

Path towards efficient paediatric formulation development based on partnering with clinical pharmacologists and clinicians, a c4c expert group White paper.

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Abstract

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 (pQTPP) 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 post-marketing 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 pQTPP 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.

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 (pQTPP). 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 (CMC) team and the Clinical Pharmacology team to maximise opportunities and expedite paediatric product development.

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 United States (US) 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 stabilizers, 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 programs possible, ranging from new age-appropriate formulations for a new chemical entity (NCE) with a full clinical program 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 more than one formulation/dosage form may be required, if all the paediatric subsets should benefit from a NCE or an off-patent product.

Paediatric formulation development is likely to be challenging and can become the time-limiting task in the overall development program. 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 commercialization. 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 (Clin Pharm) is critical to develop safe and effective, age-appropriate formulations, as expeditiously as possible.

For this reason, various networks (e.g., the Institute for Advanced Clinical Trials for children ([i-ACT](https://www.iactc.org/)) <https://www.iactc.org/>, the Maternal Infant Child Youth Research Network (MICyRN) <https://www.micyrn.ca/>, and the Pediatric Trial Network (PTN) <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 IMI2 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 US, The Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 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 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 authorized in the European Union (EEA) and outside the EU/EEA if they are part of a Paediatric Investigation Plan (PIP) from 1 May 2004 onwards. Out of almost 40,000 trials recorded, only 16-17% include subjects less than 18 years old. The proportion of trials enrolling children has increased but is still less than 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 rationalize and prioritize 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 authorizations 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 Strickley [2] on oral paediatric formulations marketed in the US, 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 minitables) 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 minitables (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 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 minitables 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.

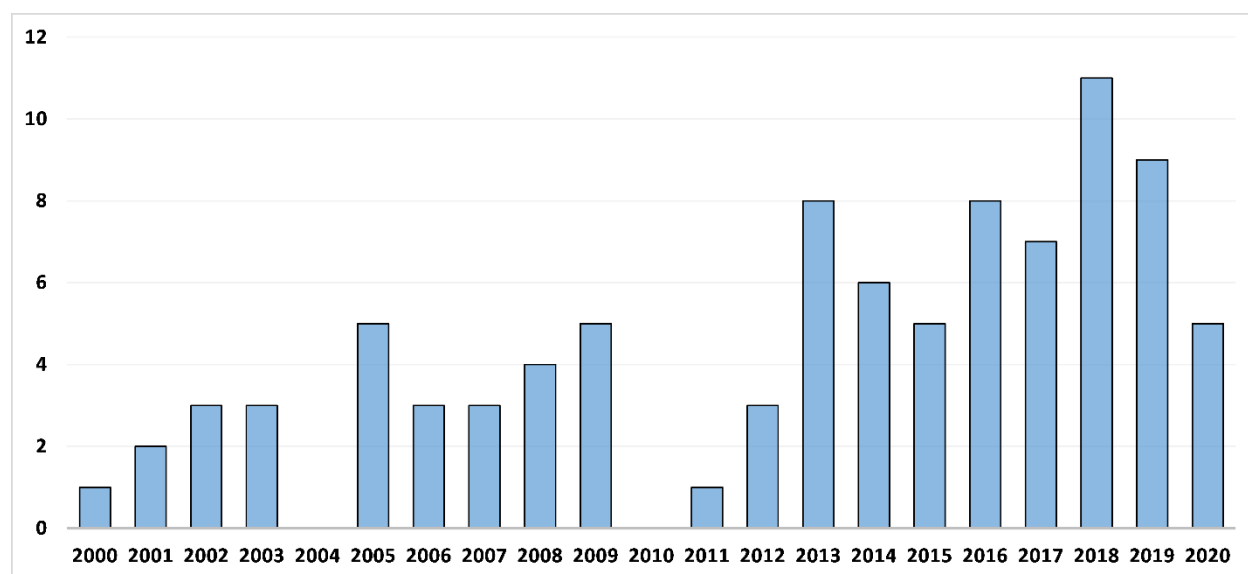


Figure 1. Number of publications about paediatric compounding per year published between 2000 and 2020. [PubMed: 2000 – 2020, search terms used: compounding OR extemporaneous; filters: Child (birth-18 years), Newborn (birth-1 month), Infant (birth-23 months), Infant (1-23 months), Preschool Child (2-5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

Although compounding is recognized as one 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 specialized and individualized 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, one recent study showed used 3D printing effectively in producing acceptable chewable isoleucine printlets in 3-16 years old for the treatment of Maple syrup urine disease (MSUD) 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 (FIP) has also set up a Pediatric Formulations Focus Group (PFFG) to develop an open-access FIP formulary of standardized oral extemporaneous paediatric preparations and to standardize 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 marketing authorisation (PUMA) is a dedicated MA for drugs that are already authorised, and no longer covered by a supplementary protection certificate (SPC) or a patent that qualifies as a SPC, 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 API, compared to the provision of a risky unlicensed or compounded medicine, is not always acknowledged by payers.

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 which 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.

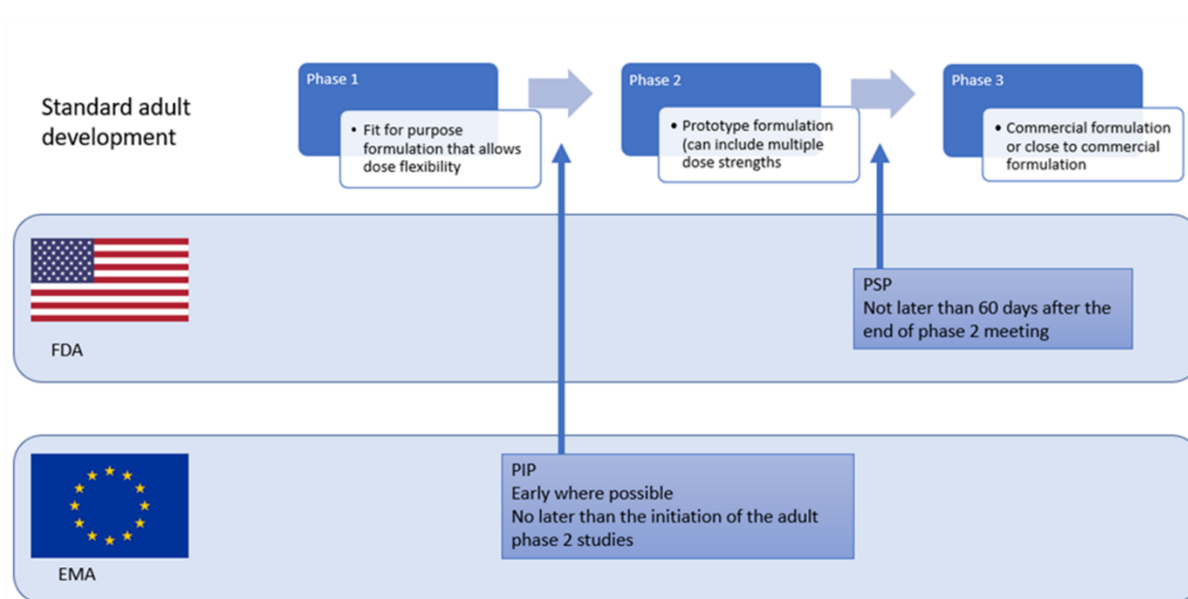


Figure 2. Standard adult product development and timeline showing when to submit a PIP (Europe) or a PSP (United States).

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 minimizes 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 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 one to minimize 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 PK and/or PD 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 (pQTPP) – 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 “Quality Target Product Profile” (QTPP) has been introduced through the International Commission on Harmonization (ICH), Q8 program [21]. In this context, the term “quality” refers to all development activities related to the active pharmaceutical ingredient (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 paediatric QTPP (pQTPP) are suggested. Table 3 lists such attributes and could serve as a blueprint for a “contract” between the CMC organization 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 2-12 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 program 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 <1000g 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 C_{max} or area under the curve (AUC) 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 pre-clinical animal studies as well as adult clinical data where this is 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 have 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].

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 minimized to streamline development and often adolescents are assumed to be able to take the adult dosage form.

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 categorized 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, ease of preparation and measuring (for liquids) [31].

In contrast there is a paucity of evidence on the acceptability of non-oral 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 one 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 these advices, 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 films [36]) and contribute to decision

making regarding formulation characteristics (e.g. size of tablets [37] or number/dose volume of minitables [38] or multiparticulates [39]). Studies performed on drug-containing products add information about the taste, which is one 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. syrup [38]) 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 characterizations 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 the ones 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 authorization of novel formulations such as minitables, orodispersible films and dispersible tablets [2]. However, there are also a number of 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 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 co-administration 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, co-administered 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 (SmPC) and package insert (PIL).

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 one 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 one 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 co-administration 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 co-administration 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 dose [51]; 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 devices [57] and may have difficulty in seeing graduations, 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 co-packaged 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 minitabets in paediatric patients. Where dose-banding is possible, multi-particulates are commonly presented in unit dose packs such as sachets or hard gelatin capsules, or customised scoops are utilized 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 minitabets 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, poly vinyl 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 one or more dilution steps, as described above. Therefore, the concentration of IV 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 devices [72] 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 which 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. Pressurized metered dose inhalers (pMDIs) are commonly used although they require co-ordination 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 under 3 years), as with nebulizers, 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 nebulizer for the delivery of beta-agonists to pre-school children [78]. Breath actuated and dry powder inhalers may overcome the need for hand-breath co-ordination although they are not recommended for children aged below 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 pre-filled syringe or pMDI), or where an administration device is co-packaged 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 (RCPCH), Neonatal and Paediatric Pharmacists (NPPG) 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/co-solvents 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 metabolizing enzymes, which could increase bilirubinaemia following displacement of bilirubin from albumin, and may cause new-born jaundice to develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue) [83,84].

Ethanol is primarily metabolized 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 metabolized 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 co-administration 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, IV 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 (likely 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]. Noticeably, 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 versus 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” (STEP) database [97] has been implemented through the European Paediatric Formulation Initiative (EuPFI) 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 EuPFI is currently developing a “Paediatric Excipient Risk Assessment (PERA) 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 organizations 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 organization 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 program, 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. On the

other hand, 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 US, there is a UNITAID sponsored approach mediated by the “Medicines Patent Pool” organization [104]. 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 (LMICs) 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 [100]. Being the first to develop a product for a rare paediatric indication in the US 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 [101,102].

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 a number of 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 [103]. 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) organization. Some of these PPPs, like 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 [104].

Setting priorities and reaching broad agreement on what is needed most for children worldwide is the mission of the Global Accelerator for Paediatric Formulations (GAP-f) 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 which 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 pre-school age children. The development and clinical evaluation, including M&S and palatability assessment of an ODT formulation is on-going. ODT formulations containing levo praziquantel (L-PZQ) and racemic praziquantel (rac-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 rac-PZQ ODT taken without water by older children [107] [108]. Medicines that are considered essential are listed by WHO on the Essential Medicines List (EML), with those for the treatment of children included in the corresponding list for children's medicines (EMLc). 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 organizations when sourcing drugs for distribution programs. For LMICs a sustainable approach offers the best opportunity to improve and secure access to age-appropriate formulations in the long term. Replacing current humanitarian donation programs 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 generating 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 pediatric 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.

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AUTHOR CONTRIBUTION

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CONFLIC OF INTEREST

The authors declare no conflict of interest.

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TABLES

Table 1. Drivers for Paediatric Product Development Strategies.

Patent status	Possible sequencing of clinical indications during development program	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 to 27 days) Infants and toddlers (28 days to 23 months) Children (2 to 11 years)^b Adolescents (12 to 16-18 years 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.
<p>^aSometimes some adolescents are included in adult clinical trials</p> <p>^bchildren are better considered in 2 sub-categories for formulation development: pre-schoolers and school age children as their ability to take medicines is very different.</p>			

Table 2. List of paediatric-use marketing authorisation (PUMA), reporting indication of use and available dosage forms. Of note, the first three PUMAs were for liquid dosage forms, whereas the three 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 months to < 18 years).	Oromucosal solution in pre-filled 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 years old).	Granules in capsules for opening; 4 strengths.

Kigabeq (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 (3mm); 2 strengths.

Table 3. Key Attributes for a Paediatric Quality Target Product Profile ^a (pQTPP).

Attribute	Targets ^b	Comments
Route of administration	Auricular/ Buccal/ IM/ IV/ Nasal/ Ophthalmic/ Oral/ Pulmonary/Rectal/SC/ Topical/ Transdermal etc.	Route depends on indication and drug properties, disease, and age of patient.
Patient age range	Entire range 0 - < 18 years, or more restricted. Define age groups, as needed.	Define age groups to a) sequence clinical studies, b) select different dosage forms for different age-groups, and c) 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; "Age-appropriate".	Dosage form must be suitable for use in the proposed paediatric population.
Dose and dose flexibility; dosage strength(s)	Paediatric dose range; dose increments, "dose banding".	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.	"Acceptability" 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 "acceptability" 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.

Attribute	Targets ^b	Comments
Primary packaging material & 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 two years minimum under long term storage conditions (ICH), according to climatic zones intended for marketing. For reconstituted products: set targets for “in-use” stability.	Sufficient stability required to facilitate the supply chain, e.g., non-refrigerated 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. “In-use stability”: 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, non-complex 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 sub-populations.	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
<p>^a Refer to 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.</p> <p>^b In cases where clinical supplies are different from commercial supplies, define separate targets.</p> <p>^c In 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 pQTTP’s for each dosage form.</p>		

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 new-born infants	From 23 – 24 weeks gestation
Neonates	0-27 days
Infants and toddlers	1 month to 23 months
Children	2 – 11 years
Pre-school children	2-5 years
School children	6-11 years
Adolescents	12 – 16 or 18 years ^a
^a Upper limit age varies among countries depending on legal age.	