


THEMED ISSUE REVIEW

Path towards efficient paediatric formulation development based on partnering with clinical pharmacologists and clinicians, a conect4children expert group white paper

Jennifer Walsh¹ | Daniel Schaufelberger² | Sonia Iurian³ | Sandra Klein⁴ |
 Hannah Batchelor⁵ | Roy Turner⁶ | Sveinbjörn Gizurarson⁷ | Luigi Boltri⁸ |
 Elisa Alessandrini⁹ | Catherine Tuleu⁹ 

¹BioCity Nottingham, Jenny Walsh Consulting Ltd, Nottingham, UK

²School of Medicine, All Children's Hospital, Schaufelberger Consulting LLC and Johns Hopkins University, St. Petersburg, FL, USA

³Department of Pharmaceutical Technology and Biopharmacy, Liliu Hatjeganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

⁴Department of Pharmacy, Institute of Biopharmaceutics and Pharmaceutical Technology, University of Greifswald, Greifswald, Germany

⁵Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

⁶Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland

⁷Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland; and Pharmacy Department, Kamuzu University of Health Sciences, Blantyre, Malawi

⁸Pharmaceutical Development, Adare Pharmaceuticals, Milan, Italy

⁹University College London School of Pharmacy, London, UK

Correspondence

Elisa Alessandrini, University College London School of Pharmacy, 29–39 Brunswick Square, London WC1N 1AX, UK.
 Email: elisa.alessandrini@ucl.ac.uk

Funding information

Innovative Medicines Initiative 2, European Union's Horizon 2020 research and innovation programme and EFPIA, Grant/Award Number: grant agreement No 777389.; Horizon 2020; European Union; Innovative Medicines Initiative

Improved global access to novel age-appropriate formulations for paediatric subsets, either of new chemical entities or existing drugs, is a priority to ensure that medicines meet the needs of these patients. However, despite regulatory incentives, the introduction to the market of paediatric formulations still lags behind adult products. This is mainly caused by additional complexities associated with the development of acceptable age-appropriate paediatric medicines. This position paper recommends the use of a paediatric Quality Target Product Profile as an efficient tool to facilitate early planning and decision making across all teams involved in paediatric formulation development during the children-centric formulation design for new chemical entities, or to repurpose/reformulate off-patent drugs. Essential key attributes of a paediatric formulation are suggested and described. Moreover, greater collaboration between formulation experts and clinical colleagues, including healthcare professionals, is advocated to lead to safe and effective, age-appropriate medicinal products. Acceptability testing should be a secondary endpoint in paediatric clinical trials to ensure postmarketing adherence is not compromised by a lack of acceptability. Not knowing the indications and the related age groups and potential dosing regimens early enough is still a major hurdle for efficient paediatric formulation development; however, the proposed paediatric Quality Target Product Profile could be a valuable collaborative tool for planning and decision making to expedite paediatric product development, particularly for those with limited experience in developing a paediatric product.

KEYWORDS

clinical pharmacology, drug delivery, drug development, paediatrics, pharmacy

1 | INTRODUCTION

Even the most advanced new therapeutics will be of limited value for children if their safety and efficacy have not been established in paediatric patient populations and if there are no age-appropriate dosage forms available. The intended clinical outcome remains elusive if a child does not take the medicine as prescribed or if the carer cannot administer the product.

The introduction of legislation in Europe (EU) and the USA over a decade ago, sometimes referred to as the *stick and carrot* approach is widely credited for an increase in the availability of age-appropriate formulations. However, much work remains to be done to assure that each child has access to the best possible medicines on a worldwide basis.

Developing age-appropriate medicines for 0–18-year-old patients tends to be inherently more complex compared to medicine development for adult patients, as illustrated by the diverse needs of paediatric patients including the requirement for different child-friendly dosage forms. Liquids are seen as the gold standard for the dose flexibility and ease of swallowing they offer, but they can be complicated to formulate, with the need for numerous excipients such as sweeteners, flavouring agents, preservatives and stabilisers, which have heightened tolerability and safety concerns in the young. Therefore, multiple factors need to be considered when establishing a development strategy for a new paediatric product.

Table 1 lists some of the key paediatric development strategy drivers, grouped according to: drug patent status; indication sequencing, age-groups, and dosage forms/formulations. There is a wide range of different paediatric development programmes possible, ranging from new age-appropriate formulations for a new chemical entity (NCE) with a full clinical programme including children, to a shorter reformulation project of an off-patent product, leveraging some data in the public domain (i.e., literature evidence, off-label use case studies etc.) yet requiring a bioequivalence study in healthy adults. Considering the wide range of age groups it becomes apparent that >1 formulation/dosage form may be required, if all the paediatric subsets should benefit from a NCE or an off-patent product.

What is already known about this subject

- The need to improve the availability of age-appropriate paediatric formulations for all children is a priority, for both new chemical entities and existing drug products that require reformulating/repurposing to ensure that medicines meet the neglected needs of the patients.

What this study adds

- Identification of key attributes to be considered for inclusion in a proposed paediatric Quality Target Product Profile. This provides a useful tool for planning and decision making during the development of paediatric formulations for both new chemical entities and off-patent drugs.
- A call for early collaboration between the chemistry, manufacturing, and control team and the Clinical Pharmacology team to maximise opportunities and expedite paediatric product development.

Paediatric formulation development is likely to be challenging and can become the time-limiting task in the overall development programme. Experience gained developing an adult formulation may only be of limited value if a very different dosage form is selected, e.g., switching from an adult tablet to a paediatric liquid formulation. Since clinical outcome is tied to adherence and patient compliance, it is highly desirable that paediatric pivotal safety and efficacy studies are conducted with the (near) final formulation, intended for commercialisation. This means that there is less time for pharmaceutical development. To overcome these challenges in complexity and time constraints, a close partnering of formulation scientists with colleagues in Clinical Pharmacology and Clinical R&D/Medical Affairs

TABLE 1 Drivers for paediatric product development strategies

Patent status	Possible sequencing of clinical indications during development programme	Age groups	Dosage forms/formulations
<ul style="list-style-type: none"> • Patent-protected. • Off-patent. 	<ul style="list-style-type: none"> • Adult,^a followed by sequential paediatric studies, decreasing age. • Adult^a followed by paediatric, single study with delayed enrolment of younger age groups. • Adult,^a followed by paediatric, but indication very different from adults. • Paediatric only. • Paediatric followed by adults. 	<ul style="list-style-type: none"> • Preterm and term new-born infants (0–27 d) • Infants and toddlers (28 d–23 mo) • Children (2–11 y)^b • Adolescents (12–16 or 18 y depending on region) • Adult/geriatrics (16/18+) 	<ul style="list-style-type: none"> • Route of administration. • Type of dosage form. • Type of manufacturing process. • Formulation (composition). • Strengths/concentrations. • Dosing devices. • Administration method, e.g. with foods. • Primary packaging type.

^aSometimes some adolescents are included in adult clinical trials;

^bChildren are better considered in 2 subcategories for formulation development: preschoolers and school age children as their ability to take medicines is very different.

(Clin Pharm) is critical to develop safe and effective, age-appropriate formulations, as expediently as possible.

For this reason, various networks (e.g., the Institute for Advanced Clinical Trials for children <https://www.iactc.org/>, the Maternal Infant Child Youth Research Network <https://www.micymr.ca/>, and the Pediatric Trial Network <https://pediatrictrials.org/>) have been set up to facilitate and expedite the clinical development of age-appropriate paediatric medicines. This is realised through a centralised coordination of research, training and knowledge, by promoting collaboration among different stakeholders, and by involving patients in research activities.

Noteworthy, conect4children (www.conect4children.org/, c4c) is a public-private consortium funded by Innovative Medicines Initiative 2 aimed to create a sustainable infrastructure promoting innovation in the design and conduct of paediatric clinical trials. One of the c4c methodology expert groups (work package 4) focuses on formulation for children (present authorship) and provides advice on formulation aspects during children's drug development. The group works closely with other dedicated paediatric scientific initiatives, such as the European Paediatric Formulation Initiative (www.eupfi.org/), the European Paediatric Translational Research Infrastructure (work package 8; www.eptri.eu/work-packages/wp8-thematic-platform-on-formulation-science/), and the International Consortium for Innovation and Quality in Pharmaceutical Development, Pediatric Working Group (www.iqconsortium.org). This work aims to combine expert opinions and recommendations of the c4c formulation group. In this paper certain key areas where the *path to better paediatric formulations* can be further improved are identified and ways for a closer collaboration between formulation scientists and their colleagues in Clin Pharm and Clinical R&D are suggested.

2 | CURRENT PAEDIATRIC PRODUCT DEVELOPMENT LANDSCAPE

One of the regulatory tools to increase availability of authorised medicines for children is the requirement for a tailored and justified development of suitable paediatric formulations. In the USA, the Food and Drug Administration (FDA) Safety and Innovation Act, signed into law on 9 July 2012, includes a provision that requires a sponsor planning to submit an application for a drug subject to the Pediatric Research Equity Act to submit a Pediatric Study Plan (iPSP) early in the development process. Part 6 of the iPSP describes Pediatric Formulation Development. In the EU, the Paediatric Regulation came into force on 26 January 2007, requiring all applications for marketing authorisations (MAs) for new drugs (covered by intellectual property rights), including new indications, pharmaceutical form or route of administration, to submit a Paediatric Investigation Plan (PIP). The quality aspects of drug development are covered in part D.II of the PIP (*part D.II.a covers Strategy in relation to quality aspects and D.II.b covers an Outline of each of the planned and/or ongoing studies and steps in the pharmaceutical development*). Moreover, the European Medicines Agency (EMA) has published some related key binding elements in PIP

decisions relating to development of age-appropriate pharmaceutical forms, strength, device use, excipients, manipulation prior administration, compatibility and acceptability testing.¹

Drivers to encourage specific product development for paediatric patients may be constrained by the lack of commercial viability of such products, as the paediatric market is small, and corresponding sales are unlikely to recoup the development costs for many products.

So, what advances have been made to bridge the lack of child-friendly products and the need of paediatric therapeutic orphans?

EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) is the European database for all interventional clinical trials on medicinal products authorised in the European Union (EEA) and outside the EU/EEA if they are part of a PIP) from 1 May 2004 onwards. Out of almost 40 000 trials recorded, only 16–17% include subjects aged <18 years. The proportion of trials enrolling children has increased but is still <1 in 5 trials.

One of the regulatory requirements in Europe (Article 43) was to develop an inventory of the needs for paediatric medicines to help rationalise and prioritise medicinal product development, including identifying the need for an age-appropriate formulation. A review of the products listed (between 2006 and 2016), suggests that only a few drugs, let alone innovative formulations have been translated into clinical trials and marketing authorisations of novel paediatric products. It is, however, difficult to keep track of new medicines for children. A central database collecting these approved paediatric drug products globally would aid not only prescribers, but also help industry to identify and select drug products that require development and thus may stimulate child-friendly global health product development.

A review by Strickley² on oral paediatric formulations marketed in the USA, Europe and Japan between 2007 and 2018, found 51 new dosage forms of which; 21 were ready-to-use (solution, suspension, soluble film, tablet, scored tablets, orally disintegrating tablet, chewable tablet, and minitabets) and 30 required manipulation (sprinkle capsule, powder for solution or suspension, granules for suspension, powder, granules, tablet, dispersible tablet (sometimes scored), tablet for oral suspension, and minitabets (sometimes described as *oral granules*). In addition, significant advances in packaging technology were reported. Recently, another important state of the art report was published by UNITAID in collaboration with World Health Organisation (WHO).³ It provides an overview of existing and pipeline technologies that could better allow for more effective administration of essential medicines to children. The report highlights potential opportunities to apply innovation to critical formulations that meet the unique needs of children such as multiparticulates including minitabets or dispersible tablets. A move away from liquids to less traditional dosage forms constitutes the extent of advances made in oral formulation development for children.

In parallel, industry still regularly receives questions from pharmacists on how to address drug compounding to obtain stable, acceptable paediatric formulations when no commercial options are deemed acceptable. This was confirmed by a high-level literature search performed by the authors indirectly showing that the need for compounding has not decreased, Figure 1.

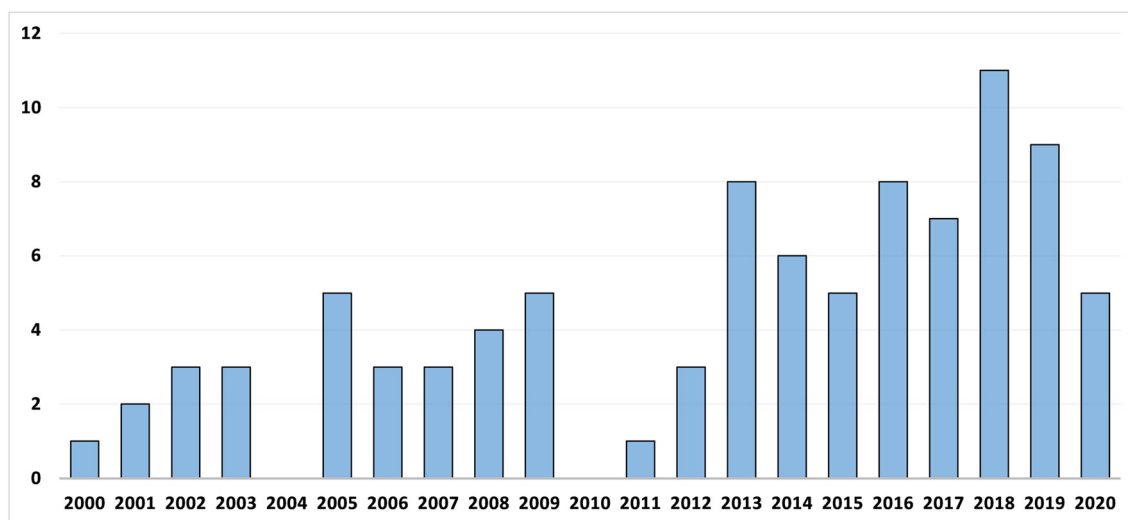


FIGURE 1 Number of publications about paediatric compounding per year published between 2000 and 2020. PubMed: 2000–2020, search terms used: compounding OR extemporaneous; filters: Child (birth–18 y), Newborn (birth–1 mo), Infant (birth–23 mo), Infant (1–23 mo), Preschool Child (2–5 y), Child (6–12 y), Adolescent (13–18 y)

Although compounding is recognised as 1 of the hazardous hospital and community pharmacy activities, with unlicensed medicines more likely to lead to an adverse effect than licensed medicines,^{4–6} it is performed very frequently to overcome the absence of appropriate dosage forms for children. However, there are attempts to modernise and improve the quality of these ad hoc formulations by applying validated standard operating procedures.⁷

The rise of 3D printing in the last decade for specialised and individualised drug delivery has attracted interest including for compounding.⁸ The potential of printed paediatric medicines in hospital pharmacy for the production of on-demand patient-specific doses is being explored.⁹ Although this responsive mode of manufacturing automates the process, it opens new lines of discussion in term of quality control and assurance. The promising leap for 3D printing from drug development to frontline care for compounding belongs to the era of digital pharmacies.¹⁰ Compounding medicinal products for patients with rare disorders is often inevitable due to the very nature of the compounds.⁷ In fact, 1 recent study showed used 3D printing effectively in producing acceptable chewable isoleucine printlets in 3–16 year olds for the treatment of maple syrup urine disease in a Spanish hospital.¹¹

One core limitation of traditional compounding practices and standards is that they vary greatly country to country, and dispensary to dispensary. There are specific initiatives to review the quality of evidence supporting and harmonising extemporaneous dispensing. For example, there is a freely accessible pan-European Paediatric Formulary (PaedForm), announced in 2013, and officially launched in December 2019, that brings together formulations of appropriate quality from all around Europe to allow pharmacists and clinicians to prepare paediatric treatments that need to be compounded.¹²

Recently, information on products and extemporaneous preparations of paediatric formulations that may be useful in the treatment of COVID-19 were shared that way.¹³ The International Pharmaceutical Federation has also set up a Pediatric Formulations Focus Group to develop an open-access International Pharmaceutical Federation formulary of standardised oral extemporaneous paediatric preparations and to standardise global compounding practices through protocols and online training.

There is an EU regulatory tool to stimulate child-centric repurposing/reformulation of off-patent or generic drugs. The paediatric-use MA (PUMA) is a dedicated MA for drugs that are already authorised, and no longer covered by a supplementary protection certificate or a patent that qualifies as a supplementary protection certificate, that covers the indication(s) and appropriate formulation(s) for medicines developed according to an agreed PIP exclusively for use in children. The idea is to respond to children's needs by teaching *old* drugs new tricks with new formulations acceptable for children but also to reduce unlicensed and off-label use through the provision of clinically validated quality products. Table 2 lists an overview of the PUMAs authorised so far. However, this regulatory tool has not been very productive. In fact, considering the long list of old inadequate products, why are there not just simply more PUMAs? The data exclusivity incentives are generally not enough to support business cases and the market price of the paediatric product varies according to country and often does not compensate for development costs, even if they are abridged. Sadly, the added value of an appropriately designed paediatric drug product of an off-patent active pharmaceutical ingredient (API) compared to the provision of a risky unlicensed or compounded medicine, is not always acknowledged by payers.

TABLE 2 List of paediatric-use marketing authorisation (PUMA), reporting indication of use and available dosage forms. Of note, the first 3 PUMAs were for liquid dosage forms, whereas the 3 most recent are for solid dosage forms

Brand name	Active substance	Indication	Dosage form
Buccolam (Shire)	Midazolam hydrochloride	Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 mo to <18 y).	Oromucosal solution in prefilled syringe; 4 strengths.
Hemangirol (Pierre Fabre)	Propranolol	Management of proliferating infantile haemangioma.	Oral solution (multidose).
Sialanar (Proveca)	Glycopyrronium bromide	Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.	Oral solution (multidose).
Alkindi (diurnal limited)	Hydrocortisone	Replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to <18 y).	Granules in capsules for opening; 4 strengths.
Kigabeg (ORPHELIA pharma SAS)	Vigabatrin	Treatment in monotherapy of infantile spasms (West's syndrome); treatment in combination with other antiepileptic medicinal products for patients with resistant partial epilepsy (focal onset seizures) <i>with or without secondary generalisation, that is where all other appropriate medicinal product combinations have proved inadequate or have not been tolerated</i> ; in infants and children from 1 month to less than 7 years of age.	Soluble tablets; 2 strengths.
Slenyto (Neurim)	Melatonin	Treatment of insomnia in children and adolescents aged 2–18 with autism Spectrum disorder (ASD) and/or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.	Prolonged-release tablet (3 mm); 2 strengths.

3 | PAEDIATRIC FORMULATIONS NEED TO BE CONSIDERED EARLY IN DEVELOPMENT

Early development strategies are often directed by clinical teams where there can be a lack of understanding of the formulation requirements, especially when it comes to paediatric patients. The PIP must be submitted no later than upon completion of the pharmacokinetic studies in adults (Figure 2). This time point was chosen to ensure that the paediatric development of the product is considered at early stage of the overall product development. It is accepted that the initial submission will in many cases be preliminary as it will be too early in the development process to have a complete and detailed plan. However, it ensures consideration of paediatric patients independently, as early as possible and not when/after the adult formulation (or a prototype) has already been developed that could bias the paediatric formulation strategy choices. Interestingly, the FDA requires submission of the iPSP no later than within 60 days of the end of Phase 2 meeting.

Certain properties are shared between adult and paediatric formulations during development, for example, maximisation of exposure and a robust and reproducible product. However, there are additional drivers in paediatric formulation development that are not always

integral to adult products. These include dose flexibility and the requirement to demonstrate acceptability of the product.

A traditional adult product development starts with dose ranging studies to assess the safety of the drug (Phase 1); at this stage a *fit for purpose* product is typically used rather than a commercial prototype. Usually, this is a minimally formulated product that allows dose flexibility where the drug is simply dispersed in water or another vehicle or filled into a capsule. However, in cases where drug solubility is low, an enabling formulation may be required to maximise exposure, particularly at higher doses to achieve the level of exposure required.

Once a suitable dose has been identified (Phase 2) a near commercial formulation will be developed for future clinical testing where the final commercial formulation would ideally be used in the Phase 3 clinical studies if possible. This approach minimises the risks associated with formulation bridging during development. In cases where a drug product may be approved based on Phase 2 data, for example, APIs for the treatment of rare diseases, ensuring the use of a commercially viable formulation at Phase 2 would further mitigate the risk of bridging studies. Formulation bridging is required to ensure that exposure obtained from early products used in clinical testing matches those from the final commercial product. Demonstration of equivalence between formulations can be difficult and clinical studies are often required; these studies are expensive and due to the inherent

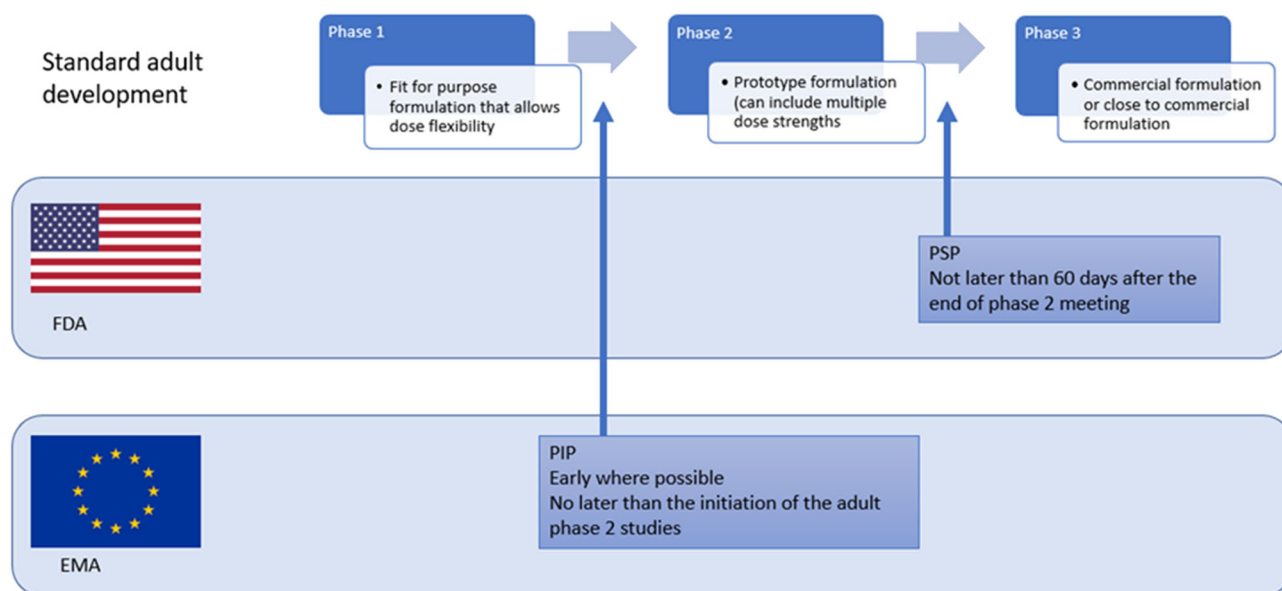


FIGURE 2 Standard adult product development and timeline showing when to submit a Paediatric Investigation Plan (PIP; Europe) or a Pediatric Study Plan (PSP, USA)

variability associated with human trials, can require high subject numbers to demonstrate equivalence.

In cases where an adult product is in development or already exists, a paediatric product will be bridged to the adult 1 to minimise the burden of clinical testing. Bridging of a paediatric product adds complexity as conducting trials in children is only permitted where there is a clinical need whereas bioequivalence studies can be conducted in healthy adults. If the bridging study is conducted in adults, consideration is required to ensure that the equivalence observed in adults will be valid in children and this is not always the case.¹⁴ When bridging from adult to paediatric populations it is important to consider anatomical and physiological differences that can influence exposure.^{15,16} There are several commercial physiologically based pharmacokinetic software packages that aid in the extrapolation of clinical data to support bridging risk assessments.¹⁷⁻¹⁹ The use of modelling and simulation (M&S) to support formulation changes is increasing and it is now an expectation that M&S will be used to inform clinical testing in paediatric populations with sections within the PIP template for example that refer to “Data related to extrapolation of safety information from adults to children can also be included. Modelling of [pharmacokinetics] and/or [pharmacodynamics] if used for decision-making should be mentioned”.²⁰ The value of these models is enhanced by the incorporation of clinical data; therefore, it is important to capture as much data as possible during development to generate the most robust model. This strategy also provides the greatest data set on the paediatric formulation possible that can underpin understanding to better support any future formulation or manufacturing process changes.

An alternative strategy to develop a flexible age-appropriate formulation that could be used in both adult and paediatric populations would negate the need for a bridging strategy, although this would

require formulation investment early in clinical testing prior to proof of concept for a new therapeutic agent, which may not be commercially viable. However, this may provide a wider array of formulation options for other patient groups. For high income countries with aging populations, the synergies between paediatric and geriatric administration have the potential for creating the economics for age-appropriate, easy to swallow formulations that could serve both, older and younger patients.

4 | PAEDIATRIC QUALITY TARGET PRODUCT PROFILE—A TOOL FOR PARTNERING

The use of a paediatric Quality Target Product Profile (pQTPP) is recommended as an efficient tool to facilitate early discussion between Clin Pharm, and Chemistry, Manufacturing and Control (CMC) teams, for planning and decision making during the development of a new age-appropriate formulation. It may be used to support paediatric centric formulation design for new chemical/molecular entities or to repurpose/reformulate an off-patent product. A Company's marketing organisation may also play a role and there is a need to balance the commercial landscape for a paediatric product with technical feasibility whilst minimising costs, which can lead to significant challenges during development. Hence close working across teams with early discussions on required key product characteristics is important for development of an agreed pQTPP.

The QTPP has been introduced through the International Commission on Harmonization (ICH), Q8 programme.²¹ In this context, the term *quality* refers to all development activities related to the API and drug product. The intention of the QTPP is to define a “prospective

summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product".²¹ Although the development of QTPPs is standard practise for pharmaceutical companies and is a regulatory expectation, it is not always familiar to those new to product development where experience may be limited. The regulatory drivers, particularly around repurposing of drugs for rare diseases that affect paediatric populations have led to new initiatives working to develop age-appropriate products where this way of working offers benefits in the development pathway.

This concept is presently further expanded and additional key attributes to be considered for inclusion in a proposed pQTPP are suggested. Table 3 lists such attributes and could serve as a blueprint for a *contract* between the CMC organisation developing a new paediatric formulation and their counterparts in clinical development and clinical pharmacology. A pQTPP should be considered a *living document*. Early in development, separate targets for clinical supplies and the intended commercial product may exist, due to the need for more dosing flexibility in early clinical studies, where optimum dose is still being established. As results from clinical studies become available, targets for the intended commercial product can be further refined.

Not knowing the indications and the related age groups and potential dosing regimens is still a major hurdle for efficient paediatric formulation development. Greater collaboration between formulation and clinical colleagues including healthcare professionals is required to maximise opportunities and expedite the development process. Combining paediatric formulation activities with analytical or other measurements relevant to paediatric drug delivery is essential and should be done in very early phases of development to allow for a better risk assessment with regard to bioavailability, compatibility, stability and taste/acceptability; this collaborative approach should help to develop better paediatric formulations from scratch and should save time when biopredictive methods are applied.

4.1 | Route of administration and patient age

The route of administration and patient age-range are key attributes that need to be aligned with the pQTPP to enable the development of a formulation strategy, since both attributes drive the selection of various age-appropriate dosage forms considered for development and supports the evolution of the remaining attributes of the pQTPP.

To help CMC teams select age-appropriate drug products based on age and route of administration various evidence-based literature and guidance are available.^{2,22-24} It is therefore crucial that the CMC team and clinical team discuss and align upfront the foreseen route of administration and patient age range so that the remaining aspects of the pQTPP can be elaborated. In the absence of a specific target, age-range information on the likely paediatric populations under consideration will enable more suitable age-appropriate dosage forms being selected, as part of the overall formulation development strategy, and avoid later issues, such as selection of unsafe excipients or unacceptable dose volumes.

The guideline on clinical investigation of medicinal products in the paediatric population (ICH E11 CHMP/ICH/2711/99)²⁵ recommends the use of age groups summarised in Table 4 in relation to clinical trials of medicines in children. These age ranges reflect biological changes: the major physiological changes after birth; the early growth spurt; gradual growth from 2 to 12 years; the pubertal and adolescent growth spurt; and development towards adult maturity. In fact, for some programmes, adolescents can be included in the original adult clinical development programme with possible impact on formulation development. The age group 2–11 years should be further subdivided in terms of the child's ability and willingness to use different dosage forms. The increasing survival of very premature babies of 23–24 weeks' gestation with extremely low birth weight <1000 g presents special pharmaceutical challenges within the 'preterm' category relating mainly to size of dose.

The selection of the route of administration is typically determined during drug discovery and target selection, and generally follows the same route of administration used for the adult product. It is therefore often a fixed attribute with no opportunity for change. Nevertheless, CMC teams can offer alternative routes of administration if deemed appropriate for the patient population and if it is technically and clinically feasible, e.g., changing from per oral to sublingual if the age of the target population allows it, or alternative dosage forms to better meet the needs of the patient's age, e.g., for acceptability or biopharmaceutical purposes.

4.2 | Target release profile and dose

A target exposure profile for a drug will be in place prior to the design of a formulation. This may be maximum concentration or area under the curve driven to ensure that the correct concentration of drug is present at the site of action for the required duration. This target exposure will drive the choice for the route of administration as well as the dose to be delivered. Target exposure will be based on preclinical animal studies as well as adult clinical data where these are available. Extrapolation from these clinical data is critical to the design and clinical evaluation of the formulation in a paediatric population. The use of M&S in paediatric clinical testing is a growing field. An EMA M&S working party has an ambition to drive greater integration of M&S in the development and regulatory assessment of medicines with a specific objective linked to the use of M&S in PIPs, as discussed in section 3.²⁶

A participant's age will also affect the route of administration and subsequent exposure due to the differences in the anatomy and physiology of paediatric populations; for example, neonates may not be ready to swallow oral products and a parenteral formulation may be more appropriate. The age-range for the product will be driven by the clinical need. Where possible the number of formulations developed is minimised to streamline development and often adolescents are assumed to be able to take the adult dosage form.

TABLE 3 Key attributes for a paediatric Quality Target Product Profile ^a (pQTPP)

Attribute	Targets ^b	Comments
Route of administration	Auricular/buccal/intramuscular/intravenous/nasal/ophthalmic/oral/pulmonary/rectal/subcutaneous/topical/transdermal etc.	Route depends on indication and drug properties, disease, and age of patient.
Patient age range	Entire range 0–<18 y, or more restricted. Define age groups, as needed.	Define age groups to: (i) sequence clinical studies; (ii) select different dosage forms for different age-groups; and (iii) define dosing-regimes per age-group (dose bands).
Target release profile	Desired pharmacokinetic and in vitro drug release profiles, i.e., for immediate or controlled/delayed release.	To provide guidance to formulators on type of dosage form/formulation concepts to choose from.
Dosage form	According to administration route; <i>age appropriate</i> .	Dosage form must be suitable for use in the proposed paediatric population.
Dose and dose flexibility; dosage strength(s)	Paediatric dose range; dose increments, <i>dose banding</i> .	Identify need for flexible dosing, according to patient age, weight or body surface area. More dosing flexibility might be needed for clinical supplies compared to commercial product. For fixed dose combinations, the ratio of active ingredients may change across age groups. Expectations need to be established upfront.
Patient acceptability	Acceptable for the proposed patient population/care giver, and disease state.	<i>Acceptability</i> depends on patient age, disease state, route of administration and dosage form. Considerations for oral dosage forms: taste, aftertaste, texture, swallowability, administration volume etc. for parenteral dosage forms: injection volume, pain (discomfort) at injection site; feedback on <i>acceptability</i> should be collected from clinical studies.
Dose preparation—manipulations	Can be easily prepared and accurately administered with low risk of dosing errors. Applies to manipulations, i.e., mixing with vehicles, food/beverage; reconstitution with water or specified diluents.	Establish user requirements (patients/care givers) and develop user-friendly handling instructions. Compatibility and stability of drug product with administration vehicle and food should be determined.
Dose administration—devices	Define type of dosing device appropriate for disease state, dosage form and dose ranges to be delivered, to ensure ease and accuracy of dosing.	Administration device (design, dimensions, materials of construction, instructions for use) should be appropriate for intended use. Compatibility with and accuracy of dosing of the drug product should be established.
Excipients (safety)	No safety concerns for the proposed patient population.	Safety of excipients for selected age group to be considered on risk/benefit basis. Regulatory acceptance and precedence may be helpful on case-by-case basis.
Primary packaging material and container closure system	Suitable for hospital and home use.	Child-resistant closure; primary packaging material may differ between the clinical and commercial products.
Stability and storage conditions	Stable for 2 years minimum under long term storage conditions (ICH), according to climatic zones intended for marketing. For reconstituted products: set targets for <i>in-use</i> stability.	Sufficient stability required to facilitate the supply chain, e.g., nonrefrigerated storage and transportation. Refrigerated storage (2–8°C) may be accepted but is less favourable. Shelf-life target for clinical supplies may be shorter due to lack of long-term stability data. <i>In-use stability</i> : product to be administered within a specified time period; consider practicality, i.e., time between preparation and administration.
Manufacturing	Minimal number of different pack types and sizes; estimate of commercial forecast.	Easy to manufacture, freedom to operate, noncomplex supply chain. Typically, low volume forecasts; risk of obsolescence for commercial product; consider launching at pilot scale.
Patient access	Broad access or limited to certain patient subpopulations.	Age-appropriate paediatric products need to be adopted by payers/health insurances. For low- and middle-income countries low-cost generic versions may be needed

^aRefer to International Commission on Harmonization (ICH) Q8 guidance document on QTPP and for additional drug product quality criteria for the intended marketed product (e.g., purity, sterility) not listed here.

^bIn cases where clinical supplies are different from commercial supplies, define separate targets.

^cIn cases where different dosage forms are required (e.g., a solid dosage form for older children and an oral solution/suspension for younger children), it is recommended to develop separate pQTPPs for each dosage form.

TABLE 4 Age groups classification according to the guideline on clinical investigation of medicinal products in the paediatric population (ICH E11 CHMP/ICH/2711/99)

Age group	Age range
Preterm newborn infants	From 23–24 wk gestation
Neonates	0–27 d
Infants and toddlers	1–23 mo
Children	2–11 y
Preschool children	2–5 y
School children	6–11 y
Adolescents	12–16 or 18 y ^a

^aUpper limit age varies among countries depending on legal age.

Moreover, special patient groups with specific (individual) features and needs should be discussed as early as possible e.g., if the disease impairs (oral) bioavailability, due to diarrhoea or malnutrition.

4.3 | Dosage form and patient acceptability

Paediatric patients are, by definition, less cooperative compared to adults, therefore requiring a more patient-centric approach to ensure adherence. The EMA highlighted the importance of acceptability, defining it as “the patient's or caregiver's ability and willingness to use a medicinal product as intended (or authorised)”.²⁷ Ensuring product acceptability through a suitable product design can have a significant impact on adherence, leading to a safe and effective therapy with the desired clinical outcome.²⁸

Acceptability of medicines is key for all patients, but especially for children, who have different sensory perceptions, i.e., taste and texture for oral dosage forms or pain perception for parenteral, which may underlie the refusal of therapy.²⁹ Acceptability is not only driven by product-related characteristics but also by patient related factors, including anatomy, physiology, pathology, development status, education, beliefs, health literacy.³⁰ Several paediatric studies have tried to identify dosage form factors categorised according to different types of dosage forms, leading to acceptable medicines. As an example, oral dosage forms factors mainly referred to size, shape, taste, aftertaste (for solid products), texture, hardness, devices needed for measuring/counting (for multiparticulates), volume, viscosity, mouthfeel, and ease of preparation and measuring (for liquids).³¹

In contrast there is a paucity of evidence on the acceptability of nonoral dosage forms in paediatric patients. For inhaled formulations, Venables et al.³² identified barriers to administration issues related to device handling (face mask/spacer), and the inability of infants and small children to hold their breath, the inconvenience of preparation, uncertainty of dose accuracy, and palatability (taste/consistency/texture). The most frequently reported barriers to parenteral formulations were the refusal of the route of administration, the fear of pain and of the effects at the site of administration, and the difficulties in

handling the administration devices. The dermal and transdermal routes were mainly associated with barriers related to texture/consistency.³² Acceptability of rectal drug administration is considered poor and influenced by factors such as the age, the state of health and cultural barriers that illustrate important differences from 1 country to another.³³

Factors affecting the acceptability, safety and access to paediatric medication and the critical acceptability attributes have been described in detail by many review papers to facilitate decision making regarding the selection and development of the most suitable paediatric medicines.^{24,34,35}

The suitability of a particular product can be best evaluated by patients and caregivers themselves. The EMA advises to include acceptability assessment in the pharmaceutical and clinical development of a drug and to continue with that throughout the product lifecycle,²⁷ but, despite this advice, there is still no official guidance on how to perform an acceptability study. Only few trials in the EuDRAC database list results of acceptability studies but as a secondary outcome. A variety of different outcome measures and assessment tools (questionnaires, facial hedonic scales, visual analogue scales or even unspecified methods) were used and overall information on the methodology used is limited.

The selection of a study design should be correlated with the aim of the study and the required information. Acceptability assessment of placebo single dosage forms could establish the appropriateness of a novel dosage form for a particular age group (e.g. orodispersible films³⁶) and contribute to decision making regarding formulation characteristics (e.g. size of tablets³⁷ or number/dose volume of minitables³⁸ or multiparticulates³⁹). Studies performed on drug-containing products add information about the taste, which is 1 of the common obstacles to patient adherence when drugs in oral dosage forms are even only partially solubilised in the mouth. In addition, the taste-masking effectiveness of the formulation may be evaluated. Acceptability can also be assessed in comparative studies against a gold standard (e.g., minitables vs. syrup³⁸) or against licensed formulations, with relevant results for use in clinical practice.^{40,41} The variability in terms of methodology has been described in a number of review papers capturing different features of study designs and assessment methods.^{28,30,34}

Although several studies have assessed acceptability according to its definition and determined the overall ability of a product to be successfully administered to the target age group e.g., swallowed for oral dosage forms, the simple ability to administer a product does not fully describe the experience of a patient that could trigger the acceptance or refusal of a long-term treatment.²⁹ Therefore, more detailed characterisations could envisage palatability, swallowability of oral dosage forms, or the recently defined usability and preference.⁴² Moreover, studies should consider the acceptability of the product from the caregivers' perspective since they are those that administer the dosage forms to infants and younger children.

Whereas literature describes tools for acceptability assessment, the criteria to be applied to decide whether a product is acceptable or not are not clearly defined, let alone quantifiable. Ranmal et al.²⁸

mentioned an arbitrary limit of 70–80% acceptance that could be considered or a more appropriate case-by-case approach with thorough justification of the selected limits.

Up to this point, acceptability studies have contributed to the understanding of children's needs regarding medication and played an important part in the shift from liquid to solid oral dosage forms, enabling the authorisation of novel formulations such as minitables, orodispersible films and dispersible tablets.² However, there are also several paediatric products that have reached the market despite limited availability of data on their acceptability. In the development of paediatric dosage forms, acceptability should therefore be taken into account as early as possible. First-in human studies could be an opportunity to assess some of the acceptability-related properties of the formulation, such as taste and texture, using visual analogue scales or facial hedonic scales. These assessments could be included in the study when the dose escalation has reached a therapeutically relevant level and could provide important insight for the paediatric drug formulation. Moreover, acceptability testing should be required as a secondary endpoint in clinical trials for paediatric medicines to ensure that clinical success of safe and effective paediatric medicines is not compromised by a lack of acceptability.

4.4 | Dose preparation—manipulation

Ideally, a paediatric dosage form is accepted by all children, but due to personal preferences, this is unlikely to be the case. Whereas in adults, in the case of initially unacceptable dosage forms, it is still possible to plead with reason and the dosage form is ultimately taken despite unwillingness, such approaches are unlikely to be successful in young children. Therefore, it could be advantageous to offer alternative administration options. Acceptability issues apply for all kinds of dosage forms but are of particular issue for oral dosage forms which are thus discussed in more detail.

A common practice for increasing the palatability and swallowability of solid oral dosage forms is the coadministration with small portions of liquids or soft foods. In the past, splitting and crushing adult dosage forms followed by suspension in aforementioned dosing vehicles were common procedures, often off-label, when a paediatric dosage form was unavailable, and manipulation of adult dosage forms was needed. Data from parents suggested that up to 40% of their children's medicines was enabled that way.^{43–45} While increasing acceptability, these dosing vehicles can also affect the integrity of the dosage form, drug stability and *in vivo* drug release, thus affecting drug exposure. To ensure that patient acceptability is achieved without comprising product safety and efficacy, such administration strategies must be verified.

The FDA recently published draft guidance providing information to sponsors who want to recommend the use of dosing vehicles or food for drug administration^{46,47} stating that all labelled vehicle types should be tested *in vivo* relative bioavailability and/or *in vitro* studies. Currently, coadministered vehicles are selected on an individual basis. *In vitro* stability/*in-use* compatibility studies are performed, and

results are supplemented by *in vivo* evaluations in adults as for instance in detail reported for the Alkindi drug product.^{48–50} Vehicles/foods that were found to be safe in these drug-specific evaluations then become part of the dosing recommendation in the summary of product characteristics and package insert leaflet.

The entire vehicle assessment procedure presents a huge burden in terms of resources and logistics involved (e.g. design and execution of bioavailability studies), as well as from the analytical point of view, starting with the question of how to select dosing vehicles to be studied, through to which parameters should be addressed in analytical testing (physical/chemical stability, palatability, drug release, bioavailability, dosing accuracy) and which analytical methods should be applied to how these analytical procedures should be validated. Moreover, although according to current guidance, it is sufficient to use 1 qualified vehicle of a specific type for these studies, it is hard to estimate whether results from such a study can then be used to draw conclusions on the safe use of all vehicles of that kind. The variety of branded products of 1 vehicle type can considerably vary in composition and properties, particularly in (but not limited to) different global regions.^{48,49} Finally, real-life dosing conditions might significantly differ from the dosing recommendations, since acceptability is subject to the preferences of the individual child; caregivers might simply disregard any dosing recommendations or restrictions and replace the recommended dosing vehicle by the child's vehicle of choice. This could also impact drug exposure and thus present risks for the paediatric patient.

All these facts should be considered when establishing the pQTPP. Ideally, a dosage form should allow coadministration with dosing vehicles that differ significantly in composition and physicochemical properties. If the dosage form does not allow for that, inclusion of an appropriate dosing vehicle in the packaging might be an alternative but would make formulation development even more challenging.

Whereas coadministration with food or dosing vehicles mainly applies for solid oral dosage forms, manipulation can also apply for other paediatric medicines. In general, the manipulation of dosage forms is a problem nowadays whenever a dosage form suitable for children is not available and a single dose of a drug must be administered that does not correspond to the adult dose⁵¹; this is exactly what a well-designed paediatric formulation development programme would avoid. Oral liquids can, for instance, often be diluted to enable the accurate measurement of a small dose volume. The same procedure is also used for intravenous injections. Although the objective of such procedures is to ensure proper dose administration, it bears the risk of inaccurate dosing due to the use of inappropriate measuring devices, inappropriate mixing, incompatibility of the original fluid with the diluent and/or instability after mixing. Incompatibility and instability could for instance result in the formation of precipitates or degradation products which in addition to inadequate dosing would present with additional safety issues. Finally, bioavailability might be altered by dilution. Similar issues present with procedures like adding drug compounds or concentrated drug solutions to infusion bags and then removing smaller portions for administration to individual paediatric

patients. The risk that manipulation introduces a medication error also arises when suppositories are cut or split and a segment is given, when partial doses of a portion of a nebuliser solution are administered, when transdermal patches are cut and segments are applied, i.e., whenever the dosage form is made to be applied as whole, but the required dose is not available.⁵²

4.5 | Administration devices

Formulations need to be easily and accurately administered to ensure the correct dose is given. It is therefore important to consider the need for and potential design of an administration device early in the product development programme.

For oral liquids, the oral syringe is the administration device of choice since they have been shown to be more accurate than dosing cups and spoons.^{53–56} However, parents and caregivers may be less familiar with oral syringes compared to other oral dosing devices⁵⁷ and may have difficulty in seeing graduations, and identifying and measuring the correct dose.^{58–61} Furthermore, the dimensions of oral syringes, including size and tip design, can impact accuracy of dosing, especially for small volumes. For example, 1.0 mL oral/enteral syringes have been found to be inaccurate when measuring small volumes (≤ 0.1 mL).⁶² It is therefore recommended that the concentration of an oral liquid medicine should allow accurate administration of the required doses and the maximum capacity (size) of a measuring device should be appropriate for the volume to be dosed.⁶³ It is necessary for the innovator to evaluate and confirm the compatibility, dosing accuracy and usability of a copackaged administration device with the drug product, although in practice it may not be used by hospital-based healthcare professionals.⁶⁴

As stated above, there has been a recent trend towards greater use of flexible solid oral dosage forms such as multiparticulates (granules, beads) and minitables in paediatric patients. Where dose-banding is possible, multiparticulates are commonly presented in unit dose packs such as sachets or hard gelatine capsules, or customised scoops are utilised whereby dose increments are achieved by administering different numbers of scoopfuls. Hence fully flexible dosing is not yet achievable through measuring device use, although innovative technologies such as an oral syringe-like dispensing platform for multiparticulates (Sympfiny) and various minitab counting and dispensing devices (e.g., Balda, Philips-Medisize) are emerging.^{65,66}

For some paediatric patients, it may be necessary to administer oral medication via an enteral feeding tube (EFT) and the delivery via this route should be evaluated. Consideration must be given to dose preparation, for example dilution of a liquid or crushing and/or dispersal of a solid oral dosage form in vehicle, potential for EFT blockage, dose recovery and rinse volumes required. Size appropriate EFTs constructed of commonly used materials such as polyurethane, polyvinyl chloride and silicon should be investigated.^{63,67–69}

As with oral syringes, the measurement of small volumes (e.g., 0.1 mL) of liquids for parenteral administration is challenging and prone to inaccuracies and dosing errors, often leading to the

requirement to conduct 1 or more dilution steps, as described above. Therefore, the concentration of intravenous liquids for paediatric administration should be selected to enable the accurate measurement of required doses. The use of standard concentrations has been advocated to improve patient safety and to take into account paediatric daily fluid allowances.^{70,71} Other administration device considerations for the parenteral route include the use of age-appropriate venous access devices⁷² and smart infusion pump systems.⁷³ In addition, needle size used for vaccination can have an impact on the occurrence of local reactions.⁷⁴ The use of pen delivery devices may reduce administration pain and discomfort compared to traditional hypodermic needles and syringes and hence may improve patient acceptability hence adherence, especially where repeated self- or caregiver-administration is required. For example, various pen devices with very fine, short and lubricated needles have been introduced for the administration of insulin. Specific paediatric insulin pen devices have been designed that facilitate dosing accuracy in young patients, allowing the dosing of half-unit dose increments.⁷⁵

Various administration devices are available for delivery of medicines directly to the lungs, although not all are suitable for all paediatric patient age groups. It is therefore important to consider the end user when designing the device and formulation for inhalation. Pressurised metered dose inhalers (pMDIs) are commonly used although they require coordination of actuation with breath intake for correct use and are therefore not suitable for young patients, for example <7 years. However, when pMDIs are used in combination with a spacer or valved holding chamber (with a facemask for those aged <3 y), as with nebulisers, they can be successfully used by almost everyone.^{76,77} For example, the use of a pMDI with spacer has been found to be at least as effective as a nebuliser for the delivery of β -agonists to preschool children.⁷⁸ Breath actuated and dry powder inhalers may overcome the need for hand-breath coordination although they are not recommended for children aged <5–7 years due to the limited and short inspiratory flow in this patient age group.^{76,77}

As parents/caregivers are often involved in the administration of medicines to children, appropriate training and support are required. All medicines are supplied with a patient information leaflet. Where a medicine and device are combined as a single entity (e.g., a prefilled syringe or pMDI), or where an administration device is copackaged with a medicine (e.g., an oral syringe, spacer), when defined as a *combination product*, evaluation of usability (human factor studies) of the medicine-device combination is required.

Incorporating pictorial aids into written instructions or verbal counselling may reduce dosing errors and improve comprehension.⁷⁹ In addition, other resources are available that provide assistance in medicine administration. For example, the Medicines for Children partnership programme (Royal College of Paediatrics and Child Health, Neonatal and Paediatric Pharmacists and WellChild), have and produced a series of free to access resources (online leaflets and films) providing practical advice on medicines administration to children. Difficulty in correctly using inhalers (especially pMDIs) has been

reported, which can lead to poor treatment outcomes. The provision of training or use of novel electronic adherence monitoring devices which can monitor actuation, inhalation and technique have the potential to improve patient adherence.^{60,80} Videos showing the correct use of inhalers are also available online (<https://www.asthma.org.uk/advice/inhaler-videos/>).

4.6 | Safety of excipients

APIs are formulated with other ingredients (excipients) into dosage forms, so they are in a format that can easily be taken by the patient. The excipients can have various functions including aiding the manufacturing process, supporting product stability, enhancing bioavailability and improving acceptability. Although excipients are generally considered to be inert, new evidence suggests that some may raise safety concerns when used in children medicines,⁸¹ especially in neonates.

Infancy and childhood are periods of rapid growth and development, with maturation of metabolic and organ systems. Therefore, as for the API, the disposition of excipients may differ compared to adults, potentially leading to adverse effects. The immature skin of neonates can lead to greater absorption of some excipients, which may be exacerbated where the skin is broken and/or occluded. Moreover, for very young children, age-related changes in the intestinal paracellular and transcellular permeability of drugs and excipients should be considered.⁸² Excipients of concern include preservatives such as benzoates, parabens and benzalkonium chloride, solvents/cosolvents such as ethanol and propylene glycol, surfactants such as polysorbates and sweeteners such as sodium saccharin, sucrose and sorbitol. Colouring agents and flavourings may also be a concern in young patients due to their potential to cause allergic reactions.

It has been reported that benzoates should not be used in neonates due to the risk of accumulation as a result of immature metabolising enzymes, which could increase bilirubinaemia following displacement of bilirubin from albumin, and may cause newborn jaundice to develop into kernicterus (nonconjugated bilirubin deposits in the brain tissue).^{83,84}

Ethanol is primarily metabolised by alcohol dehydrogenase to carbon dioxide and water via acetaldehyde and acetate, but the activity of this enzyme in neonates and young infants may be fraction of that of an adult, which may result in elevated blood levels and associated toxicity. Administration to neonates of ethanol containing medicines may lead to elevated blood levels of the metabolite acetaldehyde, which is thought to be due to the acetaldehyde to acetate conversion pathway becoming overwhelmed.^{85,86} It is therefore recommended that ethanol should not be included in medicines unless justified. The EMA has provided some suggested limits for blood alcohol concentration according to age.⁸⁷

Propylene glycol is also metabolised by alcohol dehydrogenase; toxic effects due to accumulation have been observed in neonates, infants and children.⁸⁸ The risk of toxicity may be further

exacerbated by the coadministration of these excipients (as well as other excipients of concern), within the same formulation due to polypharmacy.

Route of administration can affect toxicity. For example, polysorbates can affect API gastrointestinal absorption but are considered to have low per oral intrinsic toxicity due to low oral bioavailability. In contrast, when administered intravenously hypersensitivity reactions including anaphylactoid shock, cardiovascular and hepatotoxic effects have been reported. In addition, intravenous polysorbates may enhance the uptake of drugs into the brain.⁸⁹

Various reviews have been conducted on the use of excipients of concern in paediatric products (probably developed before the implementation of paediatric regulations, and potentially originally developed for use in adults) as well as their tolerability, exposure, and associated safety concerns.^{90–94} Notably, there are global differences regarding excipient use^{95,96} and hence product substitution could be an option to reduce excipient burden, albeit with likely supply and cost implications.

Paediatric development guidelines stipulate that excipients should be selected on a case-by-case basis and their inclusion justified considering a benefit vs. risk approach.⁸¹ However, the availability of safety information on excipients in paediatric patients can be limited. The situation is improving, for example, the EMA has published various excipient Q&A documents and reflection papers. In addition, food safety reviews, published literature (human safety and animal toxicity studies) and excipient suppliers are valuable sources of information. The Safety and Toxicity of Excipients in Paediatrics database⁹⁷ has been implemented through the European Paediatric Formulation Initiative to improve the availability of and access to published information on excipients. It is a free to use innovative repository for key safety information on over 70 excipients. Where paediatric safety data are not available, it has been proposed that juvenile animal toxicology studies are conducted to facilitate the benefit vs. risk evaluation process.⁹⁸ The development and use of a Progressive Paediatric Safety Factor have been described whereby maximum acceptable doses of an excipient in paediatric patients may be calculated, should reliable safety data in neonates, infants and children not be available.⁹⁹ In addition, the European Paediatric Formulation Initiative is currently developing a Paediatric Excipient Risk Assessment tool for assisting the selection of excipients for paediatric dose forms.

4.7 | Supply, commercial manufacturing and access

4.7.1 | Clin Pharm–CMC partnership

Paediatric clinical studies can often take longer than originally planned, due to slower than anticipated enrolment rates. Therefore, CMC organisations need to be prepared to either extend the expiration date of clinical supplies or to manufacture additional batches. Sufficient lead times need to be provided by Clin Pharm to avoid

interruptions of the supply chain. In the absence of early dose selection, the CMC organisation may be forced to develop and manufacture at risk, products outside the target dose range (e.g. lower/higher tablet strengths, concentrations and/or fill volumes for liquid dosage forms) to avoid delays in the overall programme, should those targets be revised. Developing a paediatric formulation based on an already established adult formulation (e.g., lower tablet strengths, multiparticulates, minitables) has the advantage that some knowledge around API physicochemical properties can be applied. If new dosage forms are needed, more fundamental CMC work needs to be built into the formulation and manufacturing process development. Commercial volume forecasts for paediatric products are typically low and may be further reduced if a product is offered in multiple strengths or concentrations. By contrast, this offers the opportunity to launch new paediatric products from pilot plants, thus avoiding further scale-up and leading to faster access. For markets outside of the EU and USA, there is a UNITAID sponsored approach mediated by the Medicines Patent Pool organisation.¹⁰⁰ This is a potential path forward to out-license a new product (while still patent-protected) to manufacturers in low-cost countries, so that an affordable product can become available to patients in low- and middle-income countries much earlier than through the generic route. Here again is a critical role to be played by CMC and Clin Pharm to guide development teams through successful bioequivalence studies.

The establishment of paediatric trial networks is a promising way to expedite the development process.¹⁰¹ Being the first to develop a product for a rare paediatric indication in the USA may result in a rare paediatric disease accelerated review voucher. This voucher can be applied for another, unrelated but commercially more interesting new drug application or even sold to another company. A recent example is ZOKINVY (lonafarnib), the first treatment for Hutchinson–Gilford progeria syndrome.^{102,103}

4.7.2 | Off-patent products

Once a new therapeutic agent is no longer protected by patents or exclusivities, there is no guarantee that its associated paediatric formulation(s) remain on the market. To our knowledge there are no regulatory requirements nor incentives in place. For compounds that have proven their therapeutic value it is assumed that paediatric formulations remain commercially available. This is illustrated with the case of TOPAMAX (topiramate), an antiepileptic drug that lost patent protection in 2009. The original tablets and paediatric sprinkle capsules are now offered by several generic manufacturers, thus ensuring continuity of supplies. In addition, new salt forms of the active and an additional extended-release formulation have been introduced by generic companies, further expanding the choices of different dosage forms.

Repurposing existing drugs can be a fast and cost-efficient way to make drugs available to children if the formulations are already age appropriate. Alternatively, additional efforts are required to develop new strengths/concentrations of an existing formulation, or a new

dosage form and/or formulation. Recently, Tuleu et al. postulated that when developing generic products, patient (child) and caregiver acceptability should be considered in addition to establishing bioequivalence with the originator product.¹⁰⁴ Once a new and more age-appropriate formulation has been developed, there are important considerations around pricing and reimbursement. If the new formulation is not adopted by payers and reimbursed, the potential price difference (compared to the existing, less child-friendly product) may be prohibitive and limit access. As previously discussed, in Europe, there is the possibility to get a PUMA, although only few appear to have been approved (Table 2). Medical professionals, including clinical pharmacologists, have an important role in observing and reporting unexpected effects that could lead to drug candidates for repurposing. With the safety profile already known for the general populations, repurposing could be much faster and more cost effective than developing NCEs.

Improving an existing generic product for paediatric use would require financial support for development costs, as for example there was under the European 7th Framework programme and Horizon 2020, but most likely from a Public–Private Partnership (PPP) organisation. Some of these PPPs, such as the TB Alliance, have added the development of new drugs to their mission, e.g., a Phase 1 clinical study with TBAJ-587, Diarylquinoline a potential second-generation bedaquiline compound has recently started.¹⁰⁰

Setting priorities and reaching broad agreement on what is needed most for children worldwide is the mission of the Global Accelerator for Paediatric Formulations initiative.¹⁰⁵ In some instances, reformulation efforts may also open an opportunity to make the API more suitable for paediatric formulations and include a full set of new clinical studies. This is illustrated with praziquantel, used to treat schistosomiasis, the second highest disease burden after malaria, with infected people up to 4 times more likely to be infected with diseases such as HIV.¹⁰⁶ The current formulation is a large tablet that is difficult for young children to swallow and often requires crushing to enable dosing. A PPP was established to address the gap in available treatments for preschool age children. The development and clinical evaluation, including M&S and palatability assessment of an orally disintegrating tablet (ODT) formulation is on-going. ODT formulations containing levo and racemic praziquantel (PZQ) dispersed in water were found to be more palatable than the current crushed tablet product and interestingly, higher palatability scores were reported for the racemic PZQ ODT taken without water by older children.^{107,108}

Medicines that are considered essential are listed by WHO on the Essential Medicines List, with those for the treatment of children included in the corresponding list for children's medicines. The quality of products in the worldwide supply chain remains a concern and can also be negatively affected by counterfeiting. The WHO Pre-Qualification Process sets worldwide standards for essential medicines and can be applied by philanthropic organisations when sourcing drugs for distribution programmes. For low- and middle-income countries a sustainable approach offers the best opportunity to improve and secure access to age-appropriate formulations in the long term. Replacing current humanitarian donation programmes with local

manufacturing and distribution may take a step in that direction. Conducting technology transfers and assisting in starting up manufacturing would also create employment and generate economic growth.

5 | CONCLUSION

Despite regulatory incentives, the market introduction of a paediatric formulation may still lag for several years compared to the corresponding adult products, which is often due to the additional complexities involved in developing safe and effective quality medicines for children. Patient-specific needs should be discussed as early as possible when developing formulations and clinical study designs for different age groups, to encompass their specific physiological or cognitive needs.

Developing novel paediatric formulations is not often seen as economically attractive and is at risk of contributing to health inequalities. A strong partnership is advocated in between CMC and Clin Pharm to maximise opportunities and expedite paediatric product development. The pQTPP describing relevant key attributes of a paediatric formulation provides a useful collaborative tool for planning and decision making, thus facilitating the development process.

The promotion of dialogue and collaboration between experts from different fields and specialties is facilitated by the development of a sustainable infrastructure such as c4c. C4c promotes an efficient implementation of trials by allowing collaboration between specialists, national networks and patient groups, and by providing resources and expertise in various areas of paediatric clinical trials for industry and academic research.

DISCLAIMER

The publication reflects the author's view and neither IMI nor the European Union, EFPIA, or any Associated Partners are responsible for any use that may be made of the information contained therein.

ACKNOWLEDGEMENTS

Conect4children has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777389. The Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. Conect4children has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777389. The Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

COMPETING INTERESTS

The authors declare no conflict of interest.

CONTRIBUTORS

Conceptualisation J.W., D.S., S.I., S.K., H.B., R.T., S.G., L.B., and C.T.; writing original draft J.W., D.S., S.I., S.K., H.B., R.T., S.G., and C.T.; writing—review and editing J.W., D.S., S.I., S.K., H.B., R.T., S.G.,

E.A. and C.T.. All authors have read and agreed to the published version of the manuscript.

ORCID

Catherine Tuleu  <https://orcid.org/0000-0001-8384-357X>

REFERENCES

- European Medicines Agency (EMA). Examples of key binding elements in the PIP decisions. EMA/174403/2013 Human Medicines Development and Evaluation. Published 2013. https://www.ema.europa.eu/en/documents/other/examples-key-binding-elements-paediatric-investigation-plan-decisions_en.pdf. Accessed March 12, 2021.
- Strickley RG. Pediatric Oral Formulations: An Updated Review of Commercially Available Pediatric Oral Formulations Since 2007. *J Pharm Sci* Published online. 2019;108(4):1335-1365. <https://doi.org/10.1016/j.xphs.2018.11.013>
- World Health Organisation, Unitaid. Innovative Delivery Systems for Paediatric Medicines: Technology Landscape. Published online 2020. <https://unitaid.org/assets/Innovative-delivery-systems-for-paediatric-medicines-technology-landscape.pdf>
- European Medicines Agency (EMA). Evidence of harm from off-label or unlicensed medicines in children EMEA/126327/2004. Published 2004. https://www.ema.europa.eu/en/documents/other/evidence-harm-label-unlicensed-medicines-children_en.pdf. Accessed March 12, 2021.
- Lowey A, Jackson M. How to ensure the quality and safety of unlicensed oral medicines. *Pharm J*. 2008;281(7517):240-243.
- Bellis JR, Kirkham JJ, Thiesen S, et al. Adverse drug reactions and off-label and unlicensed medicines in children: a nested case? control study of inpatients in a pediatric hospital. *BMC Med*. 2013;11(1):238. <https://doi.org/10.1186/1741-7015-11-238>
- Dooms M, Carvalho M. Compounded medication for patients with rare diseases. *Orphanet J Rare Dis*. 2018;13(1):1. <https://doi.org/10.1186/s13023-017-0741-y>
- Allen LV. 3D Printing: Pharmacy Applications Part 1 Introduction and Applications. *Int J Pharmaceut Comp*. 2016;6(1). https://compoundingtoday.com/Newsletter/Science_and_Tech_1601.cfm Accessed March 12, 2021.
- Öblom H, Sjöholm E, Rautamo M, Sandler N. Towards printed pediatric medicines in hospital pharmacies: Comparison of 2D and 3D-printed orodispersible warfarin films with conventional oral powders in unit dose sachets. *Pharmaceutics*. 2019;11(7):334. <https://doi.org/10.3390/pharmaceutics11070334>
- Araújo M, Sa-Barreto L, Gratieri T, Gelfuso G, Cunha-Filho M. The digital pharmacies era: How 3D printing technology using fused deposition modeling can become a reality. *Pharmaceutics*. 2019;11(3):128. <https://doi.org/10.3390/pharmaceutics11030128>
- Goyanes A, Madla CM, Umerji A, et al. Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: First single-centre, prospective, crossover study in patients. *Int J Pharm* Published online. 2019;567:118497. <https://doi.org/10.1016/j.ijpharm.2019.118497>
- European Directorate for the Quality of Medicines and Healthcare (edqm). European Paediatric Formulary online. Published 2019. <https://www.edqm.eu/en/news/european-paediatric-formulary-online>. Accessed March 12, 2021.
- European Directorate for the Quality of Medicines and Healthcare (edqm). Products and extemporaneous preparation of paediatric formulations that may be useful in the treatment of COVID-19. Published 2020. <https://www.edqm.eu/en/news/products-and-extemporaneous-preparation-paediatric-formulations-may-be-useful-treatment-covid>. Accessed March 12, 2021.

14. Batchelor HK, Marriott JF. Formulations for children: problems and solutions. *Br J Clin Pharmacol*. 2015;79(3):405-418. <https://doi.org/10.1111/bcp.12268>
15. Batchelor HK, Fotaki N, Klein S. Paediatric oral biopharmaceutics: Key considerations and current challenges. *Adv Drug Deliv Rev*. 2014;73:102-126. <https://doi.org/10.1016/j.addr.2013.10.006>
16. Batchelor HK, Marriott JF. Paediatric pharmacokinetics: key considerations. *Br J Clin Pharmacol*. 2015;79(3):395-404. <https://doi.org/10.1111/bcp.12267>
17. Vinks A, Emoto C, Fukuda T. Modeling and simulation in pediatric drug therapy: Application of pharmacometrics to define the right dose for children. *Clin Pharmacol Ther*. 2015;98(3):298-308. <https://doi.org/10.1002/cpt.169>
18. Lin W, Yan JH, Heimbach T, He H. Pediatric Physiologically Based Pharmacokinetic Model Development: Current Status and Challenges. *Curr Pharmacol Reports*. 2018;4(6):491-501. <https://doi.org/10.1007/s40495-018-0162-1>
19. Johnson TN, Rostami-Hodjegan A. Resurgence in the use of physiologically based pharmacokinetic models in pediatric clinical pharmacology: parallel shift in incorporating the knowledge of biological elements and increased applicability to drug development and clinical practice. *Pediatr Anesth*. 2011;21(3):291-301. <https://doi.org/10.1111/j.1460-9592.2010.03323.x>
20. Manolis E, Osman TE, Herold R, et al. Role of modeling and simulation in pediatric investigation plans. *Paediatr Anaesth*. 2011;21(3):214-221. <https://doi.org/10.1111/j.1460-9592.2011.03523.x>
21. European Medicines Agency (EMA). ICH guideline Q8 (R2) on pharmaceutical development. EMA/CHMP/ICH/167068/2004 Committee for Human Medicinal Products. Published 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-11.pdf. Accessed March 18, 2021.
22. European Medicines Agency (EMA). Reflection paper: Formulation of Choice for the Paediatric Population (EMA/CHMP/PEG/194810/2005). Published 2006. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-paediatric-population_en.pdf. Accessed June 9, 2020.
23. Krause J, Breitzkreutz J. Improving Drug Delivery in Paediatric Medicine. *Pharmaceut Med* Published online. 2008;22(1):41-50. <https://doi.org/10.1007/BF03256681>
24. Walsh J, Ranmal SR, Ernest TB, Liu F. Patient acceptability, safety and access: A balancing act for selecting age-appropriate oral dosage forms for paediatric and geriatric populations. *Int J Pharm*. 2018;536(2):547-562. <https://doi.org/10.1016/j.ijpharm.2017.07.017>
25. EMA. ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population - Step 5. Published 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e11r1-guideline-clinical-investigation-medicinal-products-pediatric-population-revision-1_en.pdf. Accessed December 2, 2020.
26. European Medicines Agency (EMA). Modelling and Simulation Working Party. <https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/modelling-simulation-working-party>. Accessed March 18, 2021.
27. European Medicines Agency (EMA). Guideline on Pharmaceutical Development of Medicines for Paediatric Use Guideline on Pharmaceutical Development of Medicines for Paediatric Use. Published 2013. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf. Accessed December 12, 2020.
28. Ranmal SR, O'Brien F, Lopez F, et al. Methodologies for assessing the acceptability of oral formulations among children and older adults: a systematic review. *Drug Discov Today*. 2018;23(4):830-847. <https://doi.org/10.1016/j.drudis.2018.01.038>
29. Hofmanová JK, Mason J, Batchelor HK. Sensory aspects of acceptability of bitter-flavoured 7.5 mm film-coated tablets in adults, preschool and school children. *Int J Pharm*. 2020;585:119511. <https://doi.org/10.1016/j.ijpharm.2020.119511>
30. Kozarewicz P. Regulatory perspectives on acceptability testing of dosage forms in children. *Int J Pharm*. 2014;469(2):245-248. <https://doi.org/10.1016/j.ijpharm.2014.03.057>
31. Mistry P, Batchelor H. Evidence of acceptability of oral paediatric medicines: a review. *J Pharm Pharmacol*. 2017;69(4):361-376. <https://doi.org/10.1111/jphp.12610>
32. Venables R, Batchelor H, Stirling H, Marriott J. Barriers to administering non-oral formulations in a paediatric population: A semi-structured interview study. *Int J Pharm*. 2016;497(1-2):12-17. <https://doi.org/10.1016/j.ijpharm.2015.11.010>
33. Jannin V, Lemagnen G, Gueroult P, Larrouture D, Tuleu C. Rectal route in the 21st Century to treat children. *Adv Drug Deliv Rev* Published online. 2014;73:34-39. <https://doi.org/10.1016/j.addr.2014.05.012>
34. Ternik R, Liu F, Bartlett JA, et al. Assessment of swallowability and palatability of oral dosage forms in children: Report from an M-CERSI pediatric formulation workshop. *Int J Pharm*. 2018;536(2):570-581. <https://doi.org/10.1016/j.ijpharm.2017.08.088>
35. Moreira M, Sarraguça M. How can oral paediatric formulations be improved? *Int J Pharm*. 2020;590:119905. <https://doi.org/10.1016/j.ijpharm.2020.119905>
36. Orlu M, Ranmal SR, Sheng Y, Tuleu C, Seddon P. Acceptability of orodispersible films for delivery of medicines to infants and preschool children. *Drug Deliv*. 2017;24(1):1243-1248. <https://doi.org/10.1080/10717544.2017.1370512>
37. Bracken L, McDonough E, Ashleigh S, et al. Can children swallow tablets? Outcome data from a feasibility study to assess the acceptability of different-sized placebo tablets in children (creating acceptable tablets [CAT]). *BMJ Open*. 2020;10(10):e036508. <https://doi.org/10.1136/bmjopen-2019-036508>
38. Klingmann V, Linderskamp H, Meissner T, et al. Acceptability of Multiple Uncoated Minitablets in Infants and Toddlers: A Randomized Controlled Trial. *J Pediatr*. 2018;201:202-207.e1. <https://doi.org/10.1016/j.jpeds.2018.05.031>
39. Lopez FL, Mistry P, Batchelor HK, et al. Acceptability of placebo multiparticulate formulations in children and adults. *Sci Rep* Published online. 2018;8(1):9210. <https://doi.org/10.1038/s41598-018-27446-6>
40. Angwa LM, Ouma C, Okoth P, et al. Acceptability, adherence, and clinical outcomes, of amoxicillin dispersible tablets versus oral suspension in treatment of children aged 2-59 Months with pneumonia, Kenya: A cluster randomized controlled trial. *Heliyon*. 2020;6(4):e03786. <https://doi.org/10.1016/j.heliyon.2020.e03786>
41. Palmeirim MS, Bosch F, Ame SM, Ali SM, Hattendorf J, Keiser J. Efficacy, safety and acceptability of a new chewable formulation versus the solid tablet of mebendazole against hookworm infections in children: An open-label, randomized controlled trial. *EClinicalMedicine*. 2020;27:100556. <https://doi.org/10.1016/j.eclinm.2020.100556>
42. Drumond N, van Riet-Nales DA, Karapinar-Çarkit F, Stegemann S. Patients' appropriateness, acceptability, usability and preferences for pharmaceutical preparations: Results from a literature review on clinical evidence. *Int J Pharm* Published online. 2017;521(1-2):294-305. <https://doi.org/10.1016/j.ijpharm.2017.02.029>
43. Hagan M. Study finds parents have difficulty in administering children's medication: FLAVORx surveys parents on children's medicine taking habits. *PR Newswire [online]*. Published online 2003. <https://www.thefreelibrary.com/Study+finds+Parents+Have+Difficulty+in+Administering+Children's...-a099726455>
44. Tomlin S. How to ensure children take their medicines as directed. *Prescriber*. 2007;18(21):53-58. <https://doi.org/10.1002/psb.153>

45. Wrubel J, Tedlie Moskowitz J, Anne Richards T, Prakke H, Acree M, Folkman S. Pediatric adherence: Perspectives of mothers of children with HIV. *Soc Sci Med*. 2005;61(11):2423-2433. <https://doi.org/10.1016/j.socscimed.2005.04.034>
46. US Food and Drug Administration (FDA). Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments - Guidance for Industry, Draft Guidance. Published 2018. <https://www.fda.gov/media/114872/download>. Accessed March 4, 2021.
47. US Food and Drug Administration (FDA). Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations Guidance for Industry, Draft Guidance. Published 2019. <https://www.fda.gov/media/121313/download>. Accessed March 4, 2021.
48. Wollmer E, Neal G, Whitaker MJ, Margetson D, Klein S. Biorelevant in vitro assessment of dissolution and compatibility properties of a novel paediatric hydrocortisone drug product following exposure of the drug product to child-appropriate administration fluids. *Eur J Pharm Biopharm*. 2018;133:277-284. <https://doi.org/10.1016/j.ejpb.2018.10.022>
49. Wollmer E, Karkossa F, Freerks L, et al. A Biopredictive In Vitro Approach for Assessing Compatibility of a Novel Pediatric Hydrocortisone Drug Product within Common Pediatric Dosing Vehicles. *Pharm Res*. 2020;37(10):203. <https://doi.org/10.1007/s11095-020-02912-x>
50. Daniel E, Digweed D, Quirke J, Voet B, Ross RJ, Davies M. Hydrocortisone Granules Are Bioequivalent When Sprinkled Onto Food or Given Directly on the Tongue. *J Endocr Soc*. 2019;3(5):847-856. <https://doi.org/10.1210/js.2018-00380>
51. Richey RH, Shah UU, Peak M, et al. Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence. *BMC Pediatr*. 2013;13(1):81. <https://doi.org/10.1186/1471-2431-13-81>
52. Richey RH, Craig JV, Shah UU, et al. MODRIC - Manipulation of drugs in children. *Int J Pharm* Published online. 2013;457(1): 339-341. <https://doi.org/10.1016/j.ijpharm.2013.08.061>
53. Griesmann K, Breikreutz J, Schubert-Zsilavec M, Abdel-Tawab M. Dosing accuracy of measuring devices provided with antibiotic oral suspensions. *Paediatr Perinat Drug Ther*. 2007;8(2):61-70. <https://doi.org/10.1185/146300907X178950>
54. Sobhani P, Christopherson J, Ambrose PJ, Corelli RL. Accuracy of Oral Liquid Measuring Devices: Comparison of Dosing Cup and Oral Dosing Syringe. *Ann Pharmacother* Published online. 2008;42(1): 46-52. <https://doi.org/10.1345/aph.1K420>
55. Dockhorn S, Feuersenger D, Schuenemann S, et al. Study of microbial contamination and dosing accuracy of oral dispensers. *J Clin Pharm Ther* Published online. 2010;35(3):279-287. <https://doi.org/10.1111/j.1365-2710.2009.01082.x>
56. Joshi P, Bavdekar SB. Liquid Drug Dosage Measurement Errors with Different Dosing Devices. *Indian J Pediatr* Published online. 2019;86(4):382-385. <https://doi.org/10.1007/s12098-019-02894-8>
57. Buddhadev MD, Patel KS, Patel VJ, Bhatt SP, Deshpande SS. Perceptions about oral liquid medication dosing devices and dosing errors by caregivers of hospitalized children. *J Pharm Res*. 2016;10(12):810-813. <http://jprsolutions.info>
58. Ryu GS, Lee YJ. Analysis of Liquid Medication Dose Errors Made by Patients and Caregivers Using Alternative Measuring Devices. *J Manag Care Pharm*. 2012;18(6):439-445. <https://doi.org/10.18553/jmcp.2012.18.6.439>
59. Tanner S, Wells M, Scarbecz M, McCann BW. DRUGS: Parents' understanding of and accuracy in using measuring devices to administer liquid oral pain medication. *J Am Dent Assoc* Published online. 2014;145(2):141-149. <https://doi.org/10.14219/jada.2013.20>
60. Walsh J, Math MC, Breikreutz J, Zerback T, Wachtel H. Devices for oral and respiratory paediatric medicines: What do healthcare professionals think? *Int J Pharm*. Published online. 2015;492(1-2):304-315. <https://doi.org/10.1016/j.ijpharm.2015.05.041>
61. Berthe-Aucejo A, Girard D, Lorrot M, et al. Evaluation of frequency of paediatric oral liquid medication dosing errors by caregivers: amoxicillin and josamycin. *Arch Dis Child* Published online. 2016;101(4):359-364. <https://doi.org/10.1136/archdischild-2015-309426>
62. Arenas-López S, Gurung K, Tibby SM, Calleja Hernández MÁ, Tuleu C. Accuracy of enteral syringes with commonly prescribed paediatric liquid medicines. *Arch Dis Child*. 2017;102(7):655-659. <https://doi.org/10.1136/archdischild-2016-312492>
63. European Medicines Agency (EMA). Quality of medicines questions and answers: Part 2. Published 2018. <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/qa-quality/quality-medicines-questions-answers-part-2#administration-of-oral-immediate-release-medicinal-products-through-enteral-feeding-tubes-new-december-2018-sect>. Accessed March 17, 2021.
64. Walsh J, van Riet-Nales D, Hermans E, et al. European Paediatric Formulation Initiative workshop report: Improving the administration of oral liquid medicines in paediatrics using dosing syringes and enteral accessories. *Eur J Pharm Biopharm*. 2020;151:91-97. <https://doi.org/10.1016/j.ejpb.2020.04.007>
65. Harris D, Hermans E, Klein S, Wagner-Hattler L, Walsh J. Age-appropriate solid oral formulations for pediatric applications with a focus on multiparticulates and minitabets: Summary of September 2019 EuPFI workshop. *Eur J Pharm Biopharm*. 2020;153: 222-225. <https://doi.org/10.1016/j.ejpb.2020.06.012>
66. Katarzyna Hofmanová J, Bennett J, Coupe AA, Bartlett J, Monahan A, Batchelor HK. A Novel Oral Syringe for Dosing and Administration of Multiparticulate Formulations: Acceptability Study in Preschool and School Children. *Pharmaceutics*. 2020;12(9):806. <https://doi.org/10.3390/pharmaceutics12090806>
67. Daniel E, Whitaker MJ, Keevil B, Wales J, Ross RJ. Accuracy of hydrocortisone dose administration via nasogastric tube. *Clin Endocrinol (Oxf)* Published online. 2019;90(1):66-73. <https://doi.org/10.1111/cen.13876>
68. Thabet Y, Walsh J, Breikreutz J. Flexible and precise dosing of enalapril maleate for all paediatric age groups utilizing orodispersible minitabets. *Int J Pharm*. 2018;541(1-2):136-142. <https://doi.org/10.1016/j.ijpharm.2018.02.037>
69. Hoover A, Sun D, Wen H, et al. In Vitro Evaluation of Nasogastric Tube Delivery Performance of Esomeprazole Magnesium Delayed-Release Capsules. *J Pharm Sci*. 2017;106(7):1859-1864. <https://doi.org/10.1016/j.xphs.2017.04.008>
70. Uppal N, Yaseen B, Seto W, Parshuram CS. Drug formulations that require less than 0.1 mL of stock solution to prepare doses for infants and children. *CMAJ* Published online. 2011;183(4): E246-E248. <https://doi.org/10.1503/cmaj.100467>
71. Perkins J, Aguado-Lorenzo V, Arenas-Lopez S. Standard concentration infusions in paediatric intensive care: the clinical approach. *J Pharm Pharmacol* Published online. 2017;69(5):537-543. <https://doi.org/10.1111/jphp.12604>
72. Scott-Warren VL, Morley RB. Paediatric vascular access. *BJA Educ* Published online. 2015;15(4):199-206. <https://doi.org/10.1093/bjaceaccp/mku050>
73. Manrique-Rodríguez S, Sánchez-Galindo AC, Fernández-Llamazares CM, Calvo-Calvo MM, Carrillo-Álvarez Á, Sanjurjo-Sáez M. Safe intravenous administration in pediatrics: A 5-year Pediatric Intensive Care Unit experience with smart pumps. *Med Intensiva (English Ed)* Published online. 2016;40(7):411-421. <https://doi.org/10.1016/j.medin.2016.08.001>
74. Beirne PV, Hennessy S, Cadogan SL, Shiely F, Fitzgerald T, Macleod F. Needle size for vaccination procedures in children and

- adolescents. *Cochrane Database Syst Rev.* 2018;6. <https://doi.org/10.1002/14651858.CD010720.pub3>
75. Hyllested-Winge J, Sparre T, Pedersen LK. NovoPen Echo[®] insulin delivery device. *Med Devices Evid Res* Published online. 2016;9: 11-18. <https://doi.org/10.2147/MDER.S59229>
 76. Pedersen S, Dubus JC, Crompton G, et al. The ADMIT series - issues in inhalation therapy. 5) Inhaler selection in children with asthma. *Prim Care Respir J* Published online. 2010;19(3):209-216. <https://doi.org/10.4104/pcrj.2010.00043>
 77. Van Aalderen WM, Garcia-Marcos L, Gappa M, et al. How to match the optimal currently available inhaler device to an individual child with asthma or recurrent wheeze. *Npj Prim Care Respir Med* Published online. 2015;25(1):14088. <https://doi.org/10.1038/npjpcrm.2014.88>
 78. Mitselou N, Hedlin G, Hederos CA. Spacers versus nebulizers in treatment of acute asthma – a prospective randomized study in pre-school children. *J Asthma* Published online. 2016;53(10):1059-1062. <https://doi.org/10.1080/02770903.2016.1185114>
 79. Chan HK, Hassali MA, Lim CJ, Saleem F, Ghani NA. Improving pediatric liquid medication labeling of the hospital information system in malaysia: Qualitative analysis of pharmacists' perceptions. *Pharm Pract (Granada)* Published online. 2016;14(2):699. <https://doi.org/10.18549/PharmPract.2016.02.699>
 80. Makhecha S, Chan A, Pearce C, Jamalzadeh A, Fleming L. Novel electronic adherence monitoring devices in children with asthma: a mixed-methods study. *BMJ Open Respir Res* Published online. 2020; 7(1):e000589. <https://doi.org/10.1136/bmjresp-2020-000589>
 81. European Medicines Agency (EMA). Guideline on pharmaceutical development of medicines for paediatric use. EMA/CHMP/QWP/805880/2012 Rev. 2 Committee for Medicinal Products for Human Use (CHMP) Paediatric Committee (PDCO). Published 2013. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf. Accessed March 17, 2021.
 82. Nicolas J-M, Bouzom F, Hugues C, Ungell A-L. Oral drug absorption in pediatrics: the intestinal wall, its developmental changes and current tools for predictions. *Biopharm Drug Dispos.* 2017;38(3): 209-230. <https://doi.org/10.1002/bdd.2052>
 83. European Medicines Agency (EMA). Questions and answers on benzoic acid and benzoates used as excipients in medicinal products for human use. EMA/CHMP/508189/2013 Committee for Human Medicinal Products (CHMP). Published 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-benzoic-acid-benzoates-used-excipients-medicinal-products-human-use_en.pdf. Accessed March 8, 2021.
 84. European Medicines Agency (EMA). Benzyl alcohol and benzoic acid group used as excipients. EMA/CHMP/272866/2013 Committee for Human Medicinal Products (CHMP). Published 2017. https://www.ema.europa.eu/en/documents/report/benzyl-alcohol-benzoic-acid-group-used-excipients-report-published-support-questions-answers-benzyl/chmp/508188/2013-t_en.pdf. Accessed March 8, 2021.
 85. European Medicines Agency (EMA). Information for the package leaflet regarding ethanol used as an excipient in medicinal products for human use. EMA/CHMP/43486/2018 Committee for Medicinal Products for Human Use (CHMP). Published 2018. https://www.ema.europa.eu/en/documents/scientific-guideline/information-package-leaflet-regarding-ethanol-used-excipient-medicinal-products-human-use_en.pdf. Accessed March 8, 2021.
 86. Pandya HC, Mulla H, Hubbard M, et al. Essential medicines containing ethanol elevate blood acetaldehyde concentrations in neonates. *Eur J Pediatr* Published online. 2016;175(6):841-847. <https://doi.org/10.1007/s00431-016-2714-x>
 87. Mead CN. Data interchange standards in healthcare IT--computable semantic interoperability: now possible but still difficult, do we really need a better mousetrap? *J Healthc Inf Manag* Published online. 2006;20(1):71-78.
 88. European Medicines Agency (EMA). Propylene glycol used as an excipient. EMA/CHMP/334655/2013 Committee for Human Medicinal Products (CHMP). Published 2017. https://www.ema.europa.eu/en/documents/report/propylene-glycol-used-excipient-report-published-support-questions-answers-propylene-glycol-used_en.pdf. Accessed March 8, 2021.
 89. European Medicines Agency (EMA). Information for the package leaflet regarding polysorbates used as excipients in medicinal products for human use. Draft. EMA/CHMP/190743/2016 Committee for Medicinal Products for Human Use (CHMP). Published 2018. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-information-package-leaflet-regarding-polysorbates-used-excipients-medicinal-products-human_en.pdf. Accessed March 8, 2021.
 90. Fabiano V, Mameli C, Zuccotti GV. Paediatric pharmacology: Remember the excipients. *Pharmacol Res* Published online. 2011;63 (5):362-365. <https://doi.org/10.1016/j.phrs.2011.01.006>
 91. Ursino MG, Poluzzi E, Caramella C, De Ponti F. Excipients in medicinal products used in gastroenterology as a possible cause of side effects. *Regul Toxicol Pharmacol* Published online. 2011;60(1): 93-105. <https://doi.org/10.1016/j.yrtph.2011.02.010>
 92. Walsh J, Cram A, Woertz K, et al. Playing hide and seek with poorly tasting paediatric medicines: Do not forget the excipients. *Adv Drug Deliv Rev.* 2014;73:14-33. <https://doi.org/10.1016/j.addr.2014.02.012>
 93. Cuzzolin L. Neonates exposed to excipients: concern about safety. *J Pediatr Neonatal Individ Med.* 2017;7(1):e070112. <https://doi.org/10.7363/070112>
 94. Valeur KS, Holst H, Allegaert K. Excipients in Neonatal Medicinal Products: Never Prescribed, Commonly Administered. *Pharmaceut Med* Published online. 2018;32(4):251-258. <https://doi.org/10.1007/s40290-018-0243-9>
 95. Nellis G, Metsvaht T, Varendi H, et al. Potentially harmful excipients in neonatal medicines: a pan-European observational study. *Arch Dis Child* Published online. 2015;100(7):694-699. <https://doi.org/10.1136/archdischild-2014-307793>
 96. Nakama KA, Dos Santos RB, Serpa P, Maciel TR, Haas SE. Organoleptic excipients used in pediatric antibiotics. *Arch Pediatr.* 2019;26(7):431-436. <https://doi.org/10.1016/j.arcped.2019.09.008>
 97. (EuPFI) EPFI. Safety and Toxicity of Excipients for Paediatrics (STEP) Database. <http://www.eupfi.org/step-database-info/>. Accessed March 18, 2021.
 98. Schmitt G. Safety of Excipients in Pediatric Formulations—A Call for Toxicity Studies in Juvenile Animals? *Children* Published online. 2015;2(2):191-197. <https://doi.org/10.3390/children2020191>
 99. Kriegel C, Festag M, Kishore RSK, Roethlisberger D, Schmitt G. Pediatric Safety of Polysorbates in Drug Formulations. *Children* Published online. 2019;7(1):1. <https://doi.org/10.3390/children7010001>
 100. TB Alliance, University of Auckland, Merck & Co. I. TBAJ-587, *Diarylquinoline*. <https://www.newtdrugs.org/pipeline/compound/tbj-587-diarylquinoline>. Accessed March 18, 2021.
 101. Hussaarts L, van der Weijde K, Dome P, Kourany-Lefoll E, Reinhard-Rupp J, de Vruh R. Product development programs for neglected tropical diseases: A crucial role for expert meetings. Flisser A, ed. *PLoS Negl Trop Dis.* 2017;11(2):e0005183. <https://doi.org/10.1371/journal.pntd.0005183>
 102. Eiger BioPharmaceuticals Inc. Eiger BioPharmaceuticals Announces FDA Approval of Zokinvy[™] (lonafarnib): The First Treatment for Hutchinson-Gilford Progeria Syndrome and Processing-Deficient Progeroid Laminopathies. Published 2020. <https://ir.eigerbio.com/static-files/eb16843e-e926-417c-acb6-6d7c0151dfa8>. Accessed February 26, 2020.

103. Medicines Patent Pool. <https://medicinespatentpool.org/>. Accessed March 19, 2021.
104. Tuleu C, Hughes DA, Clapham D, Vallet T, Ruiz F. Acceptability of generic versus innovator oral medicines: not only a matter of taste. *Drug Discov Today* Published online November 17. 2020;(2): 329-343. <https://doi.org/10.1016/j.drudis.2020.11.008>
105. World Health Organisation (WHO). Global Accelerator for Paediatric Formulations (GAP-f). <http://gap-f.org/>. Accessed March 18, 2021.
106. Hotez PJ. Schistosomiasis (Snail Fever). In: Press A, ed. *Forgotten People, Forgotten Diseases: The Neglected Tropical Diseases and Their Impact on Global Health and Development*. 2nd ed. Herndon, VA; 2013:41-56.
107. Mahende MK, Huber E, Kourany-Lefoll E, et al. Comparative palatability of orally disintegrating tablets (ODTs) of Praziquantel (L-PZQ and Rac-PZQ) versus current PZQ tablet in African children: A randomized, single-blind, crossover study. *bioRxiv* Published online. 2019;15(6):e0007370. <https://doi.org/10.1101/605170>
108. Bonate PL, Wang T, Passier P, et al. Extrapolation of praziquantel pharmacokinetics to a pediatric population: a cautionary tale. *J Pharmacokinet Pharmacodyn*. 2018;45(5):747-762. <https://doi.org/10.1007/s10928-018-9601-1>

How to cite this article: Walsh J, Schaufelberger D, Iurian S, et al. Path towards efficient paediatric formulation development based on partnering with clinical pharmacologists and clinicians, a conect4children expert group white paper. *Br J Clin Pharmacol*. 2021;1-18. <https://doi.org/10.1111/bcp.14989>