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Practical and operational considerations related to paediatric drug formulation: an industry survey

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1 Abstract

For over 15 years, US and EU regulations ensure that medicines developed for children are explicitly authorised for such use with age-appropriate forms and formulations, implying dedicated research. To shed light on how these regulations have been adopted by pharmaceutical companies and how various aspects of paediatric oral drug formulation development are currently handled, an exploratory survey was conducted. Topics included: general company policy, regulatory aspects, dosage form selection, in-vitro, in-silico and non-clinical in-vivo methods, and food effects assessment.

The survey results clearly underline the positive impact of the paediatric regulations and their overall uptake across the pharmaceutical industry. Even though significant improvements have been made in paediatric product development, major challenges remain. In this respect, dosage form selection faces a discrepancy between the youngest age groups (liquid products preference) and older subpopulations (adult formulation preference). Additionally, concerted research is needed in the development and validation of in-vitro tools and physiology based pharmacokinetic models tailored to the paediatric population, and in estimating the effect of non-standard and paediatric relevant foods. The current momentum in paediatric drug development and research should allow for an evolution in standardised methodology and guidance to develop paediatric formulations, which would benefit pharmaceutical industry and regulators.

Contents

2 Introduction

Paediatric drug research has long been predominantly governed by the extrapolation of knowledge gained in adults without actually testing medicines in children. The understanding of age-dependent physiological changes and their impact on drug disposition has long been obscure and systematic research activities only emerged in recent years (Hirschfeld and Saint-Raymond, 2011; Richey et al., 2013; Shirkey, 1999; Turner et al., 2014). The vulnerability of the paediatric population within clinical research, practical difficulties in recruiting paediatric patients, decreased commercial interest, increased cost, and a greater risk of liability, remained pivotal arguments to neglect paediatric centred research and drug development. Moreover, until recently, the small market share and comparatively smaller return on investment often caused paediatric drug development programmes to be driven by a company's product development strategy for the adult population, rather than the actual paediatric needs (Bourgeois et al., 2012; Joseph et al., 2015; Saint Raymond and Brasseur, 2005; Turner, 2015).

It took decades of concerted efforts by regulatory agencies to shift paediatric medicines development from "therapeutic or pharmaceutical orphans" to the centre stage of drug development research. This shift was driven by the Best Pharmaceuticals for Paediatrics Act (BPCA) (U.S. Governement, 2002) and the Pediatric Research Equity Act (PREA) (U.S. Governement, 2003) by the Food and Drug Administration (FDA), and the Regulation No 1901/2006 on medicinal products for paediatric use (The European Parliament and the Council of 12 December 2006, 2006) by the European Medicines Agency (EMA). The current US and EU regulations ensure that the medicines developed for children are explicitly authorised for such use with age-appropriate forms and formulations. As these regulations have now been implemented for over 15 years, it is interesting to investigate how these regulations were adopted and implemented by pharmaceutical companies into drug development. The approach to paediatric product development is still evolving and the toolbox for prediction of performance of medicines in paediatric populations is fragmented. The current publication reports the results of an industry survey that gauges how paediatric drug formulation and specifically prediction of in-vivo performance is currently being handled within the pharmaceutical industry. As oral formulations are mostly used for the paediatric population, the focus lay on oral product development. Questioned topics include: general information regarding the company policy, regulatory strategies, dosage form selection criteria, in-vitro, in-silico and non-clinical in-vivo methods in the development of paediatric formulations and food effects assessment.

3 Materials and methods

An exploratory survey was designed with the aim to get insight into how paediatric drug development is handled in the pharmaceutical industry. The topics included in the survey were not limited to activities within the framework of the regulatory requirements but also focussed on an R&D perspective. Participants were asked to consider all activities related to paediatric drug development, including successful and failed drug development projects, as well as non-commercial research-based projects.

For most questions, a multiple-choice approach was used to reduce respondent burden and allow for easier and faster evaluation of the results. In order not to restrict input, however, a free text field was added to allow comments.

To test the clarity of the questions and responses, a draft version was sent out to a potential participant in advance. The survey was adapted based on the recommendations.

The topics covered in this survey on paediatric medicines development included:

- General information regarding the company policy
- Regulatory strategies
- Dosage form selection criteria
- In-vitro, in-silico and in-vivo biopharmaceutical methods in the development of paediatric formulations
- Food effects assessment

The full questionnaire with results per question is provided as supplementary information to this manuscript. Please note that some of the questions allowed respondents to tick more than one answer. Unless otherwise specified, survey results are reported per answering option as the percentage of respondents that indicated the option.

This questionnaire was sent out to 14 major industrial research groups involved in drug formulation development and paediatric drug research. This focus was chosen since major research groups often have more experience with paediatric drug development as multiple projects are handled in parallel. No geographical restrictions were taken into account while selecting respondents. Selection of respondents was limited to pharmaceutical industry R&D scientists; no academics, healthcare professionals or regulatory agencies were contacted.

Responses to this survey were collected between April 2021 and May 2021.

4 Results and discussion

4.1 Participant demographics

In total, 12 companies provided a response to the questionnaire. Of the 12 responding companies, 2 acted as individual respondents while the other 10 companies responded as a team. As shown in Figure 1, the respondents covered a wide spectrum of expertise within the pharmaceutical industry, with formulation development and biopharmaceutics being the most represented, followed by clinical research and regulatory.

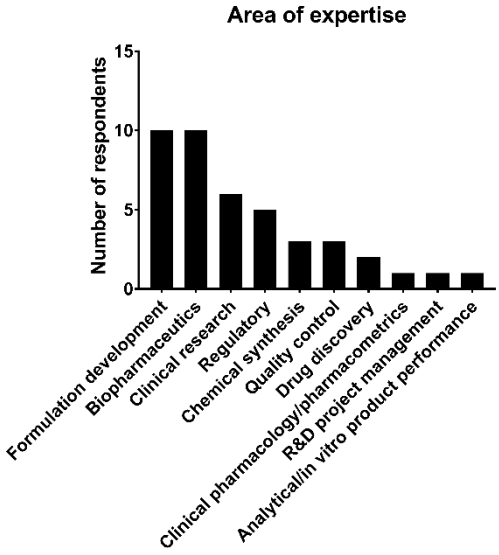

Figure 1: Summary of the areas of expertise of the 12 survey respondents.

4.1.1 Experience in (paediatric) medicines development

Seventy-five percent of respondents had a team member with at least 20 years of experience in drug development while the other 25 % had 11-15 years of experience. Experience in paediatric drug development was more limited with only 25 % of the respondents having a team member with over 15 years of experience. 41.67 % had 11-15 years of experience with the rest (33.33 %) having less than 10 years of experience. All responding companies had one or more paediatric formulations on the market.

4.1.2 Company research policy

The participating companies are active in different fields related to paediatric medicines research, including clinical research, formulation research and drug substance research, as indicated in Table 1.

	Clinical Research	**Formulation Research**	**Drug Substance Research**
No research conducted	0	0	3

Only regulatory required	4	2	3
In-house research	1	2	1
In-house research and external projects	6	7	3
No answer	1	1	2

Table 1: Number of respondents active in clinical, formulation and drug substance research related to paediatric drug development.

The majority of respondents ranked medical functions in the company as most important to identify and understand patient and caregiver needs in paediatric care, followed by marketing and market access functions, and biopharmaceutic and formulation research. Functions related to clinical pharmacology and pharmacokinetics were deemed as least important. One company raised the importance of patient advocacy groups to help and better understand the paediatric population.

4.2 Regulatory

This section of the survey sought to explore regulatory strategies and how their impact on practical and scientific considerations are managed within the paediatric product development programs.

4.2.1 Timing of regulatory submissions

When developing new drug products, a paediatric development plan is obligatory unless a waiver has been granted by the regulatory agencies. EMA expects the application of a Paediatric Investigation Plan (PIP) to be submitted early in drug development, that is, no later than upon completion of the human pharmacokinetic (PK) studies in adults, except in duly justified cases (European Medicines Agency, 2022; Penkov et al., 2017). To further clarify the timelines, the agency categorically states that "the timing of submission should not be later than the end of healthy subject or patient PK, which can coincide with the initial tolerability studies, or the initiation of the adult phase-II studies (proof-of-concept studies); it cannot be after initiation of pivotal trials or confirmatory (phase-III) trials". In the US, if required under the PREA, the sponsor should submit an initial Pediatric Study Plan (PSP) no later than 60 calendar days after the end-of-phase 2 (EOP2) meeting or such other time agreed between the sponsor and the FDA. In the absence of an EOP2 meeting, the sponsor must submit the initial PSP as early as practicable, but before the initiation of any phase 3 studies or any combined phase 2 and 3 study (US Food and Drug Administration, 2020).

The current survey indicated that 66.67 % of the responding companies submit a PIP to the EMA no later than the completion of adult human PK studies, while only 25 % of the companies do this at the end of phase 2 studies. One company (8.33 %) preferred not to answer this question.

The PSP submission timelines varied between the respondents, with 33.33 % of the companies submitting the initial PSP to the FDA within 60 days after the EOP2 meeting of the adult drug

development, 25 % of the companies doing this at the end of human adult PK studies and 25 % by the date of the Phase 2 meeting. One of the respondents (8.33 %) confirmed submitting a PSP to the FDA as close to the EOP2 meeting as possible and one respondent did not answer this question.

Some differences do exist between the two agencies regarding the expected time for submission of a proposed PIP or initial PSP by the applicant (or a request for waiver). However, efforts have recently been made for the regulatory agencies' alignment on paediatric development plans especially for rare diseases such as childhood cancer and for COVID treatments (European Medicines Agency, 2021a).

The legislative and regulatory frameworks have indirectly compelled the pharma companies to invest in infrastructure and put together dedicated expertise to ensure that the adequate paediatric research capabilities are in place to support the agreed development plans. Consequently, these regulations have a direct impact on the companies' R&D expenditure. Based on the 2017 paediatric medicine report from the EU commission to the EU parliament and the council, the average regulatory cost incurred by the pharma companies amounts to EUR 18.9 million per PIP (European Commission, 2017).

4.2.2 Requests for waivers or deferrals for paediatric drug development

While the regulatory agencies expect the pharma industries to invest more in the paediatric research programmes and provide accurate dosage forms for the use of drugs in children, they also recognize the critical challenges involved in gaining such information. Hence, a system of waivers for the medicines that are unlikely to benefit children, and a system of deferrals in relation to the timing of the paediatric measures to be conducted, have also been part of the paediatric legislations (European Commission, 2017).

The survey revealed that 83.33 % of the companies already received either a waiver or a waiver and deferral for paediatric drug development. 8.33 % received only a deferral and another 8.33 % chose not to answer the question. The general reasons to seek a waiver or deferral were: 'the indication is not relevant for paediatrics', 'no or a lack of expected therapeutic benefit for children' or 'patients of interest are too difficult or cannot be recruited'. Additional reasons were 'a too high risk/benefit ratio' or 'the adult dosage form and doses are suitable for the paediatric population'.

4.2.3 Requests for scientific advice/compliance checks

Paediatric drug development regulation is a complex arena, and the regulations as well as the drug development strategies have evolved with more paediatric medicines getting approved. Dialogue and close collaboration between all the major stakeholders is very important. In the recent past, a number of regulatory documents have been made available in the public domain, both by FDA and

EMA, to help guide companies through the submission procedures and to assist them in answering the specific queries regarding the study design and conduct. Moreover, to increase the transparency and dialogue between the health authorities and the companies, a provision of free paediatric scientific advice has been made available.

Almost all of the responding companies (91.67 %) have asked scientific advice from a regulatory agency for paediatric drug development. One company (8.33 %) chose not to answer the question. During this survey, the participating companies were also asked whether they had submitted a paediatric plan to a compliance check and, if yes, whether they experienced any issues in the procedure. Half of the companies that responded indicated that they have submitted a paediatric plan for a compliance check (50 %), and nobody reported any specific issues. One company indicated that the questions posed were resolved. Around 25 % of the companies has not yet submitted a paediatric plan for a compliance check and the other 25 % chose not to answer the question.

The survey results thus indicate that companies seize the opportunity of early consultations with the regulatory agencies, which may help them in building a rational strategy and improving the information exchange, thereby reducing the product development timelines.

4.2.4 Main regulatory challenges

When participants were questioned about the main challenges their companies had encountered with the regulatory pathway for paediatric products, the results revealed that the most common and the major challenge was the 'proposed paediatric study design', followed by 'paediatric PK'. The 'safety and use of excipients in paediatric population' and 'formulation bridging based on *in-vitro*/*in-silico* results were comparatively less frequent challenges. Additional areas reported during the survey were 'extrapolation of information from older age groups', 'scarcity of paediatric patients in certain age groups', 'pH of formulations' and 'paediatric patient recruitment'.

4.3 Dosage form selection

One of the key differences in paediatric versus adult product development is the requirement for dose flexibility (e.g., dosing by weight or body surface area), as well as the regulatory requirement to demonstrate patient compliance. A variety of oral dosage forms can be used in paediatric patients; a recent review of commercially available oral paediatric formulations identified 16 different types of formulations (Strickley, 2019). These can be sub-divided into ready to use formulations (oral solution, oral suspension, tablet, mini-tablet, oral soluble film, orally disintegrating tablet, and chewable tablet) and those that require additional processing (micro particulates, granule for oral suspension, powder for oral solution, powder for oral suspension, tablet, scored tablet, dispersible tablet, tablet for oral suspension, and concentrated oral suspension).

To ensure timely paediatric drug development, its development is often based on knowledge gained from adult drug product development. However, paediatric drug development often starts later in the drug life cycle. Consequently, it generally lags some months/years behind the adult product though still follows a development path parallel to its adult counterpart. Additionally, there is typically a desire to adapt the adult product for the paediatric population to allow for the easiest development. This may involve using an adapted formulation where there is known compatibility of the excipients with the active pharmaceutical ingredient (API). As adult oral products are most typically tablets, and since the know-how and facilities within companies are typically strongest in tablet design and manufacturing, a paediatric formulation that is based on a tablet is desirable, for example a mini-tablet or granule.

This section of the survey sought to explore the companies' strategy to select dosage forms that meet the needs for dose flexibility, acceptability, and ease of manufacturing for a paediatric product.

4.3.1 Age-specific formulation development

For most of the responding companies (41.67 %), newborns are the youngest population for which an age-specific formulation would be considered, followed by infants (33.33 %), preterm newborns (16.67 %) and preschool children (8.33 %).

Factors relevant in determining the type of dosage form to develop were ranked with 'dosing accuracy and flexibility' being indicated as most important, followed by 'in-vivo performance requirements', 'patient and caregiver needs' and 'technical constraints'; 'regulatory feedback/acceptance' was reported as the least important factor. Some companies mentioned additional factors of relevance, including 'a simple and established manufacturing process to enable rapid development/access' and 'solubility and stability aspects'.

4.3.2 Preferred paediatric platform technology

A preferred platform technology offers the opportunity to develop expertise in a particular formulation design and manufacturing process which can be of value across the full range of paediatric products. This can lead to lean and efficient development.

The survey asked about preferred platform technologies based on the age of the paediatric participant; the results are shown in Table 2.

	(Preterm) newborn, infant, toddler (0-23 m)	**Preschool child (2-5 y)**	**School age child (6-11 y)**	**Adolescents (12-18 y)**
Minitablets	5	8	8	2
Multi particulates	3	5	5	2

Syrups	6	6	4	1
Granulates	3	6	5	1
Free powder	0	1	1	0
Standard tablet	0	0	4	5
Suspension	9	9	8	2
Capsule	0	0	1	4
Dispersible tablet	5	5	4	3
Adult dosage form	0	0	6	10
Other	0	0	0	0

Table 2 Number of respondents indicating different types of dosage form as preferred platform technology by age group. Note that multiple platforms could be selected for each age band.

In the youngest populations (< 2 years), the risk of choking limits the use of certain dosage forms, making liquid formulations (suspensions and syrups) as well as dispersible tablets the preferred platforms. In addition, minitablets were preferred to multiparticulates and granulates in this youngest population. A similar trend was observed in pre-school children (2-5 years), although there was a growing proportion of those who would consider minitablets, multiparticulates and granulates. For school age children (6-11 years), the use of the adult dosage form, a standard tablet and a capsule was mentioned as preferred platform by some companies; these dosage forms can negate the need for bespoke paediatric development and are therefore very cost efficient, assuming that the dose banding does not dictate the need for multiple units. The trend of using the adult or monolithic solid dosage forms further increased for adolescents, accompanied with a decreased mentioning of liquid formulations as preferred platform technologies.

From these data, certain formulations, including syrups, suspensions, dispersible tablets, mini tablets, multiparticulates and granulates, appear to be suitable for use in all paediatric age groups, as well as in adults. There is some merit in the development of a single yet flexible type of formulation for all patients; however, this is yet to be observed in practice.

4.3.3 Excipient selection for paediatric products

As excipients often make up most of a drug's formulation, their use in paediatric formulations should be thoroughly investigated. As such, questions regarding their safety and tolerability within the paediatric population are eminent. Consequently, the opinion regarding the use of excipients and the use and research of new excipients was questioned. Regarding the selection of excipients for paediatric products, none of the responding companies is actively looking for new excipients to improve paediatric formulations. The majority of respondents (58.33 %) indicated to only look for new excipients when an acceptable formulation cannot be achieved using current standard

excipients. 33.33 % of the respondents used only the standard and well-known excipients listed in pharmacopoeia or excipients generally regarded as safe (GRAS) or mentioned in the Safety and Toxicity of Excipients for Paediatrics (STEP) database. The remaining 8.33% preferred not to answer this question. Regarding the possible use and research of new excipients which haven't been used in the past, 25 % of the respondents either never use novel excipients or avoid their use by altering the dosage form or formulation strategy. 75 % of respondents only use a novel excipient if no alternative options are available.

Considering safety is the main driving force in the selection of an excipient, it was raised that the accepted daily intake (ADI) of a pharmaceutical excipient is based on a mg/kg body weight. In this regard, the safety of excipients has recently been questioned for paediatric products and the survey asked whether this affects paediatric excipient selection. Excipient selection was most reported (66.67 %) to be based on the ADI to create uniform but flexible dosage forms across target age groups; 25 % let the age-appropriate dosage form selection drive the excipient choice and 8.33 % of the companies does not let excipient selection drive formulation type selection.

4.3.4 Taste masking of oral paediatric formulations

Taste masking of oral dosage forms is an important aspect to improve drug acceptability/palatability, patient compliance and therapy adherence in children. As such, all responding companies consider taste masking during the development of paediatric formulations. In particular, taste masking is considered for syrups and suspensions (91.67 % of respondents) and for buccal or sublingual tablets (75 %). Most respondents (75 %) also consider taste masking for immediate- or extended-release tablets/capsules. One company specifically mentioned considering taste masking for granules and minitablets.

'Non-sugary sweeteners' are the most commonly used excipients by the responding companies (83.33 %), followed by 'flavours' (66.67 %). Also a 'modifying film coat' (25 %), the 'dosing vehicle (food)' (16.67 %) and 'sugars' (16.67 %) were reported as taste masking excipients.

Measurement of taste masking efficiency is a known issue during product development [47,48]. The survey asked about how taste masking was assessed. For most companies (41.67 %), a 'sip and spit clinical study' is the general approach in initial taste masking assessment (41.67 %). Twenty-five percent of the companies uses an electronic tongue to assess taste masking. The remaining companies mentioned the 'rat BATA test' (8.33 %) or data on 'taste assessments in clinical studies/first-in-man study' (8.33 %) as the general approach for the initial measurement of taste masking. One company indicated to have no approach at the moment.

4.4 In-vitro, in-silico and in-vivo biopharmaceutical methods in the development of paediatric formulations

The efficient development of drug products requires that the disposition of APIs and the performance of formulations in the human body can be predicted prior to the execution of clinical trials. To this end, in-vitro tools, in-silico modelling and non-clinical in-vivo experiments can be of great value, provided that these approaches adequately simulate the human physiology so that relevant information on drug behaviour and disposition can be generated. Lately, significant advances have been made in the biorelevant evaluation of drug products. Most optimizations, however, were tailored to the adult population.

This section of the survey sought to identify how in-vitro, in-silico and non-clinical in-vivo techniques are scaled for the different paediatric subpopulations and how physiological differences are accounted for within these methods. Additionally, it was evaluated how often clinical trials in paediatrics are performed.

Based on the responses on this survey, conventional drug solubility, USP-based dissolution techniques and classification according to the Biopharmaceutics Classification System/Developability Classification System (BCS/DCS) are still the most used biopharmaceutical tools in industry for paediatric oral product development. This makes sense as these are some of the oldest, most tested and widely accepted tools by both regulatory authorities and academia.

These conventional approaches are followed by single-stage advanced biorelevant dissolution techniques and by modelling and simulation techniques. As compared to conventional dissolution tests, single-stage biorelevant dissolution techniques aim to better simulate physiological conditions in the gastrointestinal (GI) tract by considering, for instance, GI volumes, hydrodynamics and media composition. Modelling and simulation techniques raise interest and application due to their mechanistic character and relatively cheap insight generation compared to more labour intensive in-vitro or in-vivo tests. Both single-stage biorelevant dissolution testing and modelling and simulation are of particular interest for paediatric drug development as they allow to integrate paediatric physiology in drug and formulation evaluation.

Comparatively, the least used systems are dynamic multi-stage (or -phase) in-vitro systems. While such models, including biphasic dissolution testing, the dynamic gastric model, TNO Intestinal model (TIM) 1 and tiny-TIM, further improve the biorelevant simulation of the GI tract by introducing additional physiological factors such as fluid absorption and secretion, contractions, transit… (Vinarov et al., 2021), they also significantly increase the complexity of the generated output. Additionally,

these models come with the added disadvantages of increased cost, increased time consumption and lower throughput (Vinarov et al., 2021).

The current preference of the industry for conventional, relatively simple biopharmaceutical tools over more complex models for paediatric drug development seems related to the biggest challenges in using biopharmaceutical tools. The survey respondents voted for the unknown clinical relevance, translatability and regulatory acceptance of biopharmaceutical tools as major challenges, which obviously hamper the implementation of biorelevant techniques to evaluate drug products for the paediatric population.

4.4.1 In-vitro biopharmaceutical tools

4.4.1.1 Integration of gastric emptying into predictive in-vitro tools

The emptying of gastric contents into the small intestine (SI) can have a substantial effect on drug release and dissolution and consequently drug exposure. Integrating gastric emptying (GE) into in-vitro models has shown to improve their ability to predict in-vivo absorption in adults (Štefanič et al., 2012) and is being explored in paediatrics. In-vivo data have shown that GE is variable in the paediatric population (Stillhart et al., 2020) and dependent on the type of meal (Bonner et al., 2015). It therefore appears to be relevant to consider GE when testing paediatric drug product dissolution.

Of the participating companies, 41.67 % indicated to be taking this into account. To do so, they use a variety of tools where the majority uses the 2-stage dissolution dumping (80 %) or transfer method (60 %). Only 16.67 % of the companies indicated they use the (tiny) TNO intestinal model and 1 company uses the USP 4 open loop system.

4.4.1.2 Integration of GI pH into predictive in-vitro tools

For adults, a fasted state gastric pH of 1-2 is usually set as a baseline in in-vitro experiments. For the intestinal pH, a distinction between the small and large intestine is usually made, with the small intestinal baseline pH ranging between 6.5 and 7.4, and the large intestinal baseline pH ranging between 5.5 and 7 (Evans et al., 1988; Nugent et al., 2001). However, measurements of the GI pH in children have shown differences that should, ideally, be considered during in-vitro testing (Fallingborg et al., 1990; Mooij et al., 2012; Van Den Abeele et al., 2018).

For paediatric in-vitro work, survey responses show that most companies (75 %) use setups with a simulated gastric pH of 1-2. Only one company (8.33 %) indicated to be using higher pH levels. 16.67% of the responding companies chose not to answer this question. Even though no specific pH levels were questioned in this survey, the use of higher pH levels would be in line with literature data. As reported by Mooij et al. (Mooij et al., 2012) and Van Den Abeele et al. (Van Den Abeele et al., 2018), gastric pH levels of up to 3 have been measured for the paediatric population.

For the in-vitro simulation of small intestinal pH in the paediatric population, all responding companies use a pH between 6.5 and 7.4. This is in line with the pH profile observed by Fallingborg et al. for children aged between 8 and 14 years (Fallingborg et al., 1990) and is comparable to the profile for adults. Also for the large intestine, all responding companies use a pH range that corresponds to the baseline for adults (i.e., pH 5.5-7). It should be noted that 16.67 % of the responding companies chose not to answer this question.

4.4.1.3 Integration of biorelevant media into predictive in-vitro tools

When looking at which biorelevant media are used for paediatric in-vitro testing of formulations, most of the responding companies (83.33 %) use FaSSIF and FeSSIF version 1 and 2 while version 3 is not used (Figure 2). Additionally, some companies use custom versions of FaSSIF and FeSSIF or in-house type of biorelevant media (IHBM) of which the composition is based on literature. No companies prepare media based on in house data. Lastly, 16.67% of the responding companies chose not to answer this question.

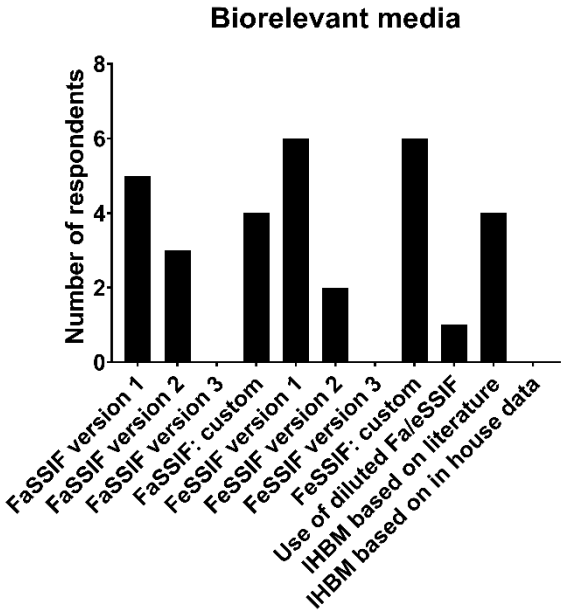

Figure 2 Types of biorelevant media and the frequency of their respective usage by the pharmaceutical industry in the evaluation of paediatric drug products, 10 responding companies in total.

4.4.1.4 Integration of biorelevant GI volumes into dissolution testing

Although data are relatively scarce, significantly lower volumes of GI fluids have been reported in paediatrics compared to adults (Goelen et al., 2021; Papadatou-Soulou et al., 2019). Obviously, altered GI volumes may affect drug dissolution and even impact BCS/DCS drug classification. When asking how fluid volumes are handled in biorelevant dissolution testing for paediatric drug development, 46.15 % of the respondents indicated to use a volume between 100-500 mL, which is in line with pharmacopoeias advised volumes for adults. However, 23.08 % of the respondents

indicated to be using a volume of 500 mL or more, being even higher. Interestingly, only 15.38 % of the companies use volumes below 100 mL, which are more representative for the paediatric physiology. Lastly, 15.38 % of the respondents chose not to answer this question.

4.4.1.5 Regulatory input on dissolution methodology

About 41.67 % of the companies indicated that their proposed in-vitro drug dissolution assay for the paediatric formulations has been questioned/scrutinized by a regulatory agency. Around 33.33 % of the companies responded that they hadn't come across any such scrutiny and 25 % of the companies chose not to answer the question. Next it was questioned whether any of the adult drug products have been subject to a change in drug solubility classification for a proposed paediatric formulation. Most companies indicated that they have not yet been subjected to any change in drug solubility classification for paediatric formulations (75 %). Only one company (8.33 %) had an adult drug product which had been subject to such a change. The remaining 16.67 % of the companies chose not to answer the question.

4.4.2 In-silico modelling and simulation

To substantiate drug development, gathering sufficient safety and efficacy data in children can be difficult due to the limited and challenging recruitment of patients. Paediatric research, therefore, needs to be more efficient with the available, limited information in-hand. In this regard, in-silico modelling techniques can play a significant role in making an optimal use of the limited opportunities for paediatric research with a limiting dataset, thereby increasing the knowledge gained from the paediatric trials (European Medicines Agency, 2008; Jadhav et al., 2009; Johnson and Rostami-Hodjegan, 2011; Manolis et al., 2011). In the recent past, various in-silico techniques that include but are not limited to population pharmacokinetic (POP-PK) modelling, study optimization tools, Bayesian approaches, physiology based pharmacokinetic (PBPK) modelling and PK-PD correlation based modelling are making a significant difference in the paediatric research.

The diverse applications of in-silico modelling tools in paediatric research have fostered a great interest in the use of these techniques within the industry as well as with the regulatory agencies. This is reflected in their frequent reference across the recently approved drug labels, regulatory guidance and concept papers. In recent years, the stronger interest of regulatory agencies in the application of modelling and simulation techniques in paediatric medicines development has also resulted in a widespread use of these tools within drug development programmes (European Medicines Agency, 2021b; US Food and Drug Administration, 2019a, 2017).

4.4.2.1 Paediatric dose estimation

During the survey, the participants were asked about the techniques they use for paediatric dose estimation. The most used in-silico tool for dose estimation for paediatrics is 'PBPK modelling' (83.33

%), which is followed by ‘allometric scaling using POP-PK modelling’ (58.33 %). ‘Simple allometric scaling’ appears to be the least used technique amongst the participants (41.67 %). Contrary to the conventional empirical or semi-mechanistic modelling approaches, the PBPK models are based on physiological considerations and integrate two classes of information: system/biology data derived from physiological characteristics of the species or population studied, and drug/formulation data derived from the relevant physicochemical and disposition attributes of the compound and/or its dosage form.

The PBPK modelling framework thus provides users with the ability to extrapolate between populations, making it possible to relate the drug information obtained from the healthy adults to the target paediatric population, provided (patho-)physiologies are well defined within the system. Additionally, models verified within healthy volunteers can also support the risk assessment by exploring the possible interactions and the effect of impaired organs/tissue characteristics within the target patient population. Therefore, the survey results, endorsing a higher use of PBPK based modelling techniques compared to the conventional in-silico techniques, are not surprising.

4.4.2.2 Integration of paediatric physiology into in-silico tools

The PBPK modelling framework separates the information based on the system biology (human physiology) from the drug and the study design parameters. The “default” system/biology data in the form of population libraries files within the commercial software platforms is the responsibility of the software providers. These files are built from an extensive analysis of demographic, anatomic and ontogeny characteristics of a target paediatric population. Customized changes within these default physiological settings are generally undertaken by the modelers to mimic the target (patient) population as closely as possible in terms of a given disease condition, pathophysiology, or sometimes to account for the effect of ontogeny and allometry on certain system parameters. Consequently, any such customized changes within the default population files should be highlighted and the rationale for the chosen system-dependent parameter values needs to be supported by relevant literature references and the responsibility for the same lies with the modelers (Dibella et al., 2016; Jones et al., 2015; Parrott et al., 2021).

When participants were further asked about how paediatric physiology was accounted for within in-silico tools, the majority of the respondents indicated ‘PBPK modelling using commercial software with customized physiological settings’ (58.33 %), which was followed by ‘PBPK modelling using commercial software with default physiological settings’ (41.67 %) and a few responded with ‘based on previous population based pharmacokinetic modelling scaling’ (25 %). The other options like ‘PBPK modelling using custom in-house software’ and ‘allometric scaling’ were only selected by 8.33 % of the respondents.

4.4.2.2.1 Integration of GI motility and transit into in-silico tools

Most of the respondents indicated that they take paediatric GI motility and GI transit into account within PBPK modelling (58.33 %). A third of the respondents mentioned that they do not take these aspects into account. Lastly, 8.33 % of the companies chose not to answer the question.

4.4.2.2.2 Integration of GI pH into in-silico tools

When asked for the GI pH-values used for paediatric populations within in-silico models, 41.67 % of the companies reported using pH 1-2 for the gastric region whilst 25 % use higher gastric pH values. The remaining 33.33% preferred not to answer this question. For both the small and large intestine, 58.33 % use pH-values corresponding to the baseline ranges used for adults (i.e., 6.5-7.4 in the small intestine and 5.5-7 in the large intestine), whilst 8.33 % reported using higher and 16.67 % reported using lower values. The remaining 16.67% preferred not to answer this question. As compared to in-vitro tools (Section 4.4.1.2), some companies appear more inclined to adjust pH values in in-silico models for the paediatric population.

4.4.2.2.3 Integration of GI fluid and their composition into in-silico tools

When questioned about whether correction factors, if any, were applied for bile salt concentrations in the paediatric population, the majority of the respondents indicated that the bile salt concentration is scaled using the commercial PBPK software (83.33 %). 8.33 % indicated downscaling of the individual bile salt concentrations specifically. Lastly, 8.33% chose not to answer this question

The survey also revealed that the majority of the respondents handle GI fluid volumes in PBPK modelling of the paediatric population by using 'the standard/default values provided within the PBPK software' (66.67 %), while the rest indicated that they decrease the volumes compared to the standard PBPK input (25 %). Interestingly, however, 8.33 % of the companies handle GI fluids as 'volumes of the adult population' and another 8.33 % chose not to answer the question. When asked for what source users use for scaling GI fluids within the paediatric population, most of the companies indicated that GI fluid volumes were not scaled up or down for the paediatric population and the default paediatric PBPK software settings are used (41.67 %). Besides, most of the others use literature dataset for up-downscaling of paediatric GI fluid volumes (33.33 %). 8.33 % of the respondents indicated using 'adult GI fluid volumes'. 16.67 % of the companies chose not to answer the question.

4.4.2.3 Sub-population scaling using in-silico models

Most of the survey participants (58.33 %) indicated using different scaling for different paediatric subpopulations and handling all the subpopulations defined by the International Council for Harmonization (ICH) separately. 25 % of the participants also use different scaling for different

subpopulations but do not use ICH categories. Only one company (8.33 %) does not consider different subpopulations and one company (8.33 %) chose not to answer the question.

4.4.2.4 Integration of metabolic capacity

Mechanistic understanding of metabolic enzyme ontogeny and their application in paediatric dose calculation is a well-known concept to the scientific fraternity and has been a well-established practice for successful in-vitro-in-vivo extrapolation (IVIVE) of drug clearance. However, the role of ontogeny of GI parameters in drug absorption and its application in designing in-vitro/in-silico characterization techniques has not been explored widely (Batchelor and Marriott, 2015; Johnson and Rostami-Hodjegan, 2011).

Based on the survey, the most used technique for integrating the metabolic capacity of the paediatric population appears to be 'allometric scaling of adult data to paediatric population' (58.33 %), followed by 'PBPK based scaling' (25 %) and 'paediatric cell cultures (hepatocytes, rCYP)' (16.67 %). 8.33 % of the responding companies use 'ontogeny profiles' and another 8.33 % chose not to answer the question.

For the scaling of enzyme and transporters abundance within in-silico tools, most of the modelers used 'scaling by commercial PBPK software' (83.33 %), which is followed by 'scaling based on proteomics data from literature' (25 %) and 'scaling based on mRNA data from literature' (25 %). 'Allometric scaling' (16.67 %) is less used as a source. Only 8.33 % of the companies indicated the use of 'in-house measured activity for probe substrates' and another 8.33 % used 'in-vivo ontogeny function'. 16.67 % of the companies chose not to answer the question. Also interesting, while scaling, most companies considered different paediatric subpopulations (67 %).

4.4.3 Clinical in-vivo studies

In response to the question, "Are clinical studies using the paediatric population performed?", most companies reported only conducting clinical studies for newly developed drugs where use is specific for paediatric patients (33.33 %). 25 % of the companies uses clinical studies for most newly developed drugs and a further 25 % when they are required by regulatory agencies. 16.67 % of the companies uses clinical studies for all newly developed drugs.

4.4.4 Non-clinical in-vivo studies

The majority (58.33 %) of the responding companies indicated that they use animals to simulate the paediatric population. However, only 33.33 % of the participants reported the use of juvenile animals for this purpose. In general, the preferred animal models include rodents (rats (41.67 %) and mice (16.67 %)) and non-rodents (dogs (25 %) and minipigs (8.33 %)).

4.5 Food effects

Understanding food–drug interactions is critical to evaluate appropriate dosing, timing, and formulation of new drug products. Food effect studies (in adults) are recommended for new products to represent a worst case scenario where a high fat meal is used under a standard protocol that is similar for both the FDA (U.S. Department of Health and Human Services Food and Drug Administration CDER, 2002) and EMA (European Medicines Agency, 2012). However, there are key differences between the feeding patterns of paediatric patients and adults both in terms of food composition and feeding frequency. In addition, the GI processing of food can be different in paediatric patients. A review of 18 fed effect studies in paediatric populations revealed that 11/18 showed the same PK result as that shown in adults, five showed different results to the adult study and two could not be compared, indicating these differences in food effects should be taken into account (Batchelor, 2015).

In paediatric populations there is evidence that a wide range of drugs are mixed with food prior to administration to ensure that medication is acceptable to the patient (Akram and Mullen, 2012). Much of the efforts to explore food effects in paediatric populations relate to using food as an aid to the administration of a medicine where the volume of food to be used is much less than a meal, thus the relevance to a fed effect study with a high fat meal is questionable. However, the amount of food that is necessary to initiate the fed state is not clear. Administration of a small amount of long chain lipid (2g) to adults was observed to delay GE (Kossena et al., 2007).

This section of the survey explored how the co-administration of a paediatric product with food (to aid palatability/acceptability) can be managed during product development.

As anticipated, the majority (91.67 %) of survey respondents actively explore co-administration of medicines with food to improve drug acceptance. Examples of foods used as co-administration vehicles include apple sauce, fruit (apple) juice, milk, yoghurt, (cereal) porridge, carrot mush, banana mush and (chocolate) pudding. These foods are similar to those listed in The British National Formulary for Children (BNF-C) (Royal pharmaceutical Society, 2020) where specific foods suitable for co-administration mentioned include: yoghurt, apple sauce, ketchup, squash puree, cereals, thin soup, jam or honey, and drinks (orange juice, apple juice, milk). However there are differences to the foods mentioned in the draft FDA guidance: formula for infants and jelly, pudding, or apple sauce for toddlers (US Food and Drug Administration, 2019b).

4.5.1 Food used to explore a fed effect in-vivo

As it is known that paediatric drug acceptance can be difficult, EMA Guidance (ICH E11) (European Medicines Agency, 2017) suggests that co-administration with food should be considered as a

strategy to improve palatability/acceptability. This approach mimics real world use and the guidance states that “real-world use behaviours in administering paediatric drugs and the mitigation of associated risks will contribute to the development of a drug product that allows for safe dose administration”. To further detail their opinion, the EMA published a reflection paper, “Formulations of choice for the paediatric population” (European Medicines Agency, 2006) which states that, “the product information should specify which commonly available foods are suitable for mixing with the preparation, and also list foods that should be avoided due to stability, compatibility or taste issues”.

In parallel, draft FDA guidance, “Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations” (US Food and Drug Administration, 2019b) states that for products that may be sprinkled onto soft foods then the sponsor should perform additional in-vivo, relative bioavailability studies using the soft foods listed in the labelling. The draft guidance also states that for a new paediatric formulation the sponsor should conduct a fed effect study in adults and then extrapolate the results to a paediatric population. The foods and quantities of foods should be selected from those commonly consumed in a paediatric population (US Food and Drug Administration, 2019b).

To explore how the industry applies these guidelines in practice, it was first questioned which meals are selected when evaluating an in-vivo food effect for a paediatric formulation. An overview of the selected meals can be found in Figure 3. The most commonly used meal is ‘food representative for toddlers/preschool children’ (66.67 %), followed by ‘food representative for newborns/infants’ (50 %) and ‘standard FDA breakfast’ (41.67 %). 16.67 % of the companies do not assess food effects in-vivo and 8.33 % use ‘low-fat, low-calorie meals’.

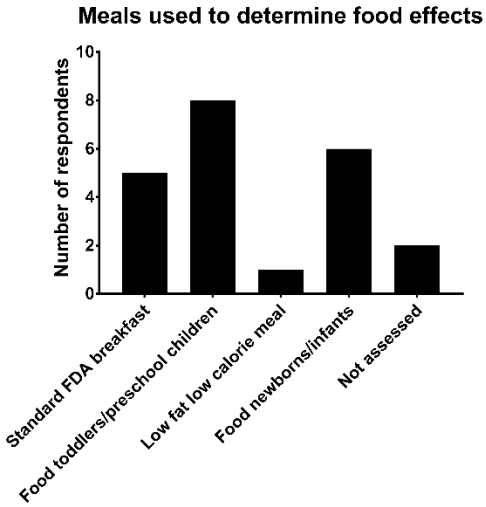

Figure 3. Range of foods used to determine the in-vivo food effects of paediatric formulations.

The FDA standard breakfast is reported to have a volume of 513 mL, which is consistent with typical meal volumes in adults (Klein et al., 2010); however, this would be a large meal for younger children. The survey revealed that 58.33 % of the companies reported using a volume representative for paediatrics whilst 16.67 % reported using a standard adult volume meal (note that two companies do not assess food effects in-vivo). Extrapolation of food volumes, such that a study in adults can be extrapolated to paediatric populations, is complex; for example, a tablespoon of apple sauce for a child may equate to a larger volume for an adult and it should be carefully considered whether the scale should be based on dose or GI physiology.

Using a scaled version of the FDA breakfast may be one option to understand food effects. In the survey, only one company (8.33 %) reported using a scaled FDA breakfast to better understand food effects in paediatric populations, while 25 % of the respondents reported that this could be considered. Cows' milk with a fat content of 3.5 % (whole milk) has a similar composition to the FDA standard breakfast meal with respect to the ratio of carbohydrate/fat/protein; it is also a more commonly used co-administration aid in paediatric populations and may be a suitable alternative (Klein et al., 2010).

4.5.2 Use of in-vitro tools to predict a food effect

In-vitro methods to predict food effects were reported to be used by half of the companies (50 %) where reported methods include: FeSSIF solubility and (physiologically based) dissolution, (tiny)TIM-1, dissolution with food added, and compendial USP (2) dissolution (with dose dispersed in soft food).

A major limitation of in-vitro tools to predict a fed effect in paediatrics has been the lack of clinical data against which such methods can be validated. Recent work has generated simulated paediatric breakfast media that may be used in in-vitro risk assessment of fed effects for future paediatric products (Freerks et al., 2021). Additional work has generated biorelevant dissolution testing conditions that include dosing with soft food and drinks (Martir et al., 2020a, 2020b). Although food effects have been modelled using PBPK, there is yet to be a detailed study that uses PBPK to predict a food effect from a co-administered vehicle in children (Riedmaier et al., 2020). The multicompartment dissolution testing apparatus that mimics GI physiology, TIM paediatric®, has been used to predict the impact on bioavailability of drug co-administration with food (Havenaar et al., 2013).

5 Conclusions

This survey gives some insight in how paediatric biopharmaceutics are handled in the pharmaceutical industry. Insight was provided by experienced scientists in 12 pharmaceutical companies which are

actively performing paediatric research and development and have paediatric drugs on the market. Questioned topics included general information regarding company policies, regulatory hurdles, selection of the appropriate dosage form, in-vitro, in-silico and non-clinical in-vivo techniques, and food effects.

Of the 74 questions which were sent out, only the questions with an interesting or unexpected outcome were discussed in this article. However, all questions and responses are available in the supplementary data. The results suggest that the participating companies had a rather conservative approach to drug development where the focus mainly lay on the use of regulatory required tests with only sometimes more extensive research.

Responses show that dosage form selection is still a major challenge in paediatric drug product development. The use of adult formulations in older age groups, adolescents and some school age children is reported, though sometimes not ideal. The use of liquids (syrups/suspensions) is still popular for the youngest age groups. Minitablets, multiparticulates and granules offer a flexible solid dosage form that is also popular for all paediatric age groups.

When testing these drugs and formulations in-vitro, the main challenge is to find a setup which allows for a good in-vitro-in-vivo correlation and is therefore biopredictive. To do so, respondents of this questionnaire often use the best researched and most widely accepted in-vitro tools such as solubility testing, standard USP dissolution testing, standard biorelevant FaSSIF and FeSSIF media and the BCS classification system. To incorporate some more physiological relevance, companies mentioned adaptations to these standardized setups, such as the inclusion of a second stage to the dissolution setup, literature-based adaptations to biorelevant media, changes in pH for solubility and dissolution media, and the use of paediatric cell cultures for metabolism assessment. However, it should be noted that the application of such changes are rather limited. For example, in the metabolism experiments, only a minority of respondents (16.67 %) actually use paediatric cell lines. In contrast, the majority of respondents (75 %) prefer scaling adult data to the paediatric population using allometric or PBPK scaling. Two other parameters where this is seen are the biorelevant media and their volumes. 51.61 % of the used media were standard, accepted biorelevant media (FaSSIF and FeSSIF version 1 and 2), while 48.39 % were adapted versions by, for example, dilution. For the fluid volumes used in-vitro, only 16.67 % of the respondents indicated the use of volumes below 100 mL while the other 66.67 % indicated the adult representative volumes of 100-500 mL.

In general, clinical studies in paediatrics are mostly only performed as a regulatory requirement though some companies seem to go the extra mile and perform clinical studies in children for all newly developed drugs. As clinical studies in children are limited due to ethical concerns, animal in-

vivo studies are often used as potential alternatives. To perform these tests, rodents are most often used as an animal model. Only a minority of companies use juvenile animal models for additional representativeness.

The current survey results clearly underline the increased interest and use of in-silico modelling techniques in paediatric drug research. User-friendly, graphical user interface (GUI) based PBPK modelling systems are now commercially available and this has resulted in the widespread use of these techniques in paediatric drug development studies. Based on the results from this survey, we see a positive trend in the use of age-specific parameters in in-silico models, with all responding companies incorporating paediatric physiology in some way. To optimize their use for these populations, specific adaptations to the software are made with regards to GI fluid volumes, enzyme/transporter ontogeny profiles and pH levels. Different sources (literature, in-house, allometric scaling…) are generally being used as a basis for these adaptations. However, the majority of the respondents still use the default values within the PBPK software. To the best of our knowledge, the probable reason for the fewer adaptations to these standard input values is the difficulties in the validation thereof.

Lastly, current practice differs between pharmaceutical companies with regard to investigating the impact of co-administration of food with paediatric products. To do so, a range of foods as well as in-vitro tools are reported. A bespoke paediatric toolbox of in-vitro, in-silico and non-clinical in-vivo methods are required to better understand the boundaries that impact upon exposure in relation to the co-administration of food and how these can be risk assessed using standardised methods.

As a summary, the survey results clearly underline the positive impact of the paediatric regulations and their overall uptake across the pharma industries. These legislations have brought a phenomenal shift in the way the paediatric product development strategies are designed and integrated in an overall development of new medicines. Even though significant improvements have been made, major challenges still remain in the implementation of paediatric physiology into in-vitro setups, more tailored and validated PBPK models, the effect of non-standard and paediatric relevant foods and age appropriate and flexible paediatric dosage forms. However, with the current momentum in paediatric drug development and research these challenges could be tackled in the upcoming years. A rational development of medicines for children is now at the forefront of paediatric research and after years of unintentional neglect, children’s needs are primarily driving the product development programmes more than ever.

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7 Conflict of interest

The author declare following competing financial interest(s)- Shriram M. Pathak is an employee of Quotient Sciences, Nottingham, United Kingdom.

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