Journal Pre-proofs

Research paper

Pediatric oral extemporaneous preparations and practices: International Pharmaceutical Federation (FIP) global study

Hala M. Fadda, Hannah Weiler, Maria Carvalho, You Zhuan Lee, Hadi Dassouki, Rasha AbuBlan, Sonia Iurian, Aasma Hamid, Gökhan Şeremet, Zhiping Li, Catherine Tuleu, Paola Minghetti, Giovanni M. Pauletti

PII: S0939-6411(24)00309-6
DOI: https://doi.org/10.1016/j.ejpb.2024.114483
Reference: EJPB 114483

To appear in: *European Journal of Pharmaceutics and Biopharmaceutics*

Received Date: 17 July 2024
Revised Date: 19 August 2024
Accepted Date: 4 September 2024

Please cite this article as: H.M. Fadda, H. Weiler, M. Carvalho, Y.Z. Lee, H. Dassouki, R. AbuBlan, S. Iurian, A. Hamid, G. Şeremet, Z. Li, C. Tuleu, P. Minghetti, G.M. Pauletti, Pediatric oral extemporaneous preparations and practices: International Pharmaceutical Federation (FIP) global study, *European Journal of Pharmaceutics and Biopharmaceutics* (2024), doi: https://doi.org/10.1016/j.ejpb.2024.114483

Pediatric Oral Extemporaneous Preparations and Practices: International Pharmaceutical Federation (FIP) Global Study

Hala M. Fadda[a,b*], Hannah Weiler[a], Maria Carvalho[c], You Zhuan Lee[d], Hadi Dassouki[e], Rasha AbuBlan[f], Sonia Iurian[g]; Aasma Hamid[h], Gökhan Şeremet[i]; Zhiping Li[j]; Catherine Tuleu[k]; Paola Minghetti,[l,m], Giovanni M. Pauletti[n,b]

[a] Department of Pharmaceutical Sciences, College of Pharmacy & Health Sciences, Butler University, IN, USA

[b] International Pharmaceutical Federation (FIP), The Hague, Netherlands

[c] Professional Compounding Centers of America, TX, USA

[d] Drug Delivery and Manufacturing Liaison for FIP Early Career Pharmaceutical Group, The Hague, Netherlands

[e] School of Pharmacy, Lebanese International University, Bekaa, Lebanon

[f] Department of Pharmacy, King Hussein Cancer Center, Amman, Jordan

[g] Department of Pharmaceutical Technology and Biopharmacy, Faculty of Pharmacy, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

[h] Department of Pharmacy, DOW University Hospital, DOW University of Health Sciences, Karachi, Pakistan

[i] Metrocity Compounding Pharmacy, Istanbul, Türkiye

[j] Department of Pharmacy, Children's Hospital of Fudan University, National Children's Medical Center, Shanghai 201102, China

[k]University College London School of Pharmacy, UCL, London, United Kingdom

[l] Department of Pharmaceutical Sciences, Università degli Studi di Milano, Milan, Italy

[m] Società Italiana Farmacisti Preparatori (SIFAP), Italy

[n] St. Louis College of Pharmacy, University of Health Sciences and Pharmacy in St. Louis, MO, USA

*Corresponding author
Hala Fadda
Department of Pharmaceutical Sciences
College of Pharmacy and Health Sciences, Butler University
4600 Sunset Ave, Indianapolis, IN 46208
E-mail: hfadda@butler.edu
Tel. +1-317-940-8574

Abstract

This publication is the first to report current, global, pediatric oral extemporaneous compounding practices. Complete survey responses were received from 470 participants actively involved in compounding across all the World Health Organization (WHO) regions. The survey addressed oral formulation of extemporaneous liquids, including the use of commercial or in-house vehicles, flavoring excipients, source of formulation recipes, and beyond use dates (BUDs). Over 90% of the survey participants prepared oral liquids. Solid dosage forms, comprising capsules and powder papers (sachets) were also frequently prepared for children, albeit to a lesser extent. The top 20 active pharmaceutical ingredients compounded for children, globally, were: omeprazole, captopril, spironolactone, propranolol, furosemide, phenobarbital, hydrochlorothiazide, ursodeoxycholic acid, sildenafil, melatonin, clonidine, enalapril, dexamethasone, baclofen, caffeine, chloral hydrate, trimethoprim, atenolol, hydrocortisone, carvedilol and prednisolone. Diuretics, drugs for acid-related disorders, and beta-blockers were the top three most frequently compounded classes per the WHO Anatomical Therapeutic Chemical (ATC) classification system. The principal need identified for the practice of extemporaneous compounding for children was the development of an international, open-access formulary that includes validated formulations, as well as updated compounding literature and guidelines. Furthermore, improved access to data from stability studies to allow compounding of formulations with extended BUDs.

Introduction

The practice of off-label prescribing in children is globally prevalent and can lead to ineffective treatment, non-adherence, and increased risk of adverse drug reactions [1-3]. Regulatory initiatives to improve development of medicines for children have surfaced globally, mandating ethical research and suitable authorization to ensure efficacy and safety. Significant pediatric regulatory initiatives include the United States' (US) Food and Drug Administration (FDA) Best Pharmaceuticals for Children Act (BPCA) of 2002 [4] and Pediatric Research Equity Act (PREA) of 2003 [5], as well as the European Union's Regulation on medicinal products for paediatric use, implemented in 2007 [6]. While these initiatives have made significant strides in increasing the number of new medicines available for children as well as providing new pediatric indications for already approved medicines [7, 8], there continues to be a lack of attention dedicated to furthering the development of older, off-patent medicines commonly used in pediatric populations. In fact, these "older" medicines predominate the World Health Organization (WHO) Model List of Essential Medicines for Children (EMLc), within which only one third of included oral preparations feature age-appropriate formulations for children aged one to five years [9]. The negative consequences of off-label prescribing are further exacerbated by this deficiency in formulation age-appropriateness, defined as meeting the specific needs of pediatric patients via personalized strengths, child-friendly dosage forms, and improved acceptability [10].

In the current paucity of commercially available, age-appropriate medicines labeled for children, pediatric extemporaneous compounding is prevalent. Poor availability of key essential medicines for children has been identified in central African countries [11], and in low resource settings, medicines that are commercially available as age-appropriate formulations in other markets, are frequently compounded [12]. Extemporaneous compounding of oral medications for children is a common practice in hospital and community pharmacies in Europe and North America when authorized age-appropriate formulations are not available or when medicines are used outside of their licensed adult indications [13-15]. Despite the widespread use of pediatric oral extemporaneous preparations, little is known about the practice of extemporaneous compounding for children on a global scale. National and regional studies in the US and Europe have shown that there is considerable variability in current practices and regulations [16, 17].

The International Pharmaceutical Federation (FIP) Pediatric Formulations Focus Group (PFFG) strives to achieve global harmonization of pediatric oral extemporaneous compounding practices and encourage

research into accessible age-appropriate formulations for children. The present study aims to identify current global pediatric oral extemporaneous compounding practices, challenges, and needs.

Methods

The FIP PFFG comprises pharmacists, pharmaceutical scientists, educators, and physicians with experience in pediatric medicines. PFFG members from the different WHO regions — Africa, the Americas, the Eastern Mediterranean, Europe, South-East Asia, and the Western Pacific — contributed to developing the data collection survey (Reference: https://www.who.int/countries/). The anonymous, web-based survey was translated into nine languages in collaboration with compounding experts from the different WHO regions. Survey languages included: Arabic, Chinese, English, French, Italian, Japanese, Portuguese, Spanish, and Turkish. The data was collected using the survey platform, Qualtrics XM (Provo, UT, USA). The introduction to the survey included a consent statement and an explanation of the study objectives and how the findings will be used. The study was exempted from full ethics review by Butler University's Institutional Review Board (IRB).

A pilot survey was developed and disseminated by PFFG members to their contacts in different geographic regions. It was reviewed for clarity and unambiguity and was refined to achieve the final survey. The official survey was launched on November 1st, 2021, and closed on June 1st, 2022. The FIP PFFG global survey was distributed through PFFG members, professional networks, contacts of compounding experts worldwide, and FIP member organizations.

The opening question to the survey was a conditional branching question to identify participants that currently compound pediatric oral extemporaneous preparations. The survey included 16 multiple-choice and open-ended questions distributed into three sections (Supplementary Fig. 1). Questions in Section 1 pertained to dosage forms and active pharmaceutical ingredients (APIs) most frequently compounded. Questions in Section 2 addressed formulation of oral extemporaneous liquids, including the use of commercial or in-house vehicles, flavoring excipients, source of formulation recipes, and beyond use dates. Questions in Section 3 pertained to pharmacy practice and included discipline, country, and geographic region of practice, as well as the challenges and additional needs associated with practice. Participants provided open ended responses to their challenges and needs, and the responses were classified into one of 14 groups. For the question regarding region of practice, participants were invited to select from any of the WHO regions, with the Region of the Americas further subdivided into North and

South America. Survey results were analyzed globally and by WHO region using Qualtrics Survey Software and Microsoft Excel. Only oral dosage forms were considered for data collection and analysis.

Results

Summary of global survey responses

The PFFG global survey received a total of 1,274 responses. Incomplete responses were excluded from the data analysis, which resulted in a total of 736 valid responses (Fig. 1). The survey was designed to collect data from compounding pharmacists and technicians who currently compound pediatric oral extemporaneous preparations. The survey, however, was distributed across many channels and likely reached other pharmacy professionals. As such, the opening question of the PFFG global survey aimed to filter out pharmacists and technicians who were not actively involved in pharmaceutical compounding. A total of 34.9% of the respondents identified that they were not involved in the compounding of pediatric oral extemporaneous preparations. Despite not being active in compounding, these professionals were expected to be related to the practice to a certain extent given their inclusion in the distributing channels of the survey.

All negative responses to the opening questions were directed to a separate question to understand the reasons why these professionals were not actively involved in pharmaceutical compounding (Fig. 1). T A similar response count was received for all the four different reasons listed and a total of 42 “other” responses were also received, including: “We advise on whether crushing tablets is appropriate then tell parents to do this at home”; “Lack of prescriptions”; “Extemporaneous preparations not considered important despite that there is lack of availability of appropriate pediatric medicines.”

The pharmacists and technicians who responded “Yes” to the opening question were actively involved in pediatric oral extemporaneous compounding and thus were considered valid participants in the PFFG global survey. In total, 479 participants from all regions of the world were included in the data analysis. The most represented WHO region in this survey is Europe (47.2%). (Fig. 2). Globally, a similar number of survey participants practice in community or compounding pharmacies (50.3%) and hospital pharmacies (47.6%), while only a small percentage of respondents practice in outsourcing facilities (2.1%). On a regional level, however, differences in pharmacy practice were seen, with Europe and South America participants predominantly practicing in community/compounding pharmacies, and participants from the other WHO regions predominantly practicing in hospital pharmacy (Fig. 3).

Dosage forms and source of active pharmaceutical ingredients (APIs)

Oral dosage forms need to be age-appropriate to promote medication adherence and, consequently, treatment efficacy [3, 18]. The PFFG global survey therefore addresses the type of oral dosage forms extemporaneously prepared. Survey results revealed that oral liquids were the most frequent extemporaneously prepared oral dosage form for children worldwide. Over 90% of the survey participants prepare oral liquids, including solutions, suspensions, and syrups (Fig. 4). Oral solid dosage forms were also frequently prepared for children, albeit to a lesser extent. Capsules and powder papers, also known as sachets, were prepared by 44% and 43% of survey participants, respectively. In contrast, oromucosal preparations were infrequently prepared on a global scale (14%). Additional findings were observed when considering each WHO region separately. In Africa, capsules were not reported by any of the survey participants. In the Eastern Mediterranean, there were no reports of oromucosal preparations. The top three oral dosage forms in Europe, the Eastern Mediterranean, North America, and South America were, in decreasing order: oral liquids, capsules, and powder papers. South-East Asia and the Western Pacific shared the same top three oral dosage forms, but powder papers are more prevalent than capsules.

All extemporaneous preparations comprise one or more APIs and excipients formulated into the corresponding dosage form. When available, APIs may be sourced as bulk powders from compounding suppliers. Alternatively, APIs included in commercial medicines, commonly tablets and capsules, may be used directly in extemporaneous preparations. Commercial tablets are cut and finely crushed, whereas commercial capsules are opened, and the powder content of the capsules is used in the extemporaneous compounding of both solid and liquid oral dosage forms. On a global scale, the different sources of APIs used to compound pediatric oral extemporaneous preparations were comparable (Fig. 5a). On a regional level, however, there were important differences to highlight. Use of bulk API powders appeared to comprise the lowest source of API in Africa, the Eastern Mediterranean, North America, and the Western Pacific (Fig. 5b). Africa features the overall lowest use of bulk API powders, with less than 7% of pharmacists and technicians using bulk APIs as opposed to almost 80% using commercial tablets. This may be explained by the lack of accessible bulk powders in low- and middle-income countries (LMICs); pharmacists must rely almost exclusively on the commercial medicines available, which were most often tablets. In contrast, South America uses predominantly bulk powders in the preparation of their pediatric oral dosage forms. South-East Asia appears to use the three different API sources to a similar extent. Important differences were also highlighted when the compounding settings were compared. Although all settings use both commercial medicines and bulk APIs, it is not surprising that outsourcing facilities use

mainly bulk APIs. Interestingly, however, community and compounding pharmacies use mainly bulks APIs, whereas hospital pharmacies rely more on crushing and opening commercial tablets and capsules (Fig. 5c). The preference for commercial medicines in the hospital setting may be explained by the budgetary constraints and sourcing complexities of hospital systems.

It is important to note that the excipient composition of tablets and capsules varies according to the commercial manufacturer, which may affect the stability of the APIs in extemporaneous preparations. Stability data of extemporaneous preparations formulated from different generics or innovator drug products were not necessarily interchangeable. Furthermore, some tablets and capsules may be challenging to manipulate, particularly those with sustained-release or enteric coatings, which may result in dose inaccuracies.

Most frequently dispensed pediatric oral extemporaneous preparations

Survey participants were presented with an open-ended question regarding their top three pediatric oral extemporaneous preparations (by volume and/or frequency). Figure 6 illustrates the top 20 APIs extemporaneously compounded into oral pediatric preparations, globally, as reported by survey participants. Carvedilol and prednisolone received a similar number of responses and were therefore tied at number 20. Reported APIs were assessed for inclusion on the WHO EMLc. The EMLc includes the most efficacious, safe, and cost-effective medicines to meet the primary health needs of a population for children up to and including 12 years of age. These essential medicines should be available and affordable for children's healthcare in appropriate and standardized quality dosage forms [19]. Of the top 20 APIs, eight were featured on the EMLc: omeprazole, spironolactone, propranolol, furosemide, phenobarbital, dexamethasone, caffeine, and trimethoprim. The APIs were classified according to the WHO Anatomical Therapeutic Chemical (ATC) classification system [20]. The ATC system classifies APIs into five different levels. The first level is comprised of 14 main anatomical/pharmacological groups. The main groups were further subdivided into the second level, which is either a pharmacological or therapeutic group. ATC 2nd level pharmacological or therapeutic subgroups were selected for classification of the most frequently extemporaneously compounded oral pediatric medicines. Analysis was conducted to identify the pharmacologic or therapeutic classes of medicines, per WHO ATC 2nd level classification, most frequently compounded globally (Fig. 7). It was determined that diuretics, drugs for acid-related disorders, and beta-blockers were the top three most frequently compounded classes. Supplementary Table 1 illustrates the WHO ATC 2nd level classification, as well as the common pediatric indications as described by the British

National Formulary (BNF) for Children [21], for each of the APIs most frequently featured in extemporaneously compounded oral pediatric preparations.

Potential reasons why APIs were frequently compounded may include lack of availability of authorized age-appropriate pediatric preparations in different geographic regions, excessive cost of available authorized preparations, shortcomings of authorized formulations regarding safety of excipients (e.g., presence of alcohol, propylene glycol, parabens) or inadequate acceptability (e.g., swallowability, palatability, frequency of administration). Insufficient stability of commercially available aqueous liquid formulations may also contribute to the need for extemporaneous compounding. For example, omeprazole is hygroscopic and rapidly degrades below pH 7.8 while exhibiting maximum stability at pH 11 [22]. One method of extemporaneously preparing omeprazole oral solution is by dissolving omeprazole capsule contents in sodium bicarbonate 8.4% w/w solution [22]. The resulting solution is to be refrigerated and has an extensive beyond use date (BUD) of 45 days, per United States Pharmacopeia (USP) beyond use dating for non-preserved aqueous solutions. Captopril undergoes oxidative degradation in aqueous solutions and is catalyzed by metal ions. Captopril solution displays higher stability at acidic pH and is extemporaneously compounded in water with the addition of ascorbic acid tablets [23]. Atenolol displays highest stability in pH 4 aqueous solutions, and exposure of atenolol solutions to ultraviolet light cause drug decomposition at acidic and neutral pHs. Atenolol suspension is extemporaneously compounded in commercial vehicles at pH 4-4.5 and is stored in amber bottles [24].

Further regional analyses into the top ten most frequently compounded medicines was conducted using responses to the multiple-choice question on APIs most frequently dispensed (by volume and/or frequency). Participants were not limited to the number of APIs they could select from the 68 APIs provided. The results are summarized into the top ten most frequently dispensed APIs for each WHO region in the supplementary section (Fig. S2).

While diuretics were the most frequently compounded globally, specifically spironolactone, furosemide, and hydrochlorothiazide (Fig. 6), a further analysis into the top ten most frequently compounded medicines per region revealed that furosemide and spironolactone were most frequently compounded in Africa, Europe, the Eastern Mediterranean, the Western Pacific, and South America (Fig. S2). Omeprazole is the most frequently compounded medicine for acid-related disorders globally and in all world regions, except Africa. Interestingly, Africa's list of top ten most frequently compounded medicines did not include an API for acid-related disorders. The most frequently compounded beta-blocking agents globally include

propranolol, atenolol, and carvedilol. Propranolol is most compounded in Europe, the Eastern Mediterranean, South-East Asia, and South America, while atenolol is most frequently compounded in Europe, and carvedilol in Africa and Europe. The most frequently compounded drugs acting on the renin-angiotensin system include captopril and enalapril. Captopril is the most frequently compounded in all regions except the Western Pacific. Enalapril is frequently compounded in Africa, Europe, and South America.

Melatonin and chloral hydrate were the most frequently compounded psycholeptics globally; however, melatonin only appears on the top ten compounding list for South America. Clobazam is another psycholeptic that appears on the list of most frequently compounded medicines only in the Western Pacific. The differences between the regional and global results may be attributable to how the survey question was presented. The most frequently compounded medicines globally (Fig. 6) were determined by analysis of responses to the question where respondents entered the top three pediatric oral extemporaneous preparations (by volume and/or frequency). While the regional trends were determined from a different question where participants selected from a list of medicines that were frequently dispensed, the results were subsequently summarized into the top ten extemporaneously compounded medicines for each region (Table S1). Hence while chloral hydrate was observed as one of the most frequently compounded APIs globally, upon regional analysis of the results, it was not one of the top 10 most frequently compounded in any of the world regions as other medicines received a higher count per region.

The systemic corticosteroids most frequently compounded globally were dexamethasone, hydrocortisone, and prednisolone. Dexamethasone and hydrocortisone also appeared on the lists of the top ten most frequently compounded medicines for the Eastern Mediterranean and North American regions, respectively. Phenobarbital is the most frequently compounded antiepileptic globally and in Africa and the Western Pacific. Antiepileptics most frequently compounded in Africa also include levetiracetam, carbamazepine and acetazolamide. Acetazolamide is a carbonic anhydrase inhibitor also indicated for open-angle glaucoma in children. Clonazepam was another antiepileptic determined to be one of the most frequently compounded medicines in North America.

Trimethoprim is the most frequently compounded antibacterial for systemic use globally; however, it does not feature in the top ten most frequently compounded medicines in any region. Vancomycin and metronidazole were antibacterials that were frequently compounded in the Eastern Mediterranean and

North America, respectively. Ursodeoxycholic acid indicated for cholestasis is frequently compounded globally, as well as in Europe, the Eastern Mediterranean, and North America. Sildenafil, indicated for pulmonary arterial hypertension in children, is frequently compounded globally as well as in Africa, Europe, the Eastern Mediterranean, and North America.

Formulation of Pediatric Oral Liquids

Liquid preparations for oral use, mainly solutions and suspensions, contain one or more active substances in a suitable vehicle. Although oral liquids may be rapidly prepared, allow dosing flexibility by variable volumes, and are easy to administer to pediatric patients, their formulation and stability can be complex. Issues with drug solubility, homogeneity, taste masking, and stability must be considered when compounding oral liquid medicines. Several categories of excipients are usually required to ensure homogenous and stable formulations, including solubilizing, or suspending agents, buffers, and preservatives, as well as excipients to enhance palatability, including sweetening and flavoring agents. However, the choice of excipients must also consider the patient's age (e.g., ethanol and propylene glycol cosolvents), which adds even more complexity to the extemporaneous preparation of oral liquid dosage forms.

The PFFG global survey shows that the formulation recipes for pediatric oral liquids were mostly obtained from journals or books. Online databases, pharmacopeias, and national formularies were utilized to similar extents, whereas in-house formularies and personal or team experiences were the least employed (Fig. 8).

Some countries, such as Portugal and Spain, have developed their own national formularies including validated standard operating procedures (SOPs). There are pharmacopeias that also include SOPs for frequently dispensed compounded medications, such as the USP Compounding Compendium and the European Pharmacopeia. These official formularies are a key contributor to the quality and safety of pharmaceutical compounding, since pharmacists are likely to use the same validated SOPs across the country [17]. In-house formularies were commonly seen in hospital pharmacies and often feature SOPs for the most frequently dispensed compounded medications.

Stability is the extent to which a product retains, within specified limits and throughout its period of storage and use, the same properties, and characteristics that it possessed at the time of its manufacture.

It is a global term that refers to the chemical, physical, microbiological, therapeutic, and toxicologic stability of a product [25]. The BUD is the date after which a compounded medication is not to be used because its stability is no longer guaranteed (United States Pharmacopeial Convention). When oral liquids are prepared, pharmacists should have evidence to support the assigned BUD. In the absence of a validated stability study, official pharmacopeial criteria should apply to determine the BUD of a given compounded medication. The PFFG global survey shows that pharmacopeia guidelines and compounding books comprise the majority of reference sources utilized to assign the BUD of pediatric oral liquids, at 68% response rate each. Online databases and scientific journals comprised 48% and 43% of responses, respectively. Validated stability studies, published in scientific journals and referenced in online databases, are the ideal reference sources; however, the extemporaneously compounded preparations must comprise the exact formulation for the stability data to be valid. For instance, if the pediatric oral liquid includes a different vehicle or a different preservative, the validated stability study no longer applies. In this case, compounding pharmacists are recommended to follow the pharmacopeia guidelines to assign the estimated BUD. Since oral vehicles vary considerably in composition, it is to be expected that pharmacopeia guidelines are commonly used to assign BUDs to pediatric oral liquids.

Acceptability of medicines in children is multi-faceted determined by context of use, patient characteristics, and product characteristics [26]. APIs commonly have an unpleasant taste which can compromise medicine acceptability, leading to children's rejection of the full dose or risk of emesis; therefore resulting in inconsistent and variable dosing [27].Taste masking of unpleasant APIs administered as oral liquids is an approach to increase patient adherence. The PFFG global survey illustrates that although the practice of flavoring occurs in every region of the world, 56% of the surveyed compounding pharmacists and technicians do not add flavors to pediatric oral liquids. The Eastern Mediterranean and South America were exceptions, however, where flavoring appears to be a common practice (Fig. 9). In South America, most pharmacists, and technicians (77%) add flavors to pediatric oral liquids. Brazil, the largest country in South America, has a long tradition of pharmaceutical compounding and specialized compounding pharmacies are widespread, which may explain why medicine acceptability is prioritized.

In North America, most pharmacists (69%) do not add flavors to the pediatric oral liquids, despite the accessibility of flavoring agents and flavoring information. However, commercial oral vehicles, the majority of which contain flavoring and sweetening agents, were popular in North America, which may explain the minimal use of flavors in this region. As for Europe, most pharmacists were found not to add

flavors (57%), however prior evidence suggests a heterogeneity in compounding practices across European countries [17].

Interestingly, the PFFG global survey shows varying practices when hospital pharmacies and community pharmacies were compared. As 68% of hospital pharmacies, versus only 45% of community or compounding pharmacies do not practice flavoring. This may be attributed to hospitals providing around-the-clock patient care, and hospitalized patients may require lifesaving compounded medications at any time of the day or night. The practice of flavoring, although a key contributor to patient adherence, may not be considered critical to the quality and safety of the compounded medications in emergency situations. In addition, hospitals in some regions commonly operate under tight budgetary constraints and therefore only essential products and ingredients are likely to be sourced.

Pediatric oral liquids were commonly prepared by adding the API(s) to a suitable vehicle, which may be locally prepared at the pharmacy or commercially manufactured by a compounding supplier. Commercial vehicles allow for straightforward and rapid preparation of oral liquids with assured quality and appropriate organoleptic characteristics for oral administration. Validated stability studies were available for a wide range of APIs in commercial vehicles, which assure an extended BUDs for the corresponding liquid preparations.

The PFFG global survey shows that 63% of pharmacists use commercial vehicles, and they were utilized in all regions of the world, predominantly in North America (Fig. 10). The most frequently used commercial vehicles were SyrSpend (Fagron), Ora-Plus, Ora-Sweet, and Ora-Blend (Paddock/Perrigo), which were manufactured by compounding suppliers that operate in North America. As a result, it is expected that commercial vehicles were highly popular in this region, with 97% of pharmacy professionals utilizing commercial vehicles. In contrast, in the regions of Africa and South America, almost 50% of the pharmacies do not commonly use commercial vehicles in the preparation of their pediatric oral liquids. In Africa, the main reasons were likely to be the limited availability of commercial vehicles and, when available, their unaffordable cost. In South America, pharmacies were likely to use locally prepared vehicles to allow for more affordable medicines. In Brazil, compounded medications were popular and widespread due to their affordable cost.

Both hospital and community pharmacies use commercial vehicles in the preparation of their pediatric oral liquids. There is a higher prevalence in the hospital setting (68%) when compared to the community setting (59%), which may be explained by the need to quickly prepare and dispense oral liquids to

hospitalized pediatric patients. Furthermore, hospitals may have specialist pediatric centers and therefore utilize commercial vehicles to accommodate a larger patient population.

Less prevalent commercial vehicles were reported in the "Other(s)" category, with commercially manufactured simple syrup constituting the most frequently described. An example of commercial simple syrup includes *Excipiente Acofar Jarabe Simple,* supplied by Acofarma (Madrid, Spain). Anhydrous commercial oral liquid vehicles, which allow for extended BUDs by default due to the low water activity, were also reported, thus representing a valuable option for compounding APIs that are lipophilic, unstable in water, or feature limited data on aqueous stability. It was additionally stated by the survey participants that there were no commercial vehicles registered in Poland for pharmaceutical compounding and that there were no commercial vehicles available in Pakistan.

Locally prepared vehicles were mostly universal vehicles described in official formularies or pharmacopoeias. Examples include the Simple Syrup BP (British Pharmacopoeia) (85% w/v sucrose) and "B.9. Vehicle for the preparation of oral suspensions, sugar-free" described in the Portuguese Galenic Formulary (CETMED, 2005). Locally prepared vehicles are a valuable option for pharmacies as they overcome the high barrier costs of commercially manufactured vehicles. In-house vehicles are commonly prepared in advance and in large quantities to facilitate the preparation of individualized medications, as needed. In-house developed vehicles are more affordable than the commercially manufactured vehicles; however, they do not commonly feature abundant stability studies and therefore scientific evidence for quality and safety is scarcer. The PFFG global survey shows that in-house developed vehicles were utilized by 51% of pharmacists in all world regions, and their use is particularly prevalent in Africa, South America, and South-East Asia (Fig. 11a). The only regions that do not commonly use in-house vehicles were North America and the Western Pacific, in which most survey participants, 69% and 81%, respectively, reported that they do not use in-house vehicles. When analyzing the data by pharmacy practice, it is observed that hospital pharmacies and outsourcing facilities were less likely to develop their own locally prepared vehicles, as opposed to the community or compounding pharmacies (Fig. 11b).

Out of the response choices provided for in-house developed vehicles, simple syrup constitutes the most frequently used in-house vehicle at 60% of reported global responses. This may be attributable to its straightforward preparation and the readily available, affordable sucrose component. Simple syrup also has low water activity and therefore a preservative is not needed if used at the pharmacopeial concentration of 85% w/v. The use of methylcellulose gel accounted for 13% of the global responses.

Methylcellulose increases viscosity and therefore improved palatability [28, 29] however it is relatively time consuming to prepare. Use of cherry syrup was reported at 3% and other less prevalent in-house developed vehicles were reported in 'other(s)', category included anhydrous vehicle, carboxymethyl cellulose gel and sugar-free vehicle.

Challenges and needs of pediatric oral extemporaneous preparation and practices

Participants were presented with an open-ended question to describe their needs and/or challenges related to pediatric oral extemporaneous compounding. Responses were classified into the groups illustrated in Figure 12. The principal need identified for the practice of extemporaneous compounding for children is the development of an international, open-access formulary that includes validated formulations, as well as updated compounding literature and guidelines. Participants further emphasized that validated formulations should contain information on preparation methodology, stability data, pH, and organoleptic properties. Pharmacists reported that it is difficult for them to find validated formulations and that there is a compelling need for a platform where expertise is exchanged, and questions were addressed. Addressing these needs will help minimize the risks reported with compounding which include use of incorrect ingredients and quantities and the formulation of unstable products [30, 31].

The second most identified need reported by pharmacists is improved access to data from stability studies to allow compounding of formulations with extended BUDs. The need for stability data under conditions of high humidity and temperatures was also noted. Pharmacists reported the need for validated formulations using safe and readily available excipients. It is necessary to develop simple formulations that can be replicated in hospital and community pharmacies. Respondents commented that data on safety and dose limits of excipients is lacking, as well as the impact of the formulation changes on drug pharmacokinetics.

It was noted by respondents that more stringent, in-process and final quality control was required in some regions, as well as national guidelines and government oversight. Government restrictions on establishing compounding facilities, restrictions on batch manufacture, and formulary restrictions were also reported. Unavailability of appropriate compounding labs, instruments, and workforce capacity were other commonly reported challenges. Furthermore, difficulty of sourcing extemporaneously compounded products from outsourcing facilities and long lead time is an obstacle for some medicines.

Additional reported barriers to compounding included time-consuming preparation and accuracy of dose, especially with low dose drugs. Other challenges included the drug dissolution process and formulating homogenous suspensions. Some APIs were only available as coated or modified release dosage forms, making compounding more challenging. Moreover, there is limited information available on the impact of interchanging tablets and capsules formulated with different excipients on physical-chemical properties and stability of compounded formulations.

Further noted obstacles to compounding included limited availability of bulk API powders and excipients as well as access to storage recipients and dosing devices. When bulk API powders are available, they are expensive or can only be purchased from manufacturers in large quantities which cannot be consumed prior to their expiration. It was also reported that commercial vehicles were not available in some world regions, or the cost is too high. Pharmacists highlighted the need for the pharmacopeial formulas for suspending vehicles as well as formulations utilizing simple vehicles that can be prepared in-house. In addition, formulas for vehicles that do not contain sugars were needed. Palatability was also reported to be a concern for oral liquids despite the inclusion of flavoring agents and sweeteners; particularly that the bitter taste of some medicines is difficult to mask.

Pharmacists reported the critical need to remain up to date with modern practices as well as concerns regarding their limited training and expertise in compounding. There were also reports on the lack of physician awareness of the practice of compounding and that prescriptions for extemporaneous medicines were often missing information. Improved communication between physicians and pharmacists was needed for accurate pediatric prescribing.

Survey responses highlighted the need for authorized, age-appropriate formulations that are affordable. While authorized liquid products may exist in some regions, the cost may be prohibitive for government funding in LMICs or for individuals to procure. Responses also noted the high cost of extemporaneously compounded formulations and the need for government subsidies for pediatric patients. High pricing variability between different extemporaneous manufacturers as well as reimbursement from insurance companies was reported to be a challenge.

Study limitations

An unequal distribution of responses from different geographic regions was attained, as illustrated in Figure 1. Furthermore, WHO geographic regions constitute a heterogenous group of countries which may

therefore limit extrapolation of some of the findings to each country within the different regions. Moreover, individuals may not identify as belonging to a region as defined by the WHO; for example, Republic of Türkiye is classified by the WHO as European while many respondents identified as belonging to the Eastern Mediterranean. Survey participants were allowed to enter their country and select their region in response to open and multiple-choice questions, respectively. To analyze the survey results consistently per WHO region, the regions reported by the survey participants were adjusted, when necessary, to align with the WHO regions.

Conclusions

The FIP PFFG global survey illustrates that the most frequently extemporaneously compounded oral pediatric medicines globally, as classified per WHO ATC pharmacological/therapeutic group, were diuretics, drugs for acid related disorders and beta-blockers. Oral liquids far exceeded capsules and powder papers (sachets) as dosage forms of choice for extemporaneous pediatric compounding. Inter-regional and inter-practice variability were observed with respect to source of APIs, source of formulation recipes, use of in-house and commercial vehicles, flavoring oral liquids, and assigning of BUDs. While there is heterogeneity in pediatric extemporaneous preparations and practices worldwide, the survey revealed there is a common global need for freely accessible formulation sources constituting safe, and simple formulations with validated stability and shelf-life.

CRediT authorship contribution statement:

Hala Fadda: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Writing -original draft, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition. **Hannah Weiler**: Formal Analysis, Writing –reviewing and editing, Visualization. **Maria Carvalho**: Methodology, Validation, Formal analysis, Investigation, Writing-original draft. **You Zhuan Lee**: Methodology, Formal analysis, Visualization, Writing-review and editing. **Hadi Dassouki**: Methodology, Investigation, Writing – review and editing. **Rasha AbuBlan**: Methodology, Investigation, Writing – review and editing. **Sonia Iurian**: Methodology, Investigation, Writing – review and editing. **Aasma Hamid**: Methodology, Writing – review and editing. **Gökhan Şeremet**: Methodology, Investigation, Writing – review and editing. **Zhiping Li**: Methodology, Investigation, Writing – review and editing. **Catherine Tuleu:** Methodology, Investigation, Writing – review and editing. **Paola Minghetti**: Methodology, Investigation, Writing – review and editing. **Giovanni M. Pauletti**: Conceptualization, methodology, Writing – review and editing.

Funding:

Butler University, College of Pharmacy and Health Sciences.

Declaration of competing interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A: Supplementary material

Supplementary material to this article can be found online at:

Acknowledgements

Organizations: American College of Apothecaries (United States); Associação Nacional dos Farmacêuticos Magistrais (ANFARMAG) (Brasil); Associação Portuguesa de Farmacêuticos Hospitalares (APFH) (Portugal); Association of Finnish Pharmacies (Finland); Australian Society of Compounding Pharmacists; Canadian Pharmacists Association; Confederación Farmacèutica Argentina (COFA); International Pharmaceutical Students' Federation (IPSF); La Sociedad Española del Medicamento Individualizado (LaSemi) (Spain); Malaysian Pharmacists Society (MPS) (Malaysia); Neonatal and Pediatric Pharmacists Group (NPPG) (United Kingdom); Pharmaceutical Society of New Zealand (PSNZ); and Società Italiana Farmacisti Preparatori (Italy).

Individuals: We would like to thank Dalia Bajis, Chistopher John and Lars-Åke Söderlund at FIP for their valuable advice on developing the study and disseminating the survey. We also appreciate Paula Cohen at FIP for administrative support.

We would also like to acknowledege the following individuals for sharing their insights on the practice of extemporaneous compounding and disseminating the survey in their respective countries. Carlos Bregni (Argentina); Lee Yong Lim (Australia); Eliete Perino (Brasil); Amanda Blazevic (Canada); Ilias Katsogiannis, (Greece); Thibault Vallet (France), Yasunori Miyazaki (Japan); Olgajordan Kiseļova (Latvia)); Sveinbjörn Gizurarson (Malawi and Iceland); Sara Hanning (New Zealand); Ebiowei Orubu (Nigeria); Malgorzata Sznitowska (Poland); Andrea Gill (United Kingdom); Lisa Ashworth and Linda F. McElhiney (United States); Machi Hampango (Zambia); and Dothan Moyo (Zimbabwe).

References

1. Petkova V, Georgieva D, Dimitrov M, Nikolova I. Off-Label Prescribing in Pediatric Population-Literature Review for 2012-2022. Pharmaceutics. 2023;15(12). doi: 10.3390/pharmaceutics15122652
2. Hwang TJ, Orenstein L, Kesselheim AS, Bourgeois FT. Completion Rate and Reporting of Mandatory Pediatric Postmarketing Studies Under the US Pediatric Research Equity Act. JAMA Pediatr. 2019;173(1):68-74. doi: 10.1001/jamapediatrics.2018.3416
3. Ivanovska V, Rademaker CM, van Dijk L, Mantel-Teeuwisse AK. Pediatric drug formulations: a review of challenges and progress. Pediatrics. 2014;134(2):361-72. doi: 10.1542/peds.2013-3225
4. Best Pharmaceuticals for Children Act, Pub. L. No. 107-109. Published 2002. Accessed March 15, 2024, https://www.congress.gov/bill/107th-congress/senate-bill/1789/text.
5. Pediatric Research Equity Act, Pub. L. No. 108-155. Publishes 2003. Accessed March 12, 2024, https://www.congress.gov/bill/107th-congress/senate-bill/1789/text.
6. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use. Published 2006. Accessed March 14, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R1901.
7. Commission to the European Parliament and Council. State of Paediatric Medicines in the EU: 10 years of the EU Pediatric Regulation. 2017, COM (2017) 626. Accessed March 14, 2024. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R1901
8. Food and Drug Administration. Pediatric Labelling Changes. Published 2024. Accessed 11 April, 2024: https://www.fda.gov/science-research/pediatrics/pediatric-labeling-changes.
9. Orubu ESF, Duncan J, Tuleu C, Turner MA, Nunn A. WHO essential medicines for children 2011-2019: age-appropriateness of enteral formulations. Arch Dis Child. 2022;107(4):317-22. doi: 10.1136/archdischild-2021-321831
10. Walsh J, Masini T, Huttner BD, Moja L, Penazzato M, Cappello B. Assessing the Appropriateness of Formulations on the WHO Model List of Essential Medicines for Children: Development of a Paediatric Quality Target Product Profile Tool. Pharmaceutics. 2022;14(3). doi: 10.3390/pharmaceutics14030473
11. Robertson J, Forte G, Trapsida J, Hill S. What essential medicines for children are on the shelf? Bull World Health Organ. 2009;87:231-7. doi:
12. Nunn A, Aindow A, Woods D. International initiatives on extemporaneous dispensing. Int J Pharm. 2012;435(2):135-7. doi: 10.1016/j.ijpharm.2012.05.055
13. Selmin F, Musazzi UM, Cilurzo F, Minghetti P. Alternatives When an Authorized Medicinal Product is Not Available. Medicine Access @ Point of Care. 2017;1:maapoc.0000005. doi: 10.5301/maapoc.0000005
14. Treadway AK, Craddock D, Leff R. Practices of pharmacies that compound extemporaneous formulations. Am J Health Syst Pharm. 2007;64(13):1403-9. doi: 10.2146/ajhp060251
15. van der Vossen A, Buljac S, Akcay K, Brugma JD, Vulto A, Hanff L. Availability of age-appropriate paediatric formulations in the Netherlands: the need in daily clinical practice remains. Eur J Hosp Pharm. 2021;28(6):306-12. doi: 10.1136/ejhpharm-2019-001977

16. Rood JM, Engels MJ, Ciarkowski SL, Wagenknecht LD, Dickinson CJ, Stevenson JG. Variability in compounding of oral liquids for pediatric patients: a patient safety concern. J Am Pharm Assoc (2003). 2014;54(4):383-9. doi: 10.1331/JAPhA.2014.13074
17. Reis De Carvalho MJ. Extemporaneously Compounded Oral Medicines in European Hospital Pharmacies: University College London; 2013.
18. Agency EM. Guideline on Pharmaceutical Development of Medicines for Paediatric Use. EMA/CHMP/QWP/805880/2012 Rev 2; EMA [Internet]. 2012.
19. World Health Organization. WHO Model List of Essential Medicines for Children - 9th List. 2023. Accessed February 12, 2024. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.03.
20. World Health Organization. Anatomic Therapeutic Chemical (ATC) and Defined Daily Dose (DDD) Toolkit. Accessed February 12, 2024: https://www.who.int/tools/atc-ddd-toolkit.
21. BNF for Children (BNFC) 2023-2024: BMJ Group and Pharmaceutical Press; 2023.
22. Omeprazole. Clinical Pharmacology database, Elsevier Inc. 2024. Accessed April 20, 2024.
23. Captopril. Clinical Pharmacology database, Elsevier Inc. 2024. Accessed. April 20, 2024.
24. Atenolol. Clinical Pharmacology databse, Elsevier, Inc. 2024. Accessed. 20, 2024.
25. Allen LV. The Art, Science and Technology of Pharmaceutical Compounding. . 6th ed. Washington DC: American Pharmacists Association; 2020.
26. Vallet T, Bensouda Y, Saito J, Mathiesen L, Pokharkar V, Klingmann V, et al. Exploring Acceptability Drivers of Oral Antibiotics in Children: Findings from an International Observational Study. Pharmaceutics. 2021;13(10). doi: 10.3390/pharmaceutics13101721
27. Karavasili C, Gkaragkounis A, Fatouros DG. Patent landscape of pediatric-friendly oral dosage forms and administration devices. Expert Opin Ther Pat. 2021;31(7):663-86. doi: 10.1080/13543776.2021.1893691
28. Colbert SE, Triplett CS, Maier JX. The role of viscosity in flavor preference: plasticity and interactions with taste. Chem Senses. 2022;47. doi: 10.1093/chemse/bjac018
29. Schluterman HM, Linardos CG, Drulia T, Marshall JD, Kearns GL. Evaluating palatability in young children: a mini-review of relevant physiology and assessment techniques. Front Pediatr. 2024;12:1350662. doi: 10.3389/fped.2024.1350662
30. Minghetti P, Pantano D, Gennari CG, Casiraghi A. Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe. Health Policy. 2014;117(3):328-33. doi: 10.1016/j.healthpol.2014.07.010
31. Gudeman J, Jozwiakowski M, Chollet J, Randell M. Potential risks of pharmacy compounding. Drugs R D. 2013;13(1):1-8. doi: 10.1007/s40268-013-0005-9

Figure Legends

Figure 1. PRISMA flow diagram indicating inclusion and exclusion criteria for the survey.

Figure 2. Responses from WHO regions, as percentage of survey participants.

Figure 3. Pharmacy practice setting, as a percentage of survey participants per WHO region.

Figure 4. Oral dosage forms prepared for children globally, as percentage of survey responses.

Figure 5 Source of APIs used in pediatric oral extemporaneous preparations, as percentage of survey responses. All sources indicates that participants use all sources of APIs (powders, tablets, and capsules when compounding).

Figure 5a. Source of APIs used in pediatric oral extemporaneous preparations, as percentage of global survey responses.

Figure 5b. Source of APIs used in pediatric oral extemporaneous preparations, as percentage of survey responses by WHO Region.

Figure5c. Source of APIs used in pediatric oral extemporaneous preparations, as percentage of survey responses by compounding practice setting.

Figure 6. Top 20 APIs most compounded globally as pediatric oral extemporaneous preparations, as percentage of frequently compounded medicines.

Figure 7. WHO Anatomic Therapeutic Classification (ATC, 2nd level) of the top 20 APIs most compounded globally, as percentage of frequently compounded medicines.

* While sildenafil falls under the urological ATC class, it is indicated for pulmonary and arterial hypertension in children.

Figure 8. Source of formulation recipes used for pediatric oral extemporaneous preparations, as percentage of survey responses.

Figure 9. Practice of flavoring oral liquids, as percentage of survey responses by WHO region.

Figure 10. Use of commercial vehicles, as percentage of survey responses by WHO region.

Figure 11. Use of vehicles developed in-house, as percentage of survey responses.

Figure 11a. Use of vehicles developed in-house, as percentage of survey responses by WHO region.

Figure 11b. Use of vehicles developed in-house, as percentage of survey responses by compounding practice setting.

Figure 12. Needs and/or challenges related to pediatric oral extemporaneous compounding, as percentage of survey responses.