healthcare facilities for children, such as precise doses, dosage form size/shape and may enable custom on-demand production within healthcare facilities. Many papers [120–123] speculate upon its logistics and implementation into hospitals and pharmacies but currently it is still an emerging field, with concerns of quality regulation at the core [123]. Most 3D printlets are to be swallowed whole and the smallest size achievable are around 1 mm.

Currently, only one 3D printed medicine is marketed [Spritam® (levetiracetam)] [49]. This ZipDose™ technology addresses some key ODT manufacturing concerns, such as low drug loading (particularly for water soluble drugs), size, slow disintegration times, poor mechanical strength [87], difficulty incorporating taste masking and enabling extended-release features [124]. ZipDose™ gives a smooth mouthfeel with only small amounts of liquid/saliva; due to its layer by layer printing technique of powder to give a porous structure [124].

Despite these technological advances that may negate some of the difficulties still pertaining with the aforementioned formulation types, issues related to cost further arise. The increased price of a medication due to the added cost of using a patented/patenting a technology or device manufacture may oppose their aim of greater medication acceptability and thus compliance, particularly in LMICs or where the market is small. For such drug delivery systems to be maximally utilized and with access unhindered, development and manufacture must allow for profit/minimal loss to be made.

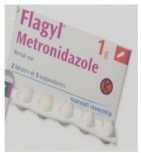
5. Rectal drug delivery

Alternatively, medicines may also be dosed via the rectal route. Much like the oral route, there is no requirement for administration by healthcare professionals (HCP) and can be useful for local and systemic treatment. Rectal formulations include solids (tablets, capsules, powders for reconstitution, suppositories), liquids (solutions, suspensions, emulsions) and semi-solids (foams, creams, gels, ointments). Opposing the limitations of oral delivery, rectal formulations can be administered to the unconscious/vomiting patient or those with swallowing issues; without incorporating concerns associated with taste masking, NGT administration, or to avoid parenteral delivery [49]. Issues with irregularity in upper GI tract are also avoided as well as minimizing first pass metabolism [49,125]. They may also be manufactured at low cost [126].

Table 5 lists some examples of commercially available rectal formulations licensed for systemic administration in under 2s. The table excludes paracetamol and ibuprofen suppositories indicated for pain/fever for 3 months onwards as many generic formulations of various strengths are available and excludes products for local treatment.

Solid dosage forms are intuitively easier to administer than liquids and in terms of its retention within the rectum, hence why suppositories may be more prevalent [49]. Generally, opinion for their use has been regarded as relatively unsafe in pre-term neonates due to unpredictable absorption and also as mucosal damage may occur, consequently causing infection [11,49]. In fact, the suppositories and rectal capsule listed in Table 5 are licensed from infant age. However, in recent years, studies for rectal administration in this age group have increased and thus also the evidence for their safe use and possible superiority to other dosage form types (mentioned later). There are several recent papers detailing *in vivo* safety and efficacy studies in neonates of rectal formulations with various APIs for different conditions [127–130]. This said, exposure of the API via the rectal route can be variable due to inter-patient and intra-patient absorption variability within the rectum, especially between the different developmental age groups. This is illustrated in several studies [131–133].

Table 5. Examples of commercially available rectal formulations for systemic administration in neonates, infants and toddlers.

Product name/ Pharmaceutical Company	Drug	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device	Size/Shape /Color	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
SUPPOSITORIES									
BACTERIAL INFECTION									
Flagyl, 2007 (Sanofi) [141] 	Metronidazole	500 mg, 1000 mg Pack sizes of 10	From 1 month: Every 8 hours for 3 days If longer than 3 days required, then every 12 hours after day 3 <1 year: quarter of a 500 mg suppository 1 < 5 years: half of a 500 mg suppository	Pull apart plastic flaps of wrapping. Insert suppository into back passage. Wash hands before and after	n/a	Cream color, Smooth, Torpedo-shaped	<20°C 3 years	PK/PD (max. concentrations after 1 hour)	Author Identified Limitations • Details not given in SmPC on how to split the suppository (no split lines on dosage form) • Splitting may cause dosing error and change the shape/size for proper and comfortable administration
JUVENILE CHRONIC ARTHRITIS									
Voltarol suppositories+, 1997 (Novartis Pharmaceuticals UK Ltd) [142] 	Diclofenac Sodium	12.5 mg, 25 mg, 50 mg, 100 mg Pack sizes of 10	From 1 year: 12.5 mg and 25 mg suppositories indicated for 1–12 years 1–12 years: 1–3 mg/kg/day divided into 2 or 3 doses	To be well inserted into rectum after passing stool	n/a	White-yellow, Smooth/ slightly rough surface, torpedo shape, slight fatty odor	<30°C 3 years	PK/PD data Limited PK data in children 6–16 years	Author Identified Limitations • Splitting instructions not provided (no split lines on dosage form) • Splitting may cause dosing error and change the shape/size for proper and comfortable administration Multiple daily doses
NAUSEA/VOMITING (DUE TO CHEMOTHERAPY/RADIOTHERAPY)									
Zofran Suppositories+, 1997 (Novartis Pharmaceuticals UK Ltd) [143]	Ondansetron	16 mg	6 month-17 years (*However, Zofran suppositories are not recommended for use in children as usual therapy is IV followed by oral administration)* 'usual' dose is one suppository	Suppository to be inserted as far as possible into the rectum (pointed end first) after passing of stool 1–2 hours before treatment and may be followed with one suppository each day for up to 5 days. Remain still after insertion for a little while to allow for suppository to melt. Try not to empty bowels within 1 hour of insertion Insertion may be easier if in squatting position/bend forward.		White, torpedo shaped	<30°C 3 years	PK/PD Efficacy studies in children aged 1–18 years (only for IV and oral formulations)	n/a

(*Continued*)

Table 5. (Continued).

Product name/ Pharmaceutical Company	Drug	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device	Size/Shape /Color	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
RECTAL CAPSULE									
MALARIA									
Artecap, 2017, (Cipla) (Strides Pharma) [144,145] 	Artesunate (for severe malaria/ emergency treatment if oral/injectable not possible/ accessible)	100 mg	6 months-6 years (5–20 kg): (WHO Public Assessment Report part 4 gives lower age limit of 2 months) 6 months<3 years: 1 suppository 3–6 years: 2 suppositories Followed by referral to a facility for parenteral treatment	n/a	n/a	n/a	<30°C 2 years (4–6 months in temp. >30°C)	PK/PD	n/a
RECTAL SOLUTION									
EPILEPSY									
Epilim Liquid+, 1999 (Sanofi) Sodium Valproate oral solution, 2007 (Wockhardt UK Ltd) [68,146,147] 	Sodium valproate Oral solution can be used for rectal administration (BNFc)	40 mg/ml Amber glass bottle, sizes of 300 ml	Neonate-17 years According to BNFc: 1–2 daily doses Neonate: 20 mg/kg once daily initially. For maintenance 10 mg/kg twice daily 1 month-11 years: 10–15 mg/kg daily initially across 1–2 doses (max. for each dose 600 mg). For maintenance 25–30 mg/kg daily across 2 doses Up to 60 mg/kg daily can be used for infantile spasms (across 2 doses) According to SmPC: Weight-based dosing Children <20 kg * (<5-7 years): 20 mg/kg once daily (severe cases, 40 mg/kg/day)	Sodium valproate oral solution may be administered rectally and retained for 15 mins (dilution with water may be needed to prevent rapid expulsion) (Method of rectal administration cannot be sourced.)	Measuring cup graduated at 5 ml, 10 ml, 15 ml and 20 ml	Cherry flavor (only relevant for oral administration)	<25°C 24 months	PK/PD Systemic clearance varies with age <10 years, up to 2 months clearance is decreased compared to adults. Clearance is at its lowest after birth. Half-life in infants <2 months ranges from 1–67 hours	Author Identified Limitations • Inaccurate measurement of solution causes dosing error • Volume of water for dilution not provided • Some solution may be expelled • Child may empty bowel following administration • Child discomfort • May be difficult for child to remain still

(*Continued*)

Table 5. (Continued).

Product name/ Pharmaceutical Company	Drug	Available doses/ packaging	Dosing: *Minimum age, Quantity and Frequency of administration*	Mode of administration	Device	Size/Shape /Color	Stability/in use/ Storage/ Shelf-life	Studies Undertaken	Limitations to product
SEIZURES/CONVULSIONS									
Desitin Rectal Solution+, 2006 (Desitin Arzneimittel GmbH) [148–150]	Diazepam (for the immediate treatment of convulsions)	Supplied as 5 mg (2 mg/ml) and 10 mg (4 mg/ml) unit-doses rectal tubes	According to SmPC: <1 year (<10 kg) not recommended Usual dose is 0.25–0.5 mg/kg Since Desitin is provided in fixed, unit-doses the dose is obtained by rounding upward to the next available dose. 1–3 years (10–15 kg): one 5 mg tube According to NPPG Position Statement: Neonates and infants (for prolonged seizures): 1.25 mg or 2.5 mg	According to SmPC: Child should be in the prone/ lateral position. The rectal tube is to be inserted half-way to the mark on nozzle. The tube is held with the spout downwards and contents should be completely emptied, using firm pressure with the index finger and thumb. To avoid suction, pressure should be maintained until it is withdrawn from the rectum. Press together the patient's buttocks for a short time. If no effect is seen after 10 minutes, the dose can be repeated in children (or every 12 hours). According to NPPG Position Statement: 1.25 mg or 2.5 mg dose is not accurately achieved from a 5 mg rectal tube for a neonate/infant. Hence, following method should be used: ENFit Blunt Fill Needle is attached to a 1 mL ENFit syringe. Withdraw 0.63 mL (1.25 mg dose) or 1.25 ml (2.5 mg dose) of liquid from a 5 mg diazepam rectal tube. Discard the Needle and attach a flexible ENFit Rectal Straw to the syringe. Draw in approximately 0.5 mL of air into syringe. After positioning the patient, carefully insert the rectal straw as far as is comfortable into the rectum. Administer the liquid in the syringe, keeping the air bubble at the plunger end of the syringe to ensure it flushes the entire dose through the rectal straw. Keep the syringe plunger depressed whilst removing the rectal straw from the patient's rectum.	Rectal tube ENFit Blunt Fill Needle ENFit syringe	Clear Colorless/slightly yellow liquid	<25°C 3 years Immediate use once opened	n/a	Author Identified Limitations • 0.25–0.5 mg/kg is recommended, however exact doses are not obtained according to SmPC. Instead, dose given is rounded up to the nearest available unit dose; of which there are only two.

+Products licenced with older 2006 EMA guidance

Rectal formulations are gaining special interest for the purposes of (emergency) pre-referral use in resource-limited countries where immediate systemic effects may be needed for life-threatening conditions such as (neonatal) sepsis, malaria, HIV or pneumonia [11,49,134]. There are several recent *in vitro* formulation studies looking at furthering the development of rectal formulations for such purposes [126,135–138].

There are common limitations associated with rectal drug delivery which include:

- Pre-administration: need for empty bowels and accurate rectal placement to optimize absorption, although the bowels empty more frequently in under 2s.

- Post-administration: possible discomfort for the child particularly if more than one daily dose is needed, premature loss of the dose (by triggered fecal incontinence). Children <2 years might find it a challenge to remain still for insertion, but especially for the short period of time required after.

Lipophilic base suppositories are known to melt at temperatures from 30°C. This poses logistical difficulty (need for refrigeration) in their usability in LMICs where temperatures are often above this [49]. Rectal formulations can be restricted with dose flexibility. As can be seen from Table 5, some formulations require splitting of the suppository yet split lines nor proper instructions on how to do to ensure accurate dosing are present. Splitting would also mean the size and shape of the formulation is altered, risking their proper and comfortable insertion [27]. The 2013 EMA Guideline [31] considers shape and size of the formulation an important factor: The age and size of the child should be considered for an appropriate size (diameter and length) of the formulation (and lengths for any required rectal tube delivery device [27]). It is also not recommended for suppositories to be cut for achieving smaller doses unless designed to do so as possible inhomogeneous drug distribution and unreproducible cutting are potential causes for dosing error. The 2006 EMA Reflection paper [27] advises for manufacturers to provide information on drug dispersion uniformity of the product. Doliprane, a paracetamol suppository shows advancement in this regard. The 100 mg dose (for 3–8 kg children; ~term neonate-1 year), has a single score line enabling accurate homogeneous 50 mg doses if required. To the knowledge of the authors Doliprane (Sanofi) may be the only suppository containing a score line.

Compared to oral formulations, rectal formulation development for children <2 years is greatly lacking; and could be explained by the concerns mentioned below, but their limited availability may also be contributing to these concerns too, creating a catch-22 situation. There have only been 6 trials investigating rectal drug delivery in children <2 years in the EU, with only one trial (ongoing) investigating a new pediatric drug formulation (omeprazole rectal capsule), reported in EudraCT since 2004. Unlike with use of oral medications, acceptability for the rectal mode of administration can be seen as more of a challenge than the product itself. However, there are limited supporting studies especially in children for the particular reasons why; as viewpoints are known to differ between geographical location, culture and due to lack of knowledge/familiarity/misconception with the dosage form [49]. For example, the UK and USA are known for their lack of acceptability to rectal administration. Thus, looking at a UK study [139] as a 'worst case scenario' the opinions of 150 parents on their perceptions of different routes of analgesic delivery for their children (including from birth) were investigated. 58% thought the rectal route most undesirable when compared to intravenous, intramuscular and oral routes, and was the most unfamiliar with 30% of parents unaware of this route of administration. Only 6% of parents thought this route to allow fast and convenient drug administration. Interestingly, it was slightly more accepted to parents of younger children. With the majority of children and parents not having had any prior experience of rectal administration, it was thought arising parental negativity (such as discomfort, embarrassment, painful, unhygienic, upsetting) was due to lack in knowledge.

Confirmed with a group of older children aged between 8–18 years in Hanning et al., 2020 [140] and showing that there are different challenges for different age groups, 64% said 'maybe' or 'not sure' to considering taking medicines rectally, with their main concerns being size of the dosage form, how to administer it, if someone else would be required for its administration and potential for misuse. Overall, consensus was that education/increasing awareness and providing direct experience were the best ways to overcome concerns and reduce misconceptions/barriers about rectal delivery.

Clearly, more acceptability studies need to be undertaken with the support of industry and HCPs to gauge other social aspects e.g. gender, religion, and ethnicity as well as formulation aspects e.g. size, shape, volume. But, inferring from the aforementioned studies regarding age, this route is less of a barrier for the youngest children. The average age to start potty training toddlers is anywhere between 18 months and 2.5 years; this means that parents and carers of under 2s have regular and more natural access to this route of administration. This should decrease the socio-cultural proctology-related taboos or even safeguarding concerns and the reticence of using this route of administration in this age group. As acknowledged, neonates amongst the pediatric population are the age group suffering with very high mortality rates and route of medicine administration plays an important part in their treatment, with rectal formulations arguably offering benefits over other dosage forms. For example: noninvasive emergency (pre-referral) treatment to give fast systemic effects (improving access for LMICs where clean water and access to healthcare like intravenous treatment/trained professionals are limiting factors), no concerns of requirement for water, swallowability, palatability, or extra need for dosing vehicles that would prevent full efficacious doses from being taken.

6. Expert opinion

The pediatric population is a heterogeneous group, and this must be considered in drug product design. Pediatric regulations have helped to bridge the gap between adult and pediatric licensed and age-appropriate medicine availability, but the gap between these two populations still remains, which encourages pediatric OL, OP and UL medicine use as a necessary requirement. Further understanding and

advancement in pediatric drug delivery is still required to minimize sub-optimal treatment concerning these issues and enable access to appropriate drug products. This is particularly important for children aged under 2 years [(pre)term-neonates, infants and toddlers]; a very niche subset of the pediatric population with added complexities. Improving understanding of these complexities will enhance progress in this field.

During the first two years of life, rapid anatomical, physiological and behavioral maturation changes create difficulty in correct disease diagnosis and also causes potential changes in drug metabolism. Compared to older children and adults, disease behavior can differ in this age group, and so, for some therapeutic areas such as oncology, a deeper understanding of this would allow the opportunity to explore the use of some drug molecules in alternative therapies for them. This could help to minimize PIP deferrals and waivers over time. However, due to this heterogeneity associated with those aged under 2, recruiting patients for clinical trials is likely to be difficult. Consequently, approval times to license medicine developments may suffer.

The appeal of flexible dosing is understandable for those aged under 2; associated to their heterogeneity. Liquid formulations offer many advantages including good dose flexibility and so remain the gold standard for dosing pediatric patients. However, with concerns of excipient safety alongside mis-dosing risk and reliance on dosing devices, (particularly for neonates born before term), the latest trends in age-appropriate drug delivery for under 2's have shown a shift toward flexible solid enteral dosage forms. Such formulations include: multiparticulates, minitablets, DTs, ODTs, ODFs and rectal formulations.

Enteral feeding tubes can be common in children under 2 years in intensive care or pre-term neonates who heavily rely on medical care once born. Administration via enteral feeding tubes requires the drug product to be liquidized prior to administration and for it be compatible with the tube. A key theme noted by HCPs is the need for clarification within SmPCs for how a medicine may be properly manipulated and administered through enteral tubes; particularly where there is polypharmacy, potent drug use, and small volumes involved in fluid restricted patients. This would make UL medicine use safer but future oral formulation developments for those aged under 2 should consider enteral tube feasibility studies if anticipated as a requirement. In LMICs, extemporaneous preparations carried out by pharmacists are utilized due to less availability and access to suitable pediatric formulations. Although UL use is not encouraged, it is agreed that the requirement for guidance in standardized preparations and methods of manufacturing or stability testing to minimize mis-dosing and safety issues are needed. Likewise, recent surveys (ongoing UK 'Parent co-Designed Drug Information for parents and Guardians Taking Neonates home' (PADDINGToN) survey [19]) show common parental concerns of neonates returning home from NICU to be dosing error and safety. Specifically: lacking detailed knowledge on the significance of the medication, proper storage conditions, experience on preparing and administering medicine (let alone through enteral tubes) and being new to their child's complex medicine regime. It is understood that instructions for medicines prior to their administration needs to be presented clearly for parents. In cases when OL and UL medicines are used, very little or no information is available, and it can be difficult for parents to seek advice from HCP's when issues such as vomiting or missed doses arise. The PADDINGToN study [19] shows that supporting medicine administration with technology such as a phone application or QR codes on packaging could help provide easy access to information when required. Dose preparation is a key consideration in dosage form design.

There are many formulation requirements to consider when formulating drug products for children aged under 2; with a desire to develop a drug product design that meets all their requirements. Further studies to enable our understanding of concepts 'acceptability' and 'age-appropriateness' are fundamental in supporting the choice of the most suitable formulations to develop. Across publications there are discrepancies in how acceptability is understood and evaluated. A more standardized approach for this assessment is also required to allow for a systematic evidence-based analysis to generate this necessary understanding.

Furthermore, medicine preference by healthcare professionals and parents may differ between countries where the norm for types of pharmaceutical treatment/dosage form vary, especially between HMICs and LMICs where there may be an education or cultural element involved. To give an example, rectal drug delivery with its surrounding stigma and perceived complicated administration, is not as widely accepted by parents in the UK compared to in neighboring European countries where it is a more conventional treatment, especially for pre-schoolers. If we can understand medicine use and opinion in different regions, there may be an opportunity to broaden use in other regions through education and shift parental misconception of non-favored/unfamiliar routes and dosage forms.

This inspires the need for a global database citing all globally licensed pediatric medicines and associated details such as licensed age group, route of administration and dose, to be created to harmonize and popularize knowledge globally. With such collaborative information easily accessed, it would incentivize post marketing studies that could capture patient experience and usage of products. A pharmaceutical platform for all children under 2 years, with strong geographical and cultural acceptance is the target. The database would facilitate drug development for the under 2's by highlighting the types of formulation in use for this age group, but also where and what the needs are. This would help identify when to innovate, re-formulate age-inappropriate OP drugs (as per under-subscribed PUMA requirements) or implement alternative administration routes (e.g. rectal route).

Logistical issues such as manufacturing feasibility, scalability and production costs that may result in high product costs (particularly if utilizing patented technology or developing for orphan diseases), may delay access of newly approved age-appropriate platforms/formulations to market, and especially

of their access in LMICs. In HMICs a concern is that physicians and national health services will continue with OL, OP and UL prescribing at the benefit of lower product costs even when a perfectly appropriate licensed product is available. Approaches are needed, with collaboration between innovators, industry and regulators, to enable novel research and new formulations into commercially viable products without greatly increasing costs, to support better and cost-effective pediatric formulations reaching those most in need. It may be misconstrued that innovation is what is always required for advancement in the availability of age-appropriate medicines for the under 2's, when only the optimization of existing platforms is needed. This is an area where further understanding is needed to best meet their requirements without affecting access.

Declaration of interest

TB Ernest is an employee of GlaxoSmithKline and hold shares in the company. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

List of Abbreviations

EU – European Union
PIP – Paediatric Investigation Plan
PDCO - Paediatric Committee
EMA – European Medicines Agency
OL – Off-label
OP – Off-patent
PUMA – Paediatric Use Marketing Authorisation
NICU – Neonatal Intensive Care Unit
ADME – Absorption, Distribution, Metabolism, Excretion
NGT – Nasogastric Tubes
SmPC – Summary of Product Characteristics
PK/PD – Pharmacokinetics and Pharmacodynamics
API - Active Pharmaceutical Ingredient
SEEN - Safe Excipient Exposure in Neonates and Small Children
ESNEE - ▫European Study on Neonatal Exposure to Excipients
UL – Unlicensed
WHO – World Health Organisation
ODT – Orodispersible Tablet
DT – Dispersible Tablet
ODF – Orodispersible Film
LMICs – Low-middle income countries
PIL – Patient Information Leaflet
NTI – Narrow Therapeutic Index
HCP – Healthcare Professionals
PADDINGToN - Parent co-Designed Drug Information for parents and Guardians Taking Neonates home

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