Accepted Manuscript

Submission Date: 2024-02-13
Accepted Date: 2024-03-25
Accepted Manuscript online: 2024-03-25

Planta Medica

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DOI: 10.1055/a-2294-5259

Please cite this article as: Hensel A, Bauer R, Heinrich M et al. Rationalizing optimal dosing of phytotherapeutics for use in children: Current status - potential solutions - actions needed. Planta Medica 2024. doi: 10.1055/a-2294-5259

Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
"Children are not small adults with respect to the treatment with medicinal products". This statement of WHO was the basis for the initiative of the European Commission for establishment of a paediatric regulation in 2007 to improve health of children by facilitating the development of medicines for children and adolescents. Seventeen years later, in the field of herbal medicinal products results are still sobering. Therefore, the Foundation Plants for Health, Society for Medicinal Plants and Natural Products Research, and German Society for Phytotherapy organized a symposium to assess the status quo for paediatric use of herbal medicinal products (HMPs), to analyse the causes for the current situation, and discuss strategies for establishing the proof of safe and efficacious HMPs for children.
Current situation for HMPs and their use in children is not fulfilling requirements of legislation. HMPs in paediatrics are effective and safe, but considering needs of children is necessary. In European countries the use, registration, and marketing of HMPs are different, depending on respective national regulations and specific traditions. EU herbal monographs are the best common denominator for such procedures. Emerging safety discussions must be considered. New approaches by real world data might be a solution. The regulatory framework is to be adapted. Defining rationalized dosing for HMPs can be achieved by extrapolation of data from adults, by using existing clinical data for children, and by using RWD. Therefore a strong need for revising restrictions for use of HMPs in children and rationalizing defined dosage regimes is obvious.

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Rationalizing optimal dosing of phytotherapeutics for use in children: Current status - potential solutions - actions needed

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Keywords: children, dosage, extrapolation, herbal medicinal products, phytotherapeutics, real world data

Abbreviations: ADME: absorption-distribution-metabolism-excretion; EC: European Commission, EMA: European Medicines Agency, EU: European Union; FDA Food and Drug Administration U.S., HMP: Herbal Medicinal Products; HMPC: Herbal Medicinal Products Committee of EMA, ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; MA: Marketing Authorisation; PbPk: whole-body physiologically-based pharmacokinetic models; PD: pharmacodynamics; PDCO: Paediatric Committee; PK: pharmacokinetics; RWD: real world data; RWE: real world evidence; THR: Traditional Herbal Registration.

Abstract

"Children are not small adults with respect to the treatment with medicinal products". This statement of *WHO* was the basis for the initiative of the European Commission for establishment of a paediatric regulation in 2007 to improve health of children by facilitating the development of medicines for children and adolescents. Seventeen years later, in the field of herbal medicinal products results are still sobering. Therefore, the *Foundation Plants for Health*, *Society for Medicinal Plants and Natural Products Research*, and German *Society for Phytotherapy* organized a symposium to assess the *status quo* for paediatric use of herbal medicinal products (HMPs), to analyse the causes for the current situation, and discuss strategies for establishing the proof of safe and efficacious HMPs for children.

The current situation for HMPs and their use in children is not fulfilling requirements of legislation. HMPs in paediatrics are effective and safe, but considering needs of children is necessary. In European countries the use, registration, and marketing of HMPs are different, depending on respective national regulations and specific traditions. EU herbal monographs are the best common denominator for such procedures. Emerging safety discussions must be considered. New approaches by real world data might be a solution. The regulatory framework is to be adapted. Defining rationalized dosing for HMPs can be achieved by extrapolation of data from adults, by using existing clinical data for children, and by using RWD. Therefore a strong need for revising restrictions for use of HMPs in children and rationalizing defined dosage regimes is obvious.

Introduction

The statement made by the WHO “Children are not small adults with respect to the treatment with medicinal products” [1] has been the basis for the initiative of the European Commission (EC) to establish the Paediatric Committee (PDCO) as a scientific board of the European Medicines Agency (EMA). On 26 January 2007, the paediatric regulation came into force in the EU (European Parliament - Council on Medicinal Products for Paediatric Use 2006). Since then, its objective has been to improve the health of children in Europe by facilitating the development and availability of medicines for children and adolescents aged 0 to 17 years. However, fifteen years later we must realize that the results in the field of herbal medicinal products HMPs are sobering.

The limitation of conducting clinical trials in paediatric patients is, mainly based on ethical, but also on practical considerations. This results in limited scientific evidence on safety and efficacy for the use of HMPs in children, while there is widespread daily use in clinical practice [2–5]. In spite of this limitation, in recent years systematic reviews were performed on the use of HMPs by children with obesity [6], respiratory tract infection [7], gastrointestinal disorders [8, 9] and attention deficit hyperactivity disorder (ADHD) [10]. General aspects of use of HMPs in children have been reviewed by [11].

On May 17th, 2022, the Foundation *Plants for Health* (PfH), the Society for Medicinal Plants and Natural Products Research (GA), and the German Society for Phytotherapy (GPT) organized an eSymposium with the following aims: (1) to present the *status quo* in various countries, (2) to analyse the reasons for the present situation, and (3) to discuss alternatives to provide evidence for the safe and effective use of HMPs in children. The eSymposium was intended to be the starting point for elaborating suitable actions for establishing rationalized recommendations and dosage regimens for HMPs in paediatrics.

This paper describes the outcome of the symposium, specifically the academic points of view, the clinical and especially the paediatric viewpoints, the regulatory perspectives, and the different regulations for HMPs for children and adolescents in several European countries. Suggestions for future initiatives rationalizing the use and distinct dosage regimens for children by extrapolation of data or by generation and interpretation of RWD are discussed.

Results and Discussion

The academic point of view

In the European Union, at least 50 % of all drug preparations used in children have only been studied in adults, and not necessarily for the same indication [12] [12, 13]. To address this problem, the European Commission (EC) implemented the regulation (EC) No 1901/2006 [14]. Currently its revision is under public consultation. One objective is to avoid unnecessary clinical trials in children, especially by extrapolation of data from clinical phase III studies with adults. The various problems raised by this approach but also possible solutions are considered. A reflection paper from 2011 addresses the lack of clinical studies with HMPs in the paediatric population , focusing on phase IV studies and the distinct characteristics of HMPs [15]. It seems worthwhile to consider the proposals from the revision of (EC) No 1901/2006 with focus on paediatric clinical studies with HMP to improve the current situation [16].

For a future evaluation of the past and current situation of rationalizing the use and dosage regimens for evidence-based HMPs, the following aspects should be considered in detail;

- Since ancient times herbal remedies have been applied for a wide range of diseases and for patients of all ages. Even today, the popularity of HMPs is steadily increasing in developed countries [17], especially for minor self-limiting diseases and often in the form of self-care based OTC products [18].If regulated and thus of good quality, HMPs are generally considered safe and thus are viewed as a smart alternative to conventional drugs. In developing countries, most people still rely on HMPs for primary health care due to missing or too costly alternatives [19].
- With the application of HMPs in children and adolescents (from 2 to 17 years) the topic of rationalizing paediatric dosages touches a delicate aspect of pharmaceutical intervention [20]. As HMPs are frequently used and easily obtainable, many of these products have not undergone clinical studies addressing efficacy and safety [21]. As for the respective clinical use in children, the situation is even worse, since we are facing a lack of high-quality clinical trials and systematic reviews on efficacy of HMPs in paediatrics [22] .
- In European countries, there is a long-term experience of HMPs, both well-established and traditionally used HMPs, including their use in paediatrics. HMPs in paediatric and adolescent population are very popular (e.g. 85 % of the German population is using HMPs [23].

- Regarding risks associated with the use of herbal preparations in children, a systematic review identified 128 case reports of possible adverse events worldwide associated with the use of herbal materials (not HMPs but not well-characterized herbal products from Chinese or Arjuveda medicine, food supplements, etc.), overarching all local traditions and product categories worldwide [24]. From this study, the following facts can be deduced: of the 128 cases, 23 % occurred in children between the age of 9 to18 years, 38 % between the age of 2 and 8 years and 37 % in children below 2 years of age. The reported adverse events included neurological (35% - seizures, central nervous system depression and lethargy), cardiovascular (10% hypertension and metabolic concerns) and gastrointestinal (14% - nausea, vomiting and diarrhoea) disorders as well as hepatotoxicity and jaundice (11%). 36 % of the cases resulted from an unintentional ingestion. Most case reports and herbs have been poorly documented [24].

  A recently published book chapter on the "Safety of Herbal Medicine" summarizes the two main dilemmas in this research area, overarching all categories of medicinal products containing herbs worldwide [25]: The data published here do not differentiate between herbal products of the different categories, different quality status and the different regulatory frameworks. There is only scarce information available on the benefits and risks of herbals' in pediatric patients [26, 27]. This lack of data creates a serious problem in the treatment of children [28].

Taking the situation in countries worldwide into account, there is in many cases a low-barrier to full access and availability of herbal products including dietary supplements outside of pharmacies, e.g. in food stores, supermarkets, and the internet, resulting in an uncontrolled and serious risk to users in terms of herbal drug safety [29].

Practical solutions for safe and effective treatments for children and adolescents with HMPs based on high-quality data must be developed. Despite of the current limited research activity in this field, this problem should be addressed by the various stakeholders. It seems reasonable to use the long-standing experience of experts, especially paediatricians, and to collect and evaluate available real-world data for HMPs. The focus must be on registered and licensed medical products. Undefined herbal products should not be covered, also as they are not underlying the EU drug law. Obviously, there is a need for financing advanced phytotherapeutic research to allow better healthcare of population groups (such as children and adolescents) still underrepresented in research, and to collect more data on the efficacy and/or safety of HMPs in these groups.

The paediatricians´ point of view

Within daily clinical practice, phytotherapy is an essential part of medical treatment of paediatric patients [11]. Clinicians use HMPs worldwide, due to long-standing empirically based tradition, documented safety, and good efficiency. This use of phytotherapy is mainly based on decades up to thousands of years of experience, partly on non-scientific sources and especially in the European phytotherapy, partly on scientific studies. We recognise, that HMPs are used only in some European countries as a part of paediatric medicine and focus on these countries, e.g. the German language countries (Germany, Austria, Switzerland, the so called DACH countries [21].

Comparable to other areas of paediatric medicine, phytotherapy is often performed outside the official marketing authorization ("off-label use"), which is due to a lack of provenand save alternatives. Possible risks are thereby shifted to the physician applying the drug and, in the case of inadequate information or self-medication, to the patient or his/her parents.

The question therefore arises how the findings obtained in clinical studies with HMPs on predominantly adult patients can be transferred to children and adolescents.

With linear reduction in size, surface areas (e.g., of skin, of absorptive surfaces in the gastrointestinal tract and lungs, and of secretory/filtering surfaces in the renal glomeruli) decrease with the second power and volume/weight (e.g., of detoxifying liver tissue) with the third power, whereas flow resistance (e.g., in blood vessels and airways) increases with the fourth power (Law of Hagen-Poiseuille). In addition, body proportions shift dramatically with development. While in the two-month-old infant, the head accounts for 50 % of total length, it is less than 10 % in the adult. The organs of children are immature. Biochemically, different enzymes develop differently with age. E.g. alcohol dehydrogenase does not reach normal activity until the end of the first year of life. Within the cytochrome P system, only CYP3A has an appreciable activity at birth, while CYP2D6 activity develops around birth and CYP1A2 activity around the 3rd month of life. Similar developments are observed for the enzymes relevant for glucuronidation and for the *N*-acetyltransferase, whereas sulfation is already functioning by the 8th week of gestation [30]. Absorption in the gastrointestinal tract is altered in premature infants, neonates, and infants under 3 years of age due to decreased gastric acid and bile acid production, decreased intestinal motility, and differences in the intestinal flora. Rectal absorption is unreliably reduced. The proportions of distribution spaces vary with age(extracellular: premature infants 50 %, newborns 45%, > 1year 25 %, adults 20-25 %; intracellular: premature infants 80 %, newborns 50 %, adults 30 %). The extracellular

fluid decreases from 33-42%, within the first 3 months to 20%, at 1 year of age. The intracellular fluid increases from 35% to 47% during childhood. Also body fluid composition changes with age: Fat content: Premature infants 3 %, newborns 12 %, >1 year 30 %, ♂ 20 % , ♀ 30 %. Total body water: 6-8 weeks of pregnancy 91 %, at 32 weeks of pregnancy 80 %, at birth 69 % - newborns lose up to 10 % weight within the first days of life. In young children the binding capacity of plasma proteins is reduced and the plasma clearance time of many substances is prolonged. From 5 months to 10 years of age, renal clearance of many substances is enhanced. Children also have a comparatively low muscle mass [31].

The pathogenesis of many relevant diseases differs in childhood and adolescence compared to adult age. During childhood and adolescence, growth and development with disturbances of the same as well as acute inflammatory processes are in the foreground, while in adulthood silent inflammation processes are resulting in degeneration, atrophy, and sclerosis.

On the German market, herbal products with (presumed) medical benefits are subject to various conditions of approval (medical devices, food supplements, traditional phytotherapy, well-established phytotherapy), whereby the boundaries are overlapping.

Several types of regulatory herbal monographs have been published. About 380 herbal drugs have been scientifically reviewed by the Commission E of the German regulatory authorities[i], 252 of them with “positive monographs”, i.e. with recommended medical use. Additionally, already 107 monographs from the European Scientific Cooperative on Phytotherapy (ESCOP) have been published, 118 + 13 monographs from WHO can be found, 252 monographs from HMPC have been published (219 traditional use, 33 well-established use), with 102 respectively 24 monographs with positive evaluation. Approvals for use in children are as follows: for traditional use: 1 × > 4 weeks, 3 × >1 year, 4 × > 3 years, 6 × > 4 years, 3 × > 6 years, for well-established use: 1 × > 2 years, 2 × > 6 years, 1 × > 8 years.

Also, for many chemically defined drugs, clinical studies of the highest two levels of evidence are lacking for paediatric use ("scientifically unproven“ as stated in the respective monographs of the drugs). That results in frequent off-label-use in pediatrics: 80 %, toddlers: 60 %, infants until adolescents 34 %, stationary use: 25 – 90 %, outpatient use: 13.2 %, depending on the disease and age [32]. Most HMPs are in a comparable situation, but they are usually used since decades, typically within the pharmacovigilance system for drugs. Therefore their safety can be regarded as largely assured. And it has to be kept in mind that the pharmacovigilance system provides the base that potential side effects of HMPs are exactly visible and controllable by the regulatory authorities.

Dosage in children must consider the distribution compartments (premature infants and newborns have different compartments than adults, water soluble active compounds will distribute preferentially into the extracellular space, which again has influence on the optimal dosage per kg body weight to be used), the increased plasma half-life due to large extracellular space (this leads to increased dosing intervals), the different metabolism (reduced dosing for premature infants and newborns) and adjustment of dose for hepatically eliminated drugs.

At present, three modes of dosage calculations for children are used:

1. Body weight (infants, young children)

$$\frac{\text{Dose Adult} \times 1.5 \times \text{kg}}{60\ \text{kg}}$$

2. Body surface area (older children)

$$\frac{\text{Dose Adult} \times \text{Surface Child}}{1.73\ \text{m}^2}$$

3. Age (Note for Guidance on Clinical Investigation, of Medicinal Products in Children).

- Infant, toddler 1/3 of the adult dose
- School child 1/2 of adult dose
- Children 10 to12 years 2/3 adult dose
- Adolescent: Adult Dose

These dose calculation methods are mainly based on clinical experience in therapeutic areas such as anaesthesiology and oncology. More rational approaches such as allometric scaling are used in clinical research, but not in clinical practice [33].

In general, for drugs with wide therapeutic range, the respective dosage is calculated by age group (infant/toddler 1/3, school child 1/2, adolescent = adult), for substances with a narrow therapeutic range it is determined according to body weight or body surface.

For about 30 HMPs, paediatric approvals for different ages (e.g., 6 months, 2 years, 4 years, etc.) based on observational studies have been published [34]. Commission E, ESCOP, and WHO monographs specify doses for children only for very few HMPs. Approximately 110 monographed herbal drugs were considered for paediatrics, for 92 drugs theoretical paediatric dosage calculations are published. Observational studies, i.e. RWD, exist for the most important drugs used in common cold and gastrointestinal disorders.

According to the EU regulation of 26.01.2007, paediatric studies performed in five age groups (!) will be a prerequisite for future approval for use in paediatric patients [35]. The "Drugs for Use in Children" have to be marked with a children's symbol starting at the latest from January 2007, but unfortunately, the paediatric committee of EMA decided in 2008, that this is not practicable. On 2.11.2017, the EU paediatric regulation was 10 years in force. Approved paediatric investigation plans exceeded more than 1000. As of 2017, 260 new medicines had been approved for the use in children. Clinical trials involving children accounted in 2007 for 8.3 %, in 2016 for 12.4 % of all studies. If there were no observations on the dosage for children available at the time of the subsequent approval, the governmental authority usually approves the registration according to §105 of the German Drug Law, based on the drug guideline from 1996. That means that the restriction - whether justified or not - „Do not use in children under 12 years of age, due to lack of sufficient investigations" has to be added. The same applies to new approvals for HMPs according to § 21 of the German drug law.

Extrapolation of adult doses to children is possible and may be somewhat easier for adolescents and perhaps for school children. However, it is complex and it is mostly non-linear. The decisions of practitioners would be facilitated by general scientifically well-founded rules. Scientifically based assessments can reduce errors.

In Germany, the regulations for reimbursement by the statutory health insurances are subjected to the regulation of governmental regulatory authorities. Reimbursement of HMPs is only possible in cases of use in children up to the age of 12, in developmentally delayed adolescents up to the age of 18, and restricted to products, which are only available in pharmacy stores. A switch of products from pharmacy-only status to other distribution channels results in an immediate loss of the reimbursement status. For example, by the change of admission of valerian extracts changed from "pharmacy-only" to "available not only at pharmacy", valerian lost its reimbursement status even for children under 12 years of age. As a consequence, data from health insurances on its use which could be included into the analysis of RWD are no longer available.

The regulatory point of view

EMA (HMPC)

During the course of an application for marketing authorisation or registration of (traditional) HMPs, various aspects have to be considered. The parents and paediatricians' interest for safe medicines and the applicants' perspectives of an interesting market must be balanced against the required evidence on efficacy and safety. For (full or bibliographic) applications for marketing authorisation, evidence on efficacy must be provided for all age groups applied as a general rule. This can be achieved by reference to controlled clinical trials. For registration applications of traditional HMP, evidence of the safety of the respective herbal preparation in the target population must be provided in the dossier. Reference to non-interventional studies and to general phytotherapeutic literature or even expert reports from paediatricians may be acceptable. However, the acceptance of such data in a registration procedure is always a case-by-case decision, as within the European Union (EU) considerable differences in the experiences with herbal treatments in children are evident. EU herbal monographs can be considered as the best common denominator for such procedures. In any case, emerging safety discussions, such as the potential carcinogenic activity of estragol in fennel, must be considered before filing an application. New approaches as the use of RWD might be a solution in future, however, the regulatory framework needs to be adapted accordingly.

The international situation

The situation in the DACH region (Germany, Austria, Switzerland)

The so-called DACH region compromises Germany, Austria and Switzerland. The respective governmental competent authorities are the Federal Institute for Drugs and Medical Devices (BfArM) for Germany, the Federal Office for Safety in Health Care (AGES) for Austria, and Swiss Medic for Switzerland. All three agencies are hosting a department for the evaluation of HMPs called department for 'Complementary and Alternative Medicines (CAM) and Traditional Medicinal Products' and a department for medicinal products for children. No information is available to which extent interaction takes place between the two departments within the related agencies. All three agencies are providing information regarding specific conditions for HMP to be placed on the corresponding markets by referring to simplified procedures, registration and to marketing authorisation in relation to well-established use conditions. Only Swiss Medic gives a specific dosing recommendation for the development of HMPs for children.

BfArM and AGES are reflecting mainly on the European Cooperation within the HMPC products and the herbal monographs published. According to the publication by HMPC dated April 2018, 14 of 33 herbal monographs based on well-established use provide a recommendation for the use in adolescents, 9 for the use in children. This allows the conclusion that in principle dosing recommendation for children can be based on published data according to well-established use conditions.

Nevertheless, for the development of medicinal products for children, further approaches such as conducting clinical trials, using extrapolation according to the ICH Guideline E11A, and RWD should be considered.

The situation in the United Kingdom (U.K.)

In U.K., HMPs must be granted a Marketing Authorisation (MA) or Traditional Herbal Registration (THR) before they can be marketed. Applications for a MA require data on quality, safety and efficacy. Whilst quality data are required for all applications, THR applications for safety and efficacy are replaced by a bibliographic review of safety data including an expert report and evidence that the product or a corresponding product has been marketed for the proposed indication for use for 30 years, including 15 years in the UK/EU/EEA. Any HMP not matching the requirements of the THR scheme will require a MA and is reviewed in line with all relevant requirements, including Paediatric Investigation Plan (PIPs). In the UK, THR products are available over-the-counter (OTC) e.g. through retail shops such as supermarkets, health food shops, pharmacies, and online platforms. They are sold without the need for advice / supervision by a healthcare professional.

Assessment, review and acceptability of THR applications, indicated for children and adolescents are undertaken on a case by case / product basis. Whilst there are no specific guidelines in the UK for assessing THR products, international and national guidelines are taken into account and various aspects are considered such as:

- Does the evidence of traditional use support the use in the proposed age group?
- Is the herbal substance/herbal preparation acceptable for use in the age group?
- Is the indication minor, self-limiting and acceptable to be used in the respective age group, without the need for advice or supervision by a healthcare professional?

- Is the pharmaceutical form / route of administration acceptable for its use in the intended age group?

- Are any dosage adjustments required for the proposed age group?

- Are there any excipients of concern, e.g., ethanol?

Concerning the respective indications for use, the following aspects have to be considered for THR products: In the UK a limited number of indications have been accepted for children under 12 years of age including teething symptoms in babies from 3 months and cuts and grazes in children from 6 years. The indications accepted for children aged 12 to 18 years are wider and they include coughs, cold and flu symptoms, minor digestive complaints, travel sickness, skin blemishes, hay fever, minor cuts & wounds, minor inflammations of the oral mucosa and relief of itching/irritation in mild athlete's foot. Indications such as stress, depressive mood, anxiety, sleep disorders, migraine prevention and fatigue would not be accepted for children and adolescents less than 18 years of age.

Concerning safety aspects, certain herbal preparations and herbal substances are not recommended for use in children and adolescents due to safety issues and a lack of adequate data to support their safety in this age group, for example, Echinacea, St John's Wort and Senna. Their safety issues were further discussed in case studies.

For marketing, it is ensured that the product information includes clear information on the dosage for each age range if applicable including information on the age group that a product is not recommended.

Following authorisation of a THR, the products are closely monitored for adverse events through the Yellow Card Scheme (www.mhra.gov.uk/yellowcard), which is an important regulatory tool to ensure continued safe use of these products. As with all medicines, if it is clear an adverse event has resulted from the use of a traditional herbal medicine, regulatory action is taken to minimise the risk of the adverse effect.

The situation in Spain

Spanish regulations regarding HMPs are based on Directive 2004/24/EC. The Spanish Medicines and Health Products Agency (AEMPS) has accepted only few HMPs for paediatric

patients. Only 80 HMPs (including 37 traditional HMPs) are accepted for paediatric patients, main indications are digestive and respiratory affections.

Most of the still small number of studies on phytotherapeutic remedies in children in Spain is biased, because data have been extracted from herbal products laboratories databases, thereby not being representative. Therefore, there is a need of more not-biased data to be able to draw robust conclusions.

According to the results and conclusions of such a small number of studies, which should be considered as preliminary and possibly biased, the situation in Spain is as follows: Regarding consumption and prescription of herbal products, 68 % of paediatricians recommend herbal products (personal communication to M.M.) and 21 % of patients hospitalized in a tertiary hospital use them in their daily life [36]. Regular prescribers are, almost in equal proportion, professionals of complementary therapies and physicians [36]. A high percentage of paediatric patients hospitalized in a tertiary hospital use complementary therapies (including phytotherapy) and its use is significantly related to the presence of underlying pathology and less regular attendance to a paediatrician. Twenty percent of outpatient paediatricians prescribe phytotherapy, in 80% of cases, it is combined with chemically defined drugs [37]. Cough and bronchial mucus are the most frequent symptoms for which phytotherapy is applied [37]. The use of herbal teas for infants is widespread, most frequently for minor digestive complaints, constipation, and sleep improvement [38]. Nearly 40 % of paediatricians prescribe dietary supplements in case of mild diseases, 31 % as a first choice whenever possible, and 22 % on parents' request. Only 15 % of paediatricians prescribe a dietary supplement in cases where pharmacological treatment is not effective [37]. Paediatricians from the Autonomous Communities of Galicia, the Valencian Country, Andalusia, and Madrid are the ones who most often recommend phytotherapy. Since most health professionals, except pharmacists, are not trained in phytotherapy, most of them prescribe herbal products according to the recommendations of the sales representatives of phytotherapy companies. Some of the reasons for the use of herbal products are the increased parental demand (increase by 59 %), and the parental perception of improvement with its use, (nearly 70 % of parents) [36]. However, there is no data regarding why herbal products are not more prescribed or used in paediatrics.

Regarding herbal products in paediatrics in Spain, much is still to be done and some questions are still unanswered: who is using and prescribing them? What and how? In which situations?

In which areas? Why are they used or not used? How can the number of approved HMP can be increased?

The Situation in Eurasian Economic Union

The Eurasian Economic Union (EAEU) includes Russia, Belarussia, Kazakhstan, Armenia and Kyrgyzstan. Established on 01. January 2015, these countries passed a common drug law with the intention to harmonize their common pharmaceutical markets. This is a very similar situation compared to the process in the EU 25 years ago. The national marketing authorizations in the EAEU need a re-registration procedure to align to the new legal base and finalization has to be reached until 31. December 2025. The main focus of the harmonization process is laid on the pharmaceutical quality of medicinal products. At a first glance, assessment of efficacy and safety is of less importance. In consequence, pre-existing paediatric use is further supported.

For new marketing applications, each use in the paediatric population requires respective studies, however, a concrete paediatric investigation plan (as known from the EU) is not required.

The paediatrician must document each off-label use of a medicinal product, which has not been approved in children, and parents' consent has to be obtained. Nevertheless, the Union of Paediatricians of Russia is alarmed that there is lack of medicines for use in children. There are no special paediatric medications available for 75 % of paediatric diseases, more than 70 % of medications prescribed to children have not been studied in the paediatric population, 90 % of medications prescribed to newborns have not been tested in this age group. This clearly shows the urgent need of developing proven medicines in children.

It can be expected that the Eurasian Economic Commission will react on the current drawback and counteract by adapting the regulation and increase demands to prove safe and efficacious use in children

Possible solutions

ICH E11A: The use of extrapolation in paediatric drug development

Recently, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use (ICH) has published the ICH E11A guideline for extrapolation of data from a reference population (usually adult) to the target paediatric population in order to establish dosing, safety and efficacy. ICH E11A aims to harmonize

approaches to paediatric extrapolation and to reduce differences between the various global regions. Additionally, ethical aims have to be considered, namely, to reduce the exposure of children to unnecessary clinical trials and to facilitate more timely access to paediatric medicines globally. Paediatric extrapolation is defined in the ICH E11(R1) guideline as "*an approach to providing evidence in support of effective and safe use of drugs in the paediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the paediatric (target) and reference (adult or other paediatric) population*". Paediatric extrapolation extends knowledge from the reference population (e.g. data on efficacy, safety, and/or dosing) to the target population, based on an assessment of the relevant similarities of the respective disease, response to therapy and drug pharmacology between the two populations.

Paediatric studies as part of adult-driven drug development may proceed under the assumption that a certain degree of similarity between the adult and paediatric condition exists. However, whether the course of disease and the expected response to the treatment are "sufficiently similar" between the respective target and reference population is not simply a "yes or no" assessment.

Discrete categories (e.g., full, partial or none) to describe the different approaches to paediatric extrapolation have been abandoned in favour of identifying the clinical trial designs which can address the remaining uncertainties based on an assessment of the existing data. The use of extrapolation reflects that (1) a continuum of dissimilarity/similarity may exist, and (2) there may be uncertainties associated with the supporting data. The extrapolation approach should address these uncertainties, utilizing clinical judgement to establish the tolerable degree of uncertainty, which may remain (e.g., false positive rate or type 1 error for the proposed clinical trial).

For extrapolation, various data sets can be used, such as (1) clinical data (PK, PK/PD, E-R) in the same condition for a drug or drugs of the same class; clinical data in other related conditions; and/or (3) clinical data in the same condition for a drug or drugs in a different class can be used. Also, nonclinical data as e.g.ADME data from animal models, *in silico*, *in vitro*, and *in vivo* data (e.g., disease-response, PK, PK/PD), semi-mechanistic, and mechanistic or juvenile nonclinical toxicology data might be used. Further data sources are RWD from e.g. disease registries (regional, national, and international), electronic health records, or health claims databases. Also, systematic reviews or meta-analyses including those that can be used to evaluate suitable biomarkers might be used for extrapolation. Further data

sources can include guidelines of clinical practice professional organizations, guidelines/consensus documents, published models and simulations (e.g., PK/PD, mechanistic), expert opinions, or standards of medicinal care/practice.

Which scenarios for selection of extrapolated doses are possible?

In cases where only PK data are needed to establish efficacy, it is mandatory to provide evidence to support the similarity of the disease and the response to treatment. It should be proven that the exposure to the drug preparation will generally provide similar responses in the reference and the target population.

If the effects on biomarkers are used to establish efficacy, validated biomarkers are recommended, but not mandatory. Biomarkers on causal pathway correlated with efficacy in the reference population may be acceptable. However, biomarkers should be justified regarding their relevance for the target population. In addition, a clear relationship between the effect on biomarkers and the efficacy in the reference population should have been established.

In order to derive sample size for PK/biomarker endpoints, quantitative methods should be used. The sample size can vary depending on variability in key drivers such as PK and PK/PD sample size.

Concerning analysis and evaluation of data, they should be described in a way that e.g. the effects on biomarkers in the target group *versus* reference population are clearly described. The therapeutic range of the effects on biomarkers for assessment of similarity should be pre-defined. The clinical relevance of the results should be discussed, including a potential impact of any sensitivity analyses. Finally, the analysis and reporting should confirm a clear dose-exposure-response relationship.

In some situations, single arm studies may be the most appropriate way of generating the required evidence. This would be the case, for example, when the standard of evidence in the reference population is a single arm trial. When designing the study, it should be defined using, for example, a pre-specified threshold for how the primary efficacy objective would be evaluated. The sample size of the studies should be calculated with focus on meeting the threshold or obtaining an estimate of sufficient precision.

External data can be used to contextualize the results, e.g. by using published literature to understand the results of the study with respect to current clinical practice, but without a formal comparison of efficacy.

Also externally controlled studies might be used for extrapolation. In some cases, it may be possible and appropriate to use external data as the formal comparator in a trial. This could be, e.g. a comparator arm in a reference population, relevant control arms from other randomized controlled trials (RCT) or real-world evidence (RWE) from target population. Using external data beyond these sources (e.g. different paediatric populations, different diseases, different endpoints) is much more challenging and should be justified. In any case, appropriate statistical methods should be used to account for differences between the study and the external control populations.

In some situations, randomized controlled efficacy studies may be needed. The respective design of controlled studies used for extrapolation may be different from those in the reference population. There can be a different relationship between false positive rate, false negative rate and sample size. If the sample size is limited, relative importance of false positive and false negative results should be considered carefully.

With extrapolation, many different design options can be used to generate data, however, not according to the traditional approach (e.g., p-value < 0.05). Extrapolation will result in a smaller sample size than for standalone efficacy studies. If the study is powered to relaxed success criteria (e.g., p-value > 0.05), this should be justified in advance. Active controlled trials could maintain conventional type I error rate, but widen the non-inferiority margin when aiming to demonstrate efficacy in line with prior expectations. It is also important to ensure that the point estimate is consistent with those of the reference population.

For quantifying the impact of reference data, it is important to understand *a priori* how much information (e.g. from reference population) is being incorporated into the design and the analysis to support the interpretation of the paediatric trial. If available information is summarized as statistical distribution, effective sample size is a good way of describing how much information is being used. Reference data may need to be modelled to match the target population more closely. Differences in study design may exist (e.g. different endpoints or endpoints measured at different times), yet the disease considered should be similar to a degree that allows extrapolation. A paediatric extrapolation plan may be based on a biomarker, surrogate endpoint, or clinical endpoint as primary endpoint in the target population, even if it is not the primary endpoint in the reference population.

Safety data generated in a reference population can define the scope and extent of data which should be collected in a target population. The extrapolation concept should include a justification of the acceptability to extrapolate safety information from the reference to the target population. The approach to the collection of safety data should reflect the scientific question(s) that needs to be answered, the knowledge gaps identified, and the uncertainties that are being addressed to support the safety of the drug in the target population. Even if extrapolation of safety data is justified, there may be additional safety issues that should be addressed in the extrapolation plan, including the need for collecting data on pre- and post-marketing safety.

Methods to predict adequate dosing in children using knowledge from adults: extrapolation by whole-body physiologically-based pharmacokinetic models

Due to safety concerns, new drugs are usually tested in adults before applying them to children. With new regulations from EMA and Food and Drug Administration (FDA), methods to predict the pharmacokinetics and pharmacodynamics in children based on data from adults have gained more interest by the pharmaceutical industry.

Simple extrapolation methods like allometry (i.e. scaling to body weight with a power of 0.75) and body surface area extrapolation provide useful estimates of the distribution and elimination of xenobiotics based on data from adults. However, these methods cannot account for the ontogeny of drug-metabolizing enzymes and transporters especially in the first year of life. More sophisticated models are whole-body physiologically-based pharmacokinetic models (PbPk). Besides size differences between age groups, such models can also account for age-related changes in the expression of drug-metabolizing enzymes and transporters and thus, allow a more precise estimation of distribution processes. Changes in organ functions, lipid content, proteins, and water are available in a database to simulate the pharmacokinetics in different age groups based on the physicochemical properties of the drugs, as well as knowledge from clinical studies in adults. PbPk is now an accepted method by regulatory authorities and provides reliable estimates of age-related changes in the pharmacokinetics but it has to be kept in mind that for most HMPa PK data are not available or cannot even be generated. The workflow can be illustrated by recent investigations on etoposide, a podophyllotoxin derivative [39]. Besides pharmacokinetic, also pharmacodynamic differences between age groups must be considered which however are often more difficult to predict.

Using controlled clinical studies with children as a source for scientific evidence? A review on European level

Clinical studies with herbal drugs or HMPs in the paediatric population are still scarce. In a systematic review from 2015, 133 controlled trials with HMPs were identified: 90 (67.7 %) were randomized, 43 (32.2 %) were randomized and double blind [40]. Most studies were performed in the People´s Republic of China (PRC) (37 studies), in the age group 6 to 2 years, and in children with respiratory diseases (36 studies). Most studies included the age group 6 to 12 years (112 studies). Only 23 studies (17 %) were conducted in European countries. In a further review on the same subject, which excluded studies from PRC, 86 randomized controlled trials with a total of 8.516 participants were included, which were mainly performed in Canada, the United States of America, in Europe, and in Iran [8]. The leading indication groups were gastrointestinal (15 studies) and dermatological diseases (12 studies).

In order to identify controlled studies published after July 2016 until April 2022, Medline/PubMed, Scopus, and the Cochrane Library were searched. Studies with ayurvedic or traditional Chinese medicine and homeopathic remedies were excluded. Six studies published between 2016 and 2021 were identified, only one of them was performed in the EU.

Looking at the funding of the clinical studies, it was obvious that at least in the recent decade they predominantly received public financial support.

In conclusion, until now valid clinical studies on HMPs in the paediatric population are very rare. This means that only little information can be gained from published data from RCTs for rationalizing distinct dosage regimes for infants and toddlers (28 days to 23 months), children (2 to 11 years) and adolescents (12 to 18 years). Implementation and realization of clinical investigations on this subject should have a high priority, and need sufficient funding.

Clinical trials vs. RWD – which is the better approach?

Increasingly more parents are considering the use of HMPs to maintain their children’s health and to treat their diseases [8]. In Germany, which has one of the longest traditions of HMPs as registered medicinal products worldwide, about 85 % of children receive at least one or more HMP(s) per year [23].

Although RCTs can provide some safety and efficacy information they are often limited in terms of sample size and length of follow-up [41]. Questions on safety can best be answered by pharmaco-epidemiological studies [42, 43] or by individual case safety reports [44, 45]. This is particularly relevant for children among whom the use of drugs is frequently off-label but recorded in routine care. Although research on pharmaco-epidemiology has grown substantially in the last 20 years, studies on paediatric patients using HMPs are still rare [46].

Two further approaches for leveraging data on the use of HMPs in children and adolescents should be explored, systematic reviews of clinical trials (which again are difficult to find in the absence of pediatric studies) and the generation of RWD in the paediatric population.

The first approach was to review clinical trials with HMPs in children (all age groups) by a systematic literature research using PubMed and Web of Science according to the PRISMA statement [40]. Details of this study have been already discussed within this paper in the section "*Using controlled clinical studies with children for scientific evidence*" and from this paper it can be concluded these data are of little use for regulatory aspects e.g. to have impact on regulatory age limits or application in practice. This means, more high-quality pediatric HMP clinical trials have to be performed, which again is in conflict with ethical and practical issues. From a more practical and regulatory perspective, instead of RCT more RWDs are needed, i.e., large non-interventional studies by which safety can best be assessed. This is particularly relevant for children among whom the use of drugs is frequently off-label but recorded in routine care.

The second approach was to launch in 2013 the PhytoVIS project - presumably the world's largest pharmaco-epidemiological study on the use of HMPs - with the intention of promoting the knowledge growth in the field of health care research for HMPs. The aim of PhytoVIS was the generation of data documenting the therapeutic usefulness of HMPs in the general population – preferably in Germany - , including special patient groups like children [47]. Overall, 2063 data sets from the paediatric population in Germany were evaluated, there of 254 from children below 2 years (12 %), 473 from patients aged 2 to 5 years (23 %), 551 from age 6 to 11 years (27 %), and 785 from age 12 to 17 years (38 %). 483 different indications were coded according to Medical Dictionary for Regulatory Activities (MedDRA LLT/PT) and 1433 HMPs were identified. Most children (68 %) were treated for common cold and fever, 14 % due to digestive complaints, 5 % because of skin diseases, 4 % due to sleep disturbances and anxiety, and 10 % because of other complaints. Interestingly, the intake of HMPs increased with age with a maximum in adolescents. Neither tolerability nor the

perceived therapeutic benefit were age-dependent. The data also showed no influence of the use within the age limits covered by the regulatory approval in relation to the small number of cases below the approved age limits. Physicians and pharmacists also were the source of recommendation in > 66 % of all data sets in both of these groups.

Based on the PhytoVIS study, the perceived effect of the therapy was rated as very good in 48 % of the patients, good to moderate in 37 %, modest in 11 %, and missing in 4.0 %. It is noteworthy that the number of respondents who assessed the effect as very good or moderate did not differ with respect to the indications. Out of all patients, 94 % experienced no adverse events. Only 0.8 % of all patients reported a marked impairment due to side effects. It is concluded that RWD in children can provide a solid information on the safety and therapeutic benefits of HMPs. Large-scale generation of RWD needs to be encouraged and supported also by public institutions, and its legal recognition should be activated.

Conclusion

A strong need for rationalizing defined dosage regimes for HMP for use in children is obvious and different approaches (extrapolation, RWD, etc.) have to be used to provide optimized drug preparation for the paediatric population.

Acknowledgement

The presentation of Robert “Skip” Nelson, MD, PhD, Pediatric Drug Development, Jansen Research and Development, Spring House, PA, U.S.A. on the ICH E11A extrapolation framework at the above mentioned symposium and commenting on the manuscript is acknowledged. Presentation and contributions from Liz Griffiths and Melanie Pires (Medicines and Healthcare products Regulatory Agency (MHRA), London, U.K) on the situation in the United Kingdom are acknowledged (at the time of presentation and contribution, Melanie Pires was employed by the MHRA).

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Ferro A. Paediatric prescribing: why children are not small adults. Br J Clin Pharmacol 2015; 79: 351–353; DOI: 10.1111/bcp.12540

[2] Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. Br J Clin Pharmacol 2015; 79: 357–369; DOI: 10.1111/bcp.12305.

[3] Petkova V, Hadzhieva B, Nedialkov P. Phytotherapeutic approaches to treatment and prophylaxis in pediatric practice. PHAR 2019; 66: 115–119; DOI: 10.3897/pharmacia.66.e37954

[4] Freire CdJ, Da Barbosa LRS, Da Costa JG, Santos RGdA, Santos AFD. Phytotherapy in pediatrics: the production of knowledge and practices in Primary Care. Rev Bras Enferm 2018; 71: 637–645; DOI: 10.1590/0034-7167-2017-0436

[5] Ullah H, Filippis A de, Baldi A, Dacrema M, Esposito C, Garzarella EU, Santarcangelo C, Tantipongpiradet A, Daglia M. Beneficial Effects of Plant Extracts and Bioactive Food Components in Childhood Supplementation. Nutrients 2021; 13; DOI: 10.3390/nu13093157

[6] Shim SB, Lee HH, Ahn HL, Lee JA, Lee HL. Effectiveness and safety of herbal medicine on children with simple obesity. Medicine: Case Reports and Study Protocols 2021; 2: e0132; DOI: 10.1097/MD9.0000000000000132

[7] Anheyer D, Cramer H, Lauche R, Saha FJ, Dobos G. Herbal Medicine in Children With Respiratory Tract Infection: Systematic Review and Meta-Analysis. Acad Pediatr 2018; 18: 8–19; DOI: 10.1016/j.acap.2017.06.006.

[8] Anheyer D, Dobos G, Cramer H. Evidenzlage pflanzlicher Präparate in der Anwendung bei Kindern und Jugendlichen. Z Phytother 2017; 37: 236–241; DOI: 10.1055/s-0042-119174

[9] Anheyer D, Frawley J, Koch AK, Lauche R, Langhorst J, Dobos G, Cramer H. Herbal Medicines for Gastrointestinal Disorders in Children and Adolescents: A Systematic Review. Pediatrics 2017; 139; DOI: 10.1542/peds.2017-0062.

[10] Anheyer D, Lauche R, Schumann D, Dobos G, Cramer H. Herbal medicines in children with attention deficit hyperactivity disorder (ADHD): A systematic review. Complement Ther Med 2017; 30: 14–23; DOI: 10.1016/j.ctim.2016.11.004

[11] Nieber K. Klinische Studien zur Anwendung pflanzlicher Arzneimittel bei Kindern - ein Überblick zur vorliegenden Literatur. Swiss Journal of Integrative Medicine 2016; 28: 5–7; DOI: 10.1159/000442756

[12] *Commission of the EU*, ed. Report from the Commission to the European Parliament and the Council State of Paediatric Medicines in the EU: 10 years of the EU Paediatric Regulation; 2017

[13] Permanand G, Mossialos E, McKee M. The EU's new paediatric medicines legislation: serving children's needs? Arch Dis Child 2007; 92: 808–811; DOI: 10.1136/adc.2006.105692

[14] *European Parliament - Council on Medicinal Products for Paediatric Use*. Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use, amended by Regulation (EC) No 1902/2006. vom 2006

[15] *European Medicines Agency EMA*, *Committee on Herbal Medicinal Products HMPC*. Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the pediatric population. EMA/HMPC/833398/2009

[16] *European Parliament*. Regulation of the European Parliament and of the concil laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006 vom 2023

[17] Welz AN, Emberger-Klein A, Menrad K. The importance of herbal medicine use in the German health-care system: prevalence, usage pattern, and influencing factors. BMC Halth Srvices Rsearch 2019; 19: 952; DOI: 10.1186/s12913-019-4739-0
[18] Lazarou R, Heinrich M. Herbal medicine: Who cares? The changing views on medicinal plants and their roles in British lifestyle. Phytotherapy Research 2019; 33: 2409–2420; DOI: 10.1002/ptr.6431
[19] Tugume P, Nyakoojo C. Ethno-pharmacological survey of herbal remedies used in the treatment of paediatric diseases in Buhunga parish, Rukungiri District, Uganda. BMC Complement Altern Med 2019; 19: 353; DOI: 10.1186/s12906-019-2763-6
[20] Wegener T. Herbal medicinal products in the paediatric population--status quo and perspectives. Wiener Mdizinische Wochenschrift 2013; 163: 46–51; DOI: 10.1007/s10354-013-0175-7
[21] Du Y, Wolf I-K, Zhuang W, Bodemann S, Knöss W, Knopf H. Use of herbal medicinal products among children and adolescents in Germany. BMC Complement Altern Med 2014; 14: 218; DOI: 10.1186/1472-6882-14-218
[22] Tomassoni AJ, Simone K. Herbal medicines for children: an illusion of safety? Curr Opin Pediatr 2001; 13: 162–169; DOI: 10.1097/00008480-200104000-00014
[23] Hümer M, Scheller G, Kapellen T, Gebauer C, Schmidt H, Kiess W. Phytotherapie in der Kinderheilkunde - Prävalenz, Indikationen und Motivation. Deutsche Medizinische Wochenschrift 2010; 135: 959–964; DOI: 10.1055/s-0030-1253683
[24] Gardiner P, Adams D, Filippelli AC, Nasser H, Saper R, White L, Vohra S. A systematic review of the reporting of adverse events associated with medical herb use among children. Glob Adv Health Med 2013; 2: 46–55; DOI: 10.7453/gahmj.2012.071
[25] Polat S, Gürol A. Safety of Herbal Medicines in Children. In: Akram M, ed. Alternative Medicine - Update. IntechOpen; 2021
[26] Snodgrass WR. Herbal products: Risks and benefits of use in children. Current Therapeutic Research 2001; 62: 724–737; DOI: 10.1016/S0011-393X(01)80079-5
[27] Çiftçi S, Samur FG. Use of Botanical Dietary Supplements in Infants and Children and Their Effects on Health. Hacettepe Üniversitesi Sağlık Bilimleri Fakültesi Dergisi 2017; 4: 30–45; DOI: 10.21020/husbfd.303011
[28] Tachjian A, Maria V, Jahangir A. Use of herbal products and potential interactions in patients with cardiovascular diseases. J Am Coll Cardiol 2010; 55: 515–525; DOI: 10.1016/j.jacc.2009.07.074
[29] Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol 2014; 4; DOI: 10.3389/fphar.2013.00177
[30] *Rietbrock N.*, *Staib H.*, *Loew D.*, ed. Klinische Pharmakologie: Enzymentwicklung während der Fetalperiode und Kindheit. 4th ed. Darmstadt: Steinkopff Verlag; 2001
[31] van den Anker J, Reed MD, Allegaert K, Kearns GL. Developmental Changes in Pharmacokinetics and Pharmacodynamics. J Clin Pharmacol 2018; 58 Suppl 10: S10-S25; DOI: 10.1002/jcph.1284
[32] Schrier L, Hadjipanayis A, Stiris T, Ross-Russell RI, Valiulis A, Turner MA, Zhao W, Cock P de, Wildt SN de, Allegaert K, van den Anker J. Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European Academy of Paediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology. Eur J Pediatr 2020; 179: 839–847; DOI: 10.1007/s00431-019-03556-9
[33] van Rongen A, Krekels EH, Calvier E am, Wildt SN de, an Vermeulen, Knibbe CA. An Update on the Use of Allometric and Other Scaling Methods to Scale Drug Clearance in Children: Towards Decision Tables. Expert Opon on Dug metabolism and Toxicology 2022; 18: 99–113; DOI: 10.1080/17425255.2021.2027907

[34] Schilcher H DW. Phytotherapie in der Kinderheilkunde. 4th ed. Stuttgart: Wissenschaftl. Verlagsgesellschaft; 2006
[35] *European Parliament and EC Council*. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for pediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 vom 12.12.2006
[36] Diaz M, Soler A, Altemira A. Alto uso de terapias complementarias en pacientes pediátricos hospitalizados en un hospital de tercer nivel. High use of complementary therapies in paediatric inpatients in a tertiary hospital. Spanish Pediatric Asociation (AEPED) Congress 2019; 2019
[37] Güemes Heras I, Santamaría-Orleans A, Colinas Herrero JF, Gómez Sorrigueta P, Ortiz González L, La Iglesia-Arnaez R de, Canals Baeza A. Use of Dietary Supplements among Spanish Pediatricians in Daily Practice: A Cross-Sectional Survey Study. J Nutr Metab 2019; 2019: 5819305; DOI: 10.1155/2019/5819305
[38] Santamaría-Orleans A, La Iglesia-Arnáez Rd, Alonso-Osorio MJ. Use recommendation of pediatric infusions by health professional. Revista de Fiitoterapia; 2017: 27–35
[39] Kersting G, Willmann S, Würthwein G, Lippert J, Boos J, Hempel G. Physiologically based pharmacokinetic modelling of high- and low-dose etoposide: from adults to children. Cancer Chemother Pharmacol 2012; 69: 397–405; DOI: 10.1007/s00280-011-1706-9
[40] Marquardt P, Kaft K, Nieber K. Clinical trials with herbal medicinal products in children: a literature analysis. Wiener Medizinische Wochenschrift 2015; 165: 236–242; DOI: 10.1007/s10354-015-0373-6
[41] Farrington R, Musgrave I, Byard RW. Potential adverse outcomes of herbal preparation use in childhood. Acta Paediatrica 2019; 108: 419–422; DOI: 10.1111/apa.14595
[42] Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonatal Ed 1999; 80: F142-4; discussion F144-5; DOI: 10.1136/fn.80.2.F142
[43] Zipursky J, Juurlink DN. Studying Drug Safety in the Real World. JAMA Intern Med 2018; 178: 1533–1534; DOI: 10.1001/jamainternmed.2018.5766
[44] Zuzak TJ, Rauber-Lüthy C, Simões-Wüst AP. Accidental intakes of remedies from complementary and alternative medicine in children--analysis of data from the Swiss Toxicological Information Centre. European Journal of Paediatrcics 2010; 169: 681–688; DOI: 10.1007/s00431-009-1087-9
[45] Bie S de, Ferrajolo C, Straus SMJM, Verhamme KMC, Bonhoeffer J, Wong ICK, Sturkenboom MCJM. Pediatric Drug Safety Surveillance in FDA-AERS: A Description of Adverse Events from GRiP Project. PLoS One 2015; 10: e0130399; DOI: 10.1371/journal.pone.0130399
[46] Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry 2007; 4: 28–37
[47] Nieber K, Raskopf E, Möller J, Kelber O, Fürst R, Shah-Hosseini K, Singh J, Kraft K, Mösgens R. Pharmaco-epidemiological research on herbal medicinal products in the paediatric population: data from the PhytoVIS study. Eur J Pediatr 2020; 179: 507–512; DOI: 10.1007/s00431-019-03532-3

[i] https://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Zulassung/zulassungsarten/besTherap/amPflanz/mono.pdf;jsessionid=E680AF1A34D2AD0CBB38220D80538559.1_cid354?__blob=publicationFile&v=3
https://buecher.heilpflanzen-welt.de/BGA-Kommission-E-Monographien/

Rationalizing optimal dosing of phytotherapeutics for use in children: Current status - potential solutions - actions needed

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Keywords: children, dosage, extrapolation, herbal medicinal products, phytotherapeutics, real world data

Abbreviations: ADME: absorption-distribution-metabolism-excretion; EC: European Commission, EMA: European Medicines Agency, EU: European Union; FDA Food and Drug Administration U.S., HMP: Herbal Medicinal Products; HMPC: Herbal Medicinal Products Committee of EMA, ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; MA: Marketing Authorisation; PbPk: whole-body physiologically-based pharmacokinetic models; PD: pharmacodynamics; PDCO: Paediatric Committee; PK: pharmacokinetics; RWD: real world data; RWE: real world evidence; THR: Traditional Herbal Registration.

Abstract

"Children are not small adults with respect to the treatment with medicinal products". This statement of *WHO* was the basis for the initiative of the European Commission for establishment of a paediatric regulation in 2007 to improve health of children by facilitating the development of medicines for children and adolescents. SeventeenFifteen years later, in the field of herbal medicinal products results are still sobering. Therefore, the *Foundation Plants for Health*, *Society for Medicinal Plants and Natural Products Research*, and German *Society for Phytotherapy* organized a symposium to assess the *status quo* for paediatric use of herbal medicinal products (HMPs), to analyse the causes for the current situation, and discuss strategies for establishing the proof of safe and efficacious HMPs for children.

The current situation for HMPs and their use in children is not fulfilling requirements of legislation. HMPs in paediatrics are effective and safe, but considering needs of children is necessary. In European countries the use, registration, and marketing of HMPs are different, depending on respective national regulations and specific traditions. EU herbal monographs are the best common denominator for such procedures. Emerging safety discussions must be considered. New approaches by real world data might be a solution. The regulatory framework is to be adapted. Defining rationalized dosing for HMPs can be achieved by extrapolation of data from adults, by using existing clinical data for children, and by using RWD. Therefore a strong need for revising restrictions for use of HMPs in children and rationalizing defined dosage regimes is obvious.

Introduction

The statement made by the WHO “Children are not small adults with respect to the treatment with medicinal products” [1] has been the basis for the initiative of the European Commission (EC) to establish the Paediatric Committee (PDCO) as a scientific board of the European Medicines Agency (EMA). On 26 January 2007, the paediatric regulation came into force in the EU (European Parliament - Council on Medicinal Products for Paediatric Use 2006). Since then, its objective has been to improve the health of children in Europe by facilitating the development and availability of medicines for children and adolescents aged 0 to 17 years. However, fifteen years later we must realize that the results in the field of herbal medicinal products HMPs are sobering.

The limitation of conducting clinical trials in paediatric patients is, mainly based on ethical, but also on practical considerations. This results in limited scientific evidence on safety and efficacy for the use of ~~herbal medicinal products (~~HMPs~~)~~ in children, while there is widespread daily use in clinical practice [2–5]. In spite of this limitation, in recent years systematic reviews were performed on the use of HMPs by children with obesity [6], respiratory tract infection [7], gastrointestinal disorders [8, 9] and attention deficit hyperactivity disorder (ADHD) [10]. General aspects of use of HMPs in children have been reviewed by [11].

On May 17th, 2022, the Foundation *Plants for Health* (PfH), the Society for Medicinal Plants and Natural Products Research (GA), and the German Society for Phytotherapy (GPT) organized an eSymposium with the following aims: (1) to present the *status quo* in various countries, (2) to analyse the reasons for the present situation, and (3) to discuss alternatives to provide evidence for the safe and effective use of HMPs in children. The eSymposium was intended to be the starting point for elaborating suitable actions for establishing rationalized recommendations and dosage regimens for HMPs in paediatrics.

This paper describes the outcome of the symposium, specifically the academic points of view, the clinical and especially the paediatric viewpoints, the regulatory perspectives, and the different regulations for HMPs for children and adolescents in several European countries. Suggestions for future initiatives rationalizing the use and distinct dosage regimens for children by extrapolation of data or by generation and interpretation of RWD are discussed.

Results and Discussion

The academic point of view

In the European Union, at least 50 % of all drug preparations used in children have only been studied in adults, and not necessarily for the same indication [12] [12, 13]. To address this problem, the European Commission (EC) implemented the regulation (EC) No 1901/2006 [14]. Currently its revision is under public consultation. One objective is to avoid unnecessary clinical trials in children, especially by extrapolation of data from clinical phase III studies with adults. The various problems raised by this approach but also possible solutions are considered. A reflection paper from 2011 addresses the lack of clinical studies with HMPs in the paediatric population , focusing on phase IV studies and the distinct characteristics of HMPs [15]. It seems worthwhile to consider the proposals from the revision of (EC) No 1901/2006 with focus on paediatric clinical studies with HMP to improve the current situation [16].

For a future evaluation of the past and current situation of rationalizing the use and dosage regimens for evidence-based HMPs, the following aspects should be considered in detail;

- Since ancient times herbal remedies have been applied for a wide range of diseases and for patients of all ages. Even today, the popularity of HMPs is steadily increasing in developed countries [17], especially for minor self-limiting diseases and often in the form of self-care based OTC products [18].If regulated and thus of good quality, HMPs are generally considered safe and thus are viewed as a smart alternative to conventional drugs. In developing countries, most people still rely on HMPs for primary health care due to missing or too costly alternatives [19].
- With the application of HMPs in children and adolescents (from 2 to 17 years) the topic of rationalizing paediatric dosages touches a delicate aspect of pharmaceutical intervention [20]. As HMPs are frequently used and easily obtainable, many of these products have not undergone clinical studies addressing efficacy and safety [21]. As for the respective clinical use in children, the situation is even worse, since we are facing a lack of high-quality clinical trials and systematic reviews on efficacy of HMPs in paediatrics [22] .
- In European countries, there is a long-term experience of HMPs, both well-established and traditionally used HMPs, including their use in paediatrics. HMPs in paediatric and

adolescent population are very popular (e.g. 85 % of the German population is using HMPs [23].

- Regarding risks associated with the use of herbal preparations in children, a systematic review identified 128 case reports of possible adverse events worldwide associated with the use of herbal materials (not HMPs but not well-characterized herbal products from Chinese or Arjuveda medicine, food supplements, etc.), overarching all local traditions and product categories worldwide [24]. From this study, the following facts can be deduced: of the 128 cases, 23 % occurred in children between the age of 9 to18 years, 38 % between the age of 2 and 8 years and 37 % in children below 2 years of age. The reported adverse events included neurological (35% - seizures, central nervous system depression and lethargy), cardiovascular (10% hypertension and metabolic concerns) and gastrointestinal (14% - nausea, vomiting and diarrhoea) disorders as well as hepatotoxicity and jaundice (11%). 36 % of the cases resulted from an unintentional ingestion. Most case reports and herbs have been poorly documented [24] ~~(Gardiner et al. 2013)~~.

  A recently published book chapter on the "Safety of Herbal Medicine" summarizes the two main dilemmas in this research area, overarching all categories of medicinal products containing herbs worldwide [25]: The data published here do not differentiate between herbal products of the different categories, different quality status and the different regulatory frameworks. There is only scarce information available on the benefits and risks of herbals' in pediatric patients [26, 27]. This lack of data creates a serious problem in the treatment of children [28].

Taking the situation in countries worldwide into account, there is in many cases a low-barrier to full access and availability of herbal products including dietary supplements outside of pharmacies, e.g. in food stores, supermarkets, and the internet, resulting in an uncontrolled and serious risk to users in terms of herbal drug safety [29].

Practical solutions for safe and effective treatments for children and adolescents with HMPs based on high-quality data must be developed. Despite of the current limited research activity in this field, this problem should be addressed by the various stakeholders. It seems reasonable to use the long-standing experience of experts, especially paediatricians, and to collect and evaluate available real-world data for HMPs. The focus must be on registered and licensed medical products. Undefined herbal products should not be covered, also as they are not underlying the EU drug law. Obviously, there is a need for financing advanced phytotherapeutic research to allow better healthcare of population groups (such as children

and adolescents) still underrepresented in research, and to collect more data on the efficacy and/or safety of HMPs in these groups.

The paediatricians´ point of view

Within daily clinical practice, phytotherapy is an essential part of medical treatment of paediatric patients [11]. Clinicians use HMPs worldwide, due to long-standing empirically based tradition, documented safety, and good efficiency. This use of phytotherapy is mainly based on decades up to thousands of years of experience, partly on non-scientific sources and especially in the European phytotherapy, partly on scientific studies. We recognise, that HMPs are used only in some European countries as a part of paediatric medicine and focus on these countries, e.g. the German language countries (Germany, Austria, Switzerland, the so called DACH countries [21].

Comparable to other areas of paediatric medicine, phytotherapy is often performed outside the official marketing authorization ("off-label use"), which is due to a lack of proven and save~~or well-tolerated~~ alternatives. Possible risks are thereby shifted to the physician applying the drug and, in the case of inadequate information or self-medication, to the patient or his/her parents.

The question therefore arises how the findings obtained in clinical studies with HMPs on predominantly adult patients can be transferred to children and adolescents.

With linear reduction in size, surface areas (e.g., of skin, of absorptive surfaces in the gastrointestinal tract and lungs, and of secretory/filtering surfaces in the renal glomeruli) decrease with the second power and volume/weight (e.g., of detoxifying liver tissue) with the third power, whereas flow resistance (e.g., in blood vessels and airways) increases with the fourth power (Law of Hagen-Poiseuille). In addition, body proportions shift dramatically with development. While in the two-month-old infant, the head accounts for 50 % of total length, it is less than 10 % in the adult. The organs of children are immature. Biochemically, different enzymes develop differently with age. E.g. alcohol dehydrogenase does not reach normal activity until the end of the first year of life. Within the cytochrome P system, only CYP3A has an appreciable activity at birth, while CYP2D6 activity develops around birth and CYP1A2 activity around the 3rd month of life. Similar developments are observed for the enzymes relevant for glucuronidation and for the *N*-acetyltransferase, whereas sulfation is already functioning by the 8th week of gestation [30]. Absorption in the gastrointestinal tract is altered in premature infants, neonates, and infants under 3 years of age due to decreased gastric acid and bile acid production, decreased intestinal motility, and differences in the

intestinal flora. Rectal absorption is unreliably reduced. The proportions of distribution spaces vary with age(extracellular: premature infants 50 %, newborns 45%, > 1year 25 %, adults 20-25 %; intracellular: premature infants 80 %, newborns 50 %, adults 30 %). The extracellular fluid decreases from 33-42%, within the first 3 months to 20%, at 1 year of age. The intracellular fluid increases from 35% to 47% during childhood. Also body fluid composition changes with age: Fat content: Premature infants 3 %, newborns 12 %, >1 year 30 %, ♂ 20 % , ♀ 30 %. Total body water: 6-8 weeks of pregnancy 91 %, at 32 weeks of pregnancy 80 %, at birth 69 % - newborns lose up to 10 % weight within the first days of life. In young children the binding capacity of plasma proteins is reduced and the plasma clearance time of many substances is prolonged. From 5 months to 10 years of age, renal clearance of many substances is enhanced. Children also have a comparatively low muscle mass [31].

The pathogenesis of many relevant diseases differs in childhood and adolescence compared to adult age.. During childhood and adolescence, growth and development with disturbances of the same as well as acute inflammatory processes are in the foreground, while in adulthood silent inflammation processes are resulting in degeneration, atrophy, and sclerosis.

On the German market, herbal products with (presumed) medical benefits are subject to various conditions of approval (medical devices, food supplements, traditional phytotherapy, well-established phytotherapy), whereby the boundaries are overlapping.

Several types of regulatory herbal monographs have been published. About 380 herbal drugs have been scientifically reviewed by the Commission E of the German regulatory authorities[i], 252 of them with “positive monographs”, i.e. with recommended medical use. Additionally, already 107 monographs from the European Scientific Cooperative on Phytotherapy (ESCOP) have been published. 118 + 13 monographs from WHO can be found, 252 monographs from HMPC have been published (219 traditional use, 33 well-established use), with 102 respectively 24 monographs with positive evaluation. Approvals for use in children are as follows: for traditional use: 1 × > 4 weeks, 3 × >1 year, 4 × > 3 years, 6 × > 4 years, 3 × > 6 years, for well-established use: 1 × > 2 years, 2 × > 6 years, 1 × > 8 years.

Also, for many chemically defined drugs, clinical studies of the highest two levels of evidence are lacking for paediatric use ("scientifically unproven“ as stated in the respective monographs of the drugs). That results in frequent off-label-use in pediatrics: 80 %, toddlers: 60 %, infants until adolescents 34 %, stationary use: 25 – 90 %, outpatient use: 13.2 %, depending on the disease and age [32]. Most HMPs are in a comparable situation, but they are usually used since decades, typically within the pharmacovigilance system for drugs.

Therefore their safety can be regarded as largely assured. And it has to be kept in mind that the pharmacovigilance system provides the base that potential side effects of HMPs are exactly visible and controllable by the regulatory authorities.

~~In Germany, the regulations for reimbursement by the statutory health insurances are subjected to the regulation of governmental regulatory authorities. Reimbursement of HMPs is only possible in cases of use in children up to the age of 12, in developmentally delayed adolescents up to the age of 18, and restricted to products, which are only available in pharmacy stores. A switch of products from pharmacy-only status to other distribution channels results in an immediate loss of the reimbursement status. For example, by the change of admission of valerian extracts changed from "pharmacy-only" to "available not only at pharmacy", valerian lost its reimbursement status even for children under 12 years of age. As a consequence, data from health insurances on its use which could be included into the analysis of RWD are no longer available.~~

Dosage in children must consider the distribution compartments (premature infants and newborns have different compartments than adults, water soluble active compounds will distribute preferentially into the extracellular space, which again has influence on the optimal dosage per kg body weight to be used), the increased plasma half-life due to large extracellular space (this leads to increased dosing intervals), the different metabolism (reduced dosing for premature infants and newborns) and adjustment of dose for hepatically eliminated drugs.

At present, three modes of dosage calculations for children are used:

1. Body weight (infants, young children)

$$\frac{\text{Dose Adult} \times 1.5 \times \text{kg}}{60\ \text{kg}}$$

2. Body surface area (older children)

$$\frac{\text{Dose Adult} \times \text{Surface Child}}{1.73\ \text{m}^2}$$

3. Age (Note for Guidance on Clinical Investigation, of Medicinal Products in Children).

- Infant, toddler 1/3 of the adult dose
- School child 1/2 of adult dose
- Children 10 to12 years 2/3 adult dose
- Adolescent: Adult Dose

These dose calculation methods are mainly based on clinical experience in therapeutic areas such as anaesthesiology and oncology. More rational approaches such as allometric scaling are used in clinical research, but not in clinical practice [33].

In general, for drugs with wide therapeutic range, the respective dosage is calculated by age group (infant/toddler 1/3, school child 1/2, adolescent = adult), for substances with a narrow therapeutic range it is determined according to body weight or body surface.

For about 30 HMPs, paediatric approvals for different ages (e.g., 6 months, 2 years, 4 years, etc.) based on observational studies have been published [34]. Commission E, ESCOP, and WHO monographs specify doses for children only for very few HMPs. Approximately 110 monographed herbal drugs were considered for paediatrics, for 92 drugs theoretical paediatric dosage calculations are published. Observational studies, i.e. RWD, exist for the most important drugs used in common cold and gastrointestinal disorders.

According to the EU regulation of 26.01.2007, paediatric studies performed in five age groups (!) will be a prerequisite for future approval for use in paediatric patients [35]. The "Drugs for Use in Children" have to be marked with a children's symbol starting at the latest from January 2007, but unfortunately, the paediatric committee of EMA decided in 2008, that this is not practicable. On 2.11.2017, the EU paediatric regulation was 10 years in force. Approved paediatric investigation plans exceeded more than 1000. As of 2017, 260 new medicines had been approved for the use in children. Clinical trials involving children accounted in 2007 for 8.3 %, in 2016 for 12.4 % of all studies. If there were no observations on the dosage for children available at the time of the subsequent approval, the governmental authority usually approves the registration according to §105 of the German Drug Law, based on the drug guideline from 1996. That means that the restriction - whether justified or not - „Do not use in children under 12 years of age, due to lack of sufficient investigations“ has to be added. The same applies to new approvals for HMPs according to § 21 of the German drug law.

Extrapolation of adult doses to children is possible and may be somewhat easier for adolescents and perhaps for school children. However, it is complex and it is mostly non-linear. The decisions of practitioners would be facilitated by general scientifically well-founded rules. Scientifically based assessments can reduce errors.

In Germany, the regulations for reimbursement by the statutory health insurances are subjected to the regulation of governmental regulatory authorities. Reimbursement of HMPs is only possible in cases of use in children up to the age of 12, in developmentally delayed

adolescents up to the age of 18, and restricted to products, which are only available in pharmacy stores. A switch of products from pharmacy-only status to other distribution channels results in an immediate loss of the reimbursement status. For example, by the change of admission of valerian extracts changed from "pharmacy-only" to "available not only at pharmacy", valerian lost its reimbursement status even for children under 12 years of age. As a consequence, data from health insurances on its use which could be included into the analysis of RWD are no longer available.

The regulatory point of view

EMA (HMPC)

During the course of an application for marketing authorisation or registration of (traditional) HMPs, various aspects have to be considered. The parents and paediatricians' interest for safe medicines and the applicants' perspectives of an interesting market must be balanced against the required evidence on efficacy and safety. For (full or bibliographic) applications for marketing authorisation, evidence on efficacy must be provided for all age groups applied as a general rule. This can be achieved by reference to controlled clinical trials. For registration applications of traditional HMP, evidence of the safety of the respective herbal preparation in the target population must be provided in the dossier. Reference to non-interventional studies and to general phytotherapeutic literature or even expert reports from paediatricians may be acceptable. However, the acceptance of such data in a registration procedure is always a case-by-case decision, as within the European Union (EU) considerable differences in the experiences with herbal treatments in children are evident. EU herbal monographs can be considered as the best common denominator for such procedures. In any case, emerging safety discussions, such as the potential carcinogenic activity of estragol in fennel, must be considered before filing an application. New approaches as the use of RWD might be a solution in future, however, the regulatory framework needs to be adapted accordingly.

The international situation

The situation in the DACH region (Germany, Austria, Switzerland)

The so-called DACH region compromises Germany, Austria and Switzerland. The respective governmental competent authorities are the Federal Institute for Drugs and Medical Devices

(BfArM) for Germany, the Federal Office for Safety in Health Care (AGES) for Austria, and Swiss Medic for Switzerland. All three agencies are hosting a department for the evaluation of HMPs called department for 'Complementary and Alternative Medicines (CAM) and Traditional Medicinal Products' and a department for medicinal products for children. No information is available to which extent interaction takes place between the two departments within the related agencies. All three agencies are providing information regarding specific conditions for HMP to be placed on the corresponding markets by referring to simplified procedures, registration and to marketing authorisation in relation to well-established use conditions. Only Swiss Medic gives a specific dosing recommendation for the development of HMPs for children.

BfArM and AGES are reflecting mainly on the European Cooperation within the HMPC products and the herbal monographs published. According to the publication by HMPC dated April 2018, 14 of 33 herbal monographs based on well-established use provide a recommendation for the use in adolescents, 9 for the use in children. This allows the conclusion that in principle dosing recommendation for children can be based on published data according to well-established use conditions.

Nevertheless, for the development of medicinal products for children, further approaches such as conducting clinical trials, using extrapolation according to the ICH Guideline E11A, and RWD should be considered.

The situation in the United Kingdom (U.K.)

In U.K., HMPs must be granted a Marketing Authorisation (MA) or Traditional Herbal Registration (THR) before they can be marketed. Applications for a MA require data on quality, safety and efficacy. Whilst quality data are required for all applications, THR applications for safety and efficacy are replaced by a bibliographic review of safety data including an expert report and evidence that the product or a corresponding product has been marketed for the proposed indication for use for 30 years, including 15 years in the UK/EU/EEA. Any HMP not matching the requirements of the THR scheme will require a MA and is reviewed in line with all relevant requirements, including Paediatric Investigation Plan (PIPs). In the UK, THR products are available over-the-counter (OTC) e.g. through retail shops such as supermarkets, health food shops, pharmacies, and online platforms. They are sold without the need for advice / supervision by a healthcare professional.

Assessment, review and acceptability of THR applications, indicated for children and adolescents are undertaken on a case by case / product basis. Whilst there are no specific guidelines in the UK for assessing THR products, international and national guidelines are taken into account and various aspects are considered such as:

- Does the evidence of traditional use support the use in the proposed age group?
- Is the herbal substance/herbal preparation acceptable for use in the age group?
- Is the indication minor, self-limiting and acceptable to be used in the respective age group, without the need for advice or supervision by a healthcare professional?
- Is the pharmaceutical form / route of administration acceptable for its use in the intended age group?
- Are any dosage adjustments required for the proposed age group?
- Are there any excipients of concern, e.g., ethanol?

Concerning the respective indications for use, the following aspects have to be considered for THR products: In the UK a limited number of indications have been accepted for children under 12 years of age including teething symptoms in babies from 3 months and cuts and grazes in children from 6 years. The indications accepted for children aged 12 to 18 years are wider and they include coughs, cold and flu symptoms, minor digestive complaints, travel sickness, skin blemishes, hay fever, minor cuts & wounds, minor inflammations of the oral mucosa and relief of itching/irritation in mild athlete's foot. Indications such as stress, depressive mood, anxiety, sleep disorders, migraine prevention and fatigue would not be accepted for children and adolescents less than 18 years of age.

Concerning safety aspects, certain herbal preparations and herbal substances are not recommended for use in children and adolescents due to safety issues and a lack of adequate data to support their safety in this age group, for example, Echinacea, St John's Wort and Senna. Their safety issues were further discussed in case studies.

For marketing, it is ensured that the product information includes clear information on the dosage for each age range if applicable including information on the age group that a product is not recommended.

Following authorisation of a THR, the products are closely monitored for adverse events through the Yellow Card Scheme (www.mhra.gov.uk/yellowcard), which is an important regulatory tool to ensure continued safe use of these products. As with all medicines, if it is clear an adverse event has resulted from the use of a traditional herbal medicine, regulatory action is taken to minimise the risk of the adverse effect.

The situation in Spain

Spanish regulations regarding HMPs are based on Directive 2004/24/EC. The Spanish Medicines and Health Products Agency (AEMPS) has accepted only few HMPs for paediatric patients. Only 80 HMPs (including 37 traditional HMPs) are accepted for paediatric patients, main indications are digestive and respiratory affections.

Most of the still small number of studies on phytotherapeutic remedies in children in Spain is biased, because data have been extracted from herbal products laboratories databases, thereby not being representative. Therefore, there is a need of more not-biased data to be able to draw robust conclusions.

According to the results and conclusions of such a small number of studies, which should be considered as preliminary and possibly biased, the situation in Spain is as follows: Regarding consumption and prescription of herbal products, 68 % of paediatricians recommend herbal products (personal communication to M.M.) and 21 % of patients hospitalized in a tertiary hospital use them in their daily life [36]. Regular prescribers are, almost in equal proportion, professionals of complementary therapies and physicians [36]. A high percentage of paediatric patients hospitalized in a tertiary hospital use complementary therapies (including phytotherapy) and its use is significantly related to the presence of underlying pathology and less regular attendance to a paediatrician. Twenty percent of outpatient paediatricians prescribe phytotherapy, in 80% of cases, it is combined with chemically defined drugs [37]. Cough and bronchial mucus are the most frequent symptoms for which phytotherapy is applied [37]. The use of herbal teas for infants is widespread, most frequently for minor digestive complaints, constipation, and sleep improvement [38]. Nearly 40 % of paediatricians prescribe dietary supplements in case of mild diseases, 31 % as a first choice whenever possible, and 22 % on parents' request. Only 15 % of paediatricians prescribe a dietary supplement in cases where pharmacological treatment is not effective [37]. Paediatricians from the Autonomous Communities of Galicia, the Valencian Country, Andalusia, and Madrid are the ones who most often recommend phytotherapy. Since most

health professionals, except pharmacists, are not trained in phytotherapy, most of them prescribe herbal products according to the recommendations of the sales representatives of phytotherapy companies. Some of the reasons for the use of herbal products are the increased parental demand (increase by 59 %), and the parental perception of improvement with its use, (nearly 70 % of parents) [36]. However, there is no data regarding why herbal products are not more prescribed or used in paediatrics.

Regarding herbal products in paediatrics in Spain, much is still to be done and some questions are still unanswered: who is using and prescribing them? What and how? In which situations? In which areas? Why are they used or not used? How can the number of approved HMP can be increased?

The Situation in Eurasian Economic Union

The Eurasian Economic Union (EAEU) includes Russia, Belarussia, Kazakhstan, Armenia and Kyrgyzstan. Established on 01. January 2015, these countries passed a common drug law with the intention to harmonize their common pharmaceutical markets. This is a very similar situation compared to the process in the EU 25 years ago. The national marketing authorizations in the EAEU need a re-registration procedure to align to the new legal base and finalization has to be reached until 31. December 2025. The main focus of the harmonization process is laid on the pharmaceutical quality of medicinal products. At a first glance, assessment of efficacy and safety is of less importance. In consequence, pre-existing paediatric use is further supported.

For new marketing applications, each use in the paediatric population requires respective studies, however, a concrete paediatric investigation plan (as known from the EU) is not required.

The paediatrician must document each off-label use of a medicinal product, which has not been approved in children, and parents' consent has to be obtained. Nevertheless, the Union of Paediatricians of Russia is alarmed that there is lack of medicines for use in children. There are no special paediatric medications available for 75 % of paediatric diseases, more than 70 % of medications prescribed to children have not been studied in the paediatric population, 90 % of medications prescribed to newborns have not been tested in this age group. This clearly shows the urgent need of developing proven medicines in children.

It can be expected that the Eurasian Economic Commission will react on the current drawback

and counteract by adapting the regulation and increase demands to prove safe and efficacious use in children

Possible solutions

ICH E11A: The use of extrapolation in paediatric drug development

Recently, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use (ICH) has published the ICH E11A guideline for extrapolation of data from a reference population (usually adult) to the target paediatric population in order to establish dosing, safety and efficacy. ICH E11A aims to harmonize approaches to paediatric extrapolation and to reduce differences between the various global regions. Additionally, ethical aims have to be considered, namely, to reduce the exposure of children to unnecessary clinical trials and to facilitate more timely access to paediatric medicines globally. Paediatric extrapolation is defined in the ICH E11(R1) guideline as "*an approach to providing evidence in support of effective and safe use of drugs in the paediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the paediatric (target) and reference (adult or other paediatric) population*". Paediatric extrapolation extends knowledge from the reference population (e.g. data on efficacy, safety, and/or dosing) to the target population, based on an assessment of the relevant similarities of the respective disease, response to therapy and drug pharmacology between the two populations.

Paediatric studies as part of adult-driven drug development may proceed under the assumption that a certain degree of similarity between the adult and paediatric condition exists. However, whether the course of disease and the expected response to the treatment are "sufficiently similar" between the respective target and reference population is not simply a "yes or no" assessment.

Discrete categories (e.g., full, partial or none) to describe the different approaches to paediatric extrapolation have been abandoned in favour of identifying the clinical trial designs which can address the remaining uncertainties based on an assessment of the existing data. The use of extrapolation reflects that (1) a continuum of dissimilarity/similarity may exist, and (2) there may be uncertainties associated with the supporting data. The extrapolation approach should address these uncertainties, utilizing clinical judgement to establish the tolerable degree of uncertainty, which may remain (e.g., false positive rate or type 1 error for the proposed clinical trial).

For extrapolation, various data sets can be used, such as (1) clinical data (PK, PK/PD, E-R) in the same condition for a drug or drugs of the same class; clinical data in other related conditions; and/or (3) clinical data in the same condition for a drug or drugs in a different class can be used. Also, nonclinical data as e.g. (ADME data from animal models, *in silico*, *in vitro*, and *in vivo* data (e.g., disease-response, PK, PK/PD), semi-mechanistic, and mechanistic or juvenile nonclinical toxicology data might be used. Further data sources are RWD from e.g. disease registries (regional, national, and international), electronic health records, or health claims databases. Also, systematic reviews or meta-analyses including those that can be used to evaluate suitable biomarkers might be used for extrapolation. Further data sources can include guidelines of and clinical practice professional organizations, guidelines/consensus documents, published models and simulations (e.g., PK/PD, mechanistic), expert opinions, or standards of medicinal care/practice.

Which scenarios for selection of extrapolated doses are possible?

In cases where only PK data are needed to establish efficacy, it is mandatory to provide evidence to support the similarity of the disease and the response to treatment. It should be proven that the exposure to the drug preparation will generally provide similar responses in the reference and the target population.

If the effects on biomarkers are used to establish efficacy, validated biomarkers are recommended, but not mandatory. Biomarkers on causal pathway correlated with efficacy in the reference population may be acceptable. However, biomarkers should be justified regarding their relevance for the target population. In addition, a clear relationship between the effect on biomarkers and the efficacy in the reference population should have been established.

In order to derive sample size for PK/biomarker endpoints, quantitative methods should be used. The sample size can vary depending on variability in key drivers such as PK and PK/PD sample size.

Concerning analysis and evaluation of data, they should be described in a way that e.g. the effects on biomarkers in the target group *versus* reference population are clearly described. The therapeutic range of the effects on biomarkers for assessment of similarity should be pre-defined. The clinical relevance of the results should be discussed, including a potential impact of any sensitivity analyses. Finally, the analysis and reporting should confirm a clear dose-exposure-response relationship.

In some situations, single arm studies may be the most appropriate way of generating the required evidence. This would be the case, for example, when the standard of evidence in the reference population is a single arm trial. When designing the study, it should be defined using, for example, a pre-specified threshold for how the primary efficacy objective would be evaluated. The sample size of the studies should be calculated with focus on meeting the threshold or obtaining an estimate of sufficient precision.

External data can be used to contextualize the results, e.g. by using published literature to understand the results of the study with respect to current clinical practice, but without a formal comparison of efficacy.

Also externally controlled studies might be used for extrapolation. In some cases, it may be possible and appropriate to use external data as the formal comparator in a trial. This could be, e.g. a comparator arm in a reference population, relevant control arms from other randomized controlled trials (RCT) or real-world evidence (RWE) from target population. Using external data beyond these sources (e.g. different paediatric populations, different diseases, different endpoints) is much more challenging and should be justified. In any case, appropriate statistical methods should be used to account for differences between the study and the external control populations.

In some situations, randomized controlled efficacy studies may be needed. The respective design of controlled studies used for extrapolation may be different from those in the reference population. There can be a different relationship between false positive rate, false negative rate and sample size. If the sample size is limited, relative importance of false positive and false negative results should be considered carefully.

With extrapolation, many different design options can be used to generate data, however, not according to the traditional approach (e.g., p-value < 0.05). Extrapolation will result in a smaller sample size than for standalone efficacy studies. If the study is powered to relaxed success criteria (e.g., p-value > 0.05), this should be justified in advance. Active controlled trials could maintain conventional type I error rate, but widen the non-inferiority margin when aiming to demonstrate efficacy in line with prior expectations. It is also important to ensure that the point estimate is consistent with those of the reference population.

For quantifying the impact of reference data, it is important to understand *a priori* how much information (e.g. from reference population) is being incorporated into the design and the

analysis to support the interpretation of the paediatric trial. If available information is summarized as statistical distribution, effective sample size is a good way of describing how much information is being used. Reference data may need to be modelled to match the target population more closely. Differences in study design may exist (e.g. different endpoints or endpoints measured at different times), yet the disease considered should be similar to a degree that allows extrapolation. A paediatric extrapolation plan may be based on a biomarker, surrogate endpoint, or clinical endpoint as primary endpoint in the target population, even if it is not the primary endpoint in the reference population.

Safety data generated in a reference population can define the scope and extent of data which should be collected in a target population. The extrapolation concept should include a justification of the acceptability to extrapolate safety information from the reference to the target population. The approach to the collection of safety data should reflect the scientific question(s) that needs to be answered, the knowledge gaps identified, and the uncertainties that are being addressed to support the safety of the drug in the target population. Even if extrapolation of safety data is justified, there may be additional safety issues that should be addressed in the extrapolation plan, including the need for collecting data on pre- and post-marketing safety.

Methods to predict adequate dosing in children using knowledge from adults: extrapolation by whole-body physiologically-based pharmacokinetic models

Due to safety concerns, new drugs are usually tested in adults before applying them to children. With new regulations from EMA and Food and Drug Administration (FDA), methods to predict the pharmacokinetics and pharmacodynamics in children based on data from adults have gained more interest by the pharmaceutical industry.

Simple extrapolation methods like allometry (i.e. scaling to body weight with a power of 0.75) and body surface area extrapolation provide useful estimates of the distribution and elimination of xenobiotics based on data from adults. However, these methods cannot account for the ontogeny of drug-metabolizing enzymes and transporters especially in the first year of life. More sophisticated models are whole-body physiologically-based pharmacokinetic models (PbPk). Besides size differences between age groups, such models can also account for age-related changes in the expression of drug-metabolizing enzymes and transporters and thus, allow a more precise estimation of distribution processes. Changes in organ functions,

lipid content, proteins, and water are available in a database to simulate the pharmacokinetics in different age groups based on the physicochemical properties of the drugs, as well as knowledge from clinical studies in adults. PbPk is now an accepted method by regulatory authorities and provides reliable estimates of age-related changes in the pharmacokinetics but it has to be kept in mind that for most HMPa PK data are not available or cannot even be generated. The workflow can be illustrated by recent investigations on etoposide, a podophyllotoxin derivative [39]. Besides pharmacokinetic, also pharmacodynamic differences between age groups must be considered which however are often more difficult to predict.

Using controlled clinical studies with children as a source for scientific evidence? A review on European level

Clinical studies with herbal drugs or HMPs in the paediatric population are still scarce. In a systematic review from 2015, 133 controlled trials with HMPs were identified: 90 (67.7 %) were randomized, 43 (32.2 %) were randomized and double blind [40]. Most studies were performed in the People´s Republic of China (PRC) (37 studies), in the age group 6 to 2 years, and in children with respiratory diseases (36 studies). Most studies included the age group 6 to 12 years (112 studies). Only 23 studies (17 %) were conducted in European countries. In a further review on the same subject, which excluded studies from PRC, 86 randomized controlled trials with a total of 8.516 participants were included, which were mainly performed in Canada, the United States of America, in Europe, and in Iran [8]. The leading indication groups were gastrointestinal (15 studies) and dermatological diseases (12 studies).

In order to identify controlled studies published after July 2016 until April 2022, Medline/PubMed, Scopus, and the Cochrane Library were searched. Studies with ayurvedic or traditional Chinese medicine and homeopathic remedies were excluded. Six studies published between 2016 and 2021 were identified, only one of them was performed in the EU.

Looking at the funding of the clinical studies, it was obvious that at least in the recent decade they predominantly received public financial support.

In conclusion, until now valid clinical studies on HMPs in the paediatric population are very rare. This means that only little information can be gained from published data from RCTs for rationalizing distinct dosage regimes for infants and toddlers (28 days to 23 months), children (2 to 11 years) and adolescents (12 to 18 years). Implementation and realization of clinical investigations on this subject should have a high priority, and need sufficient funding.

Clinical trials vs. RWD – which is the better approach?

Increasingly more parents are considering the use of HMPs to maintain their children's health and to treat their diseases [8]. In Germany, which has one of the longest traditions of HMPs as registered medicinal products worldwide, about 85 % of children receive at least one or more HMP(s) per year [23].

Although RCTs can provide some safety and efficacy information they are often limited in terms of sample size and length of follow-up [41]. Questions on safety can best be answered by pharmaco-epidemiological studies [42, 43] or by individual case safety reports [44, 45]. This is particularly relevant for children among whom the use of drugs is frequently off-label but recorded in routine care. Although research on pharmaco-epidemiology has grown substantially in the last 20 years, studies on paediatric patients using HMPs are still rare [46].

Two further approaches for leveraging data on the use of HMPs in children and adolescents should be explored, systematic reviews of clinical trials (which again are difficult to find in the absence of pediatric studies) and the generation of RWD in the paediatric population.

The first approach was to review clinical trials with HMPs in children (all age groups) by a systematic literature research using PubMed and Web of Science according to the PRISMA statement [40]~~(Marquardt et al. 2015)~~. Details of this study have been already discussed within this paper in the section "*Using controlled clinical studies with children for scientific evidence*" and from this paper it can be concluded these data are of little use for regulatory aspects e.g. to have impact on regulatory age limits or application in practice. This means, more high-quality pediatric HMP clinical trials have to be performed, which again is in conflict with ethical and practical issues. From a more practical and regulatory perspective, instead of RCT more RWDs are needed, i.e., large non-interventional studies by which safety can best be assessed. This is particularly relevant for children among whom the use of drugs is frequently off-label but recorded in routine care.

The second approach was to launch in 2013 the PhytoVIS project - presumably the world's largest pharmaco-epidemiological study on the use of HMPs - with the intention of promoting the knowledge growth in the field of health care research for HMPs. The aim of PhytoVIS was the generation of data documenting the therapeutic usefulness of HMPs in the general population – preferably in Germany - , including special patient groups like children [47]. Overall, 2063 data sets from the paediatric population in Germany were evaluated, there of

254 from children below 2 years (12 %), 473 from patients aged 2 to 5 years (23 %), 551 from age 6 to 11 years (27 %), and 785 from age 12 to 17 years (38 %). 483 different indications were coded according to Medical Dictionary for Regulatory Activities (MedDRA LLT/PT) and 1433 HMPs were identified. Most children (68 %) were treated for common cold and fever, 14 % due to digestive complaints, 5 % because of skin diseases, 4 % due to sleep disturbances and anxiety, and 10 % because of other complaints. Interestingly, the intake of HMPs increased with age with a maximum in adolescents. Neither tolerability nor the perceived therapeutic benefit were age-dependent. The data also showed no influence of the use within the age limits covered by the regulatory approval in relation to the small number of cases below the approved age limits. Physicians and pharmacists also were the source of recommendation in > 66 % of all data sets in both of these groups.

Based on the PhytoVIS study, the perceived effect of the therapy was rated as very good in 48 % of the patients, good to moderate in 37 %, modest in 11 %, and missing in 4.0 %. It is noteworthy that the number of respondents who assessed the effect as very good or moderate did not differ with respect to the indications. Out of all patients, 94 % experienced no adverse events. Only 0.8 % of all patients reported a marked impairment due to side effects. It is concluded that RWD in children can provide a solid information on the safety and therapeutic benefits of HMPs. Large-scale generation of RWD needs to be encouraged and supported also by public institutions, and its legal recognition should be activated.

Conclusion

A strong need for rationalizing defined dosage regimes for HMP for use in children is obvious and different approaches (extrapolation, RWD, etc.) have to be used to provide optimized drug preparation for the paediatric population.

Acknowledgement

The presentation of Robert “Skip” Nelson, MD, PhD, Pediatric Drug Development, Jansen Research and Development, Spring House, PA, U.S.A. on the ICH E11A extrapolation framework at the above mentioned symposium and commenting on the manuscript is acknowledged. Presentation and contributions from Liz Griffiths and Melanie Pires (Medicines and Healthcare products Regulatory Agency (MHRA), London, U.K) on the

situation in the United Kingdom are acknowledged (at the time of presentation and contribution, Melanie Pires was employed by the MHRA).

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Ferro A. Paediatric prescribing: why children are not small adults. Br J Clin Pharmacol 2015; 79: 351–353; DOI: 10.1111/bcp.12540

[2] Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. Br J Clin Pharmacol 2015; 79: 357–369; DOI: 10.1111/bcp.12305.

[3] Petkova V, Hadzhieva B, Nedialkov P. Phytotherapeutic approaches to treatment and prophylaxis in pediatric practice. PHAR 2019; 66: 115–119; DOI: 10.3897/pharmacia.66.e37954

[4] Freire CdJ, Da Barbosa LRS, Da Costa JG, Santos RGdA, Santos AFD. Phytotherapy in pediatrics: the production of knowledge and practices in Primary Care. Rev Bras Enferm 2018; 71: 637–645; DOI: 10.1590/0034-7167-2017-0436

[5] Ullah H, Filippis A de, Baldi A, Dacrema M, Esposito C, Garzarella EU, Santarcangelo C, Tantipongpiradet A, Daglia M. Beneficial Effects of Plant Extracts and Bioactive Food Components in Childhood Supplementation. **Nutrients 2021; 13; DOI: 10.3390/nu13093157**

[6] Shim SB, Lee HH, Ahn HL, Lee JA, Lee HL. Effectiveness and safety of herbal medicine on children with simple obesity. Medicine: Case Reports and Study Protocols 2021; 2: e0132; DOI: 10.1097/MD9.0000000000000132

[7] Anheyer D, Cramer H, Lauche R, Saha FJ, Dobos G. Herbal Medicine in Children With Respiratory Tract Infection: Systematic Review and Meta-Analysis. **Acad Pediatr 2018; 18: 8–19; DOI: 10.1016/j.acap.2017.06.006.**

[8] Anheyer D, Dobos G, Cramer H. Evidenzlage pflanzlicher Präparate in der Anwendung bei Kindern und Jugendlichen. Z Phytother 2017; 37: 236–241; DOI: 10.1055/s-0042-119174

[9] Anheyer D, Frawley J, Koch AK, Lauche R, Langhorst J, Dobos G, Cramer H. Herbal Medicines for Gastrointestinal Disorders in Children and Adolescents: A Systematic Review. Pediatrics 2017; 139; DOI: 10.1542/peds.2017-0062.

[10] Anheyer D, Lauche R, Schumann D, Dobos G, Cramer H. Herbal medicines in children with attention deficit hyperactivity disorder (ADHD): A systematic review. **Complement Ther Med 2017; 30: 14–23; DOI: 10.1016/j.ctim.2016.11.004**

[11] Nieber K. Klinische Studien zur Anwendung pflanzlicher Arzneimittel bei Kindern - ein Überblick zur vorliegenden Literatur. Swiss Journal of Integrative Medicine 2016; 28: 5–7; DOI: 10.1159/000442756

[12] *Commission of the EU*, ed. Report from the Commission to the European Parliament and the Council State of Paediatric Medicines in the EU: 10 years of the EU Paediatric Regulation; 2017

[13] Permanand G, Mossialos E, McKee M. The EU's new paediatric medicines legislation: serving children's needs? Arch Dis Child 2007; 92: 808–811; DOI: 10.1136/adc.2006.105692

[14] *European Parliament - Council on Medicinal Products for Paediatric Use*. Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use, amended by Regulation (EC) No 1902/2006. vom 2006

[15] *European Medicines Agency EMA*, *Committee on Herbal Medicinal Products HMPC*. Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the pediatric population. EMA/HMPC/833398/2009

[16] *European Parliament*. Regulation of the European Parliament and of the concil laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006 vom 2023

[17] Welz AN, Emberger-Klein A, Menrad K. The importance of herbal medicine use in the German health-care system: prevalence, usage pattern, and influencing factors. BMC Halth Srvices Rsearch 2019; 19: 952; DOI: 10.1186/s12913-019-4739-0
[18] Lazarou R, Heinrich M. Herbal medicine: Who cares? The changing views on medicinal plants and their roles in British lifestyle. Phytotherapy Research 2019; 33: 2409–2420; DOI: 10.1002/ptr.6431
[19] Tugume P, Nyakoojo C. Ethno-pharmacological survey of herbal remedies used in the treatment of paediatric diseases in Buhunga parish, Rukungiri District, Uganda. BMC Complement Altern Med 2019; 19: 353; DOI: 10.1186/s12906-019-2763-6
[20] Wegener T. Herbal medicinal products in the paediatric population--status quo and perspectives. Wiener Mdizinische Wochenschrift 2013; 163: 46–51; DOI: 10.1007/s10354-013-0175-7
[21] Du Y, Wolf I-K, Zhuang W, Bodemann S, Knöss W, Knopf H. Use of herbal medicinal products among children and adolescents in Germany. BMC Complement Altern Med 2014; 14: 218; DOI: 10.1186/1472-6882-14-218
[22] Tomassoni AJ, Simone K. Herbal medicines for children: an illusion of safety? **Curr Opin Pediatr 2001; 13: 162–169; DOI: 10.1097/00008480-200104000-00014**
[23] Hümer M, Scheller G, Kapellen T, Gebauer C, Schmidt H, Kiess W. Phytotherapie in der Kinderheilkunde - Prävalenz, Indikationen und Motivation. Deutsche Medizinische Wochenschrift 2010; 135: 959–964; DOI: 10.1055/s-0030-1253683
[24] Gardiner P, Adams D, Filippelli AC, Nasser H, Saper R, White L, Vohra S. A systematic review of the reporting of adverse events associated with medical herb use among children. Glob Adv Health Med 2013; 2: 46–55; DOI: 10.7453/gahmj.2012.071
[25] Polat S, Gürol A. Safety of Herbal Medicines in Children. In: Akram M, ed. Alternative Medicine - Update. IntechOpen; 2021
[26] Snodgrass WR. Herbal products: Risks and benefits of use in children. Current Therapeutic Research 2001; 62: 724–737; DOI: 10.1016/S0011-393X(01)80079-5
[27] Çiftçi S, Samur FG. Use of Botanical Dietary Supplements in Infants and Children and Their Effects on Health. Hacettepe Üniversitesi Sağlık Bilimleri Fakültesi Dergisi 2017; 4: 30–45; DOI: 10.21020/husbfd.303011
[28] Tachjian A, Maria V, Jahangir A. Use of herbal products and potential interactions in patients with cardiovascular diseases. J Am Coll Cardiol 2010; 55: 515–525; DOI: 10.1016/j.jacc.2009.07.074
[29] Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol 2014; 4; DOI: 10.3389/fphar.2013.00177
[30] *Rietbrock N., Staib H., Loew D.*, ed. **Klinische Pharmakologie: Enzymentwicklung während der Fetalperiode und Kindheit. 4th ed. Darmstadt: Steinkopff Verlag; 2001**
[31] van den Anker J, Reed MD, Allegaert K, Kearns GL. Developmental Changes in Pharmacokinetics and Pharmacodynamics. J Clin Pharmacol 2018; 58 Suppl 10: S10-S25; DOI: 10.1002/jcph.1284
[32] Schrier L, Hadjipanayis A, Stiris T, Ross-Russell RI, Valiulis A, Turner MA, Zhao W, Cock P de, Wildt SN de, Allegaert K, van den Anker J. Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European Academy of Paediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology. Eur J Pediatr 2020; 179: 839–847; DOI: 10.1007/s00431-019-03556-9
[33] van Rongen A, Krekels EH, Calvier E am, Wildt SN de, an Vermeulen, Knibbe CA. An Update on the Use of Allometric and Other Scaling Methods to Scale Drug Clearance in Children: Towards

Decision Tables. Expert Opon on Dug metabolism and Toxicology 2022; 18: 99–113; DOI: 10.1080/17425255.2021.2027907
[34] Schilcher H DW. **Phytotherapie in der Kinderheilkunde. 4th ed.** Stuttgart: Wissenschaftl. Verlagsgesellschaft; 2006
[35] *European Parliament and EC Council*. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for pediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 vom 12.12.2006
[36] Diaz M, Soler A, Altemira A. Alto uso de terapias complementarias en pacientes pediátricos hospitalizados en un hospital de tercer nivel. High use of complementary therapies in paediatric inpatients in a tertiary hospital. Spanish Pediatric Asociation (AEPED) Congress 2019; 2019
[37] Güemes Heras I, Santamaría-Orleans A, Colinas Herrero JF, Gómez Sorrigueta P, Ortiz González L, La Iglesia-Arnaez R de, Canals Baeza A. Use of Dietary Supplements among Spanish Pediatricians in Daily Practice: A Cross-Sectional Survey Study. J Nutr Metab 2019; 2019: 5819305; DOI: 10.1155/2019/5819305
[38] Santamaría-Orleans A, La Iglesia-Arnáez Rd, Alonso-Osorio MJ. Use recommendation of pediatric infusions by health professional. Revista de Fiitoterapia; 2017: 27–35
[39] Kersting G, Willmann S, Würthwein G, Lippert J, Boos J, Hempel G. Physiologically based pharmacokinetic modelling of high- and low-dose etoposide: from adults to children. Cancer Chemother Pharmacol 2012; 69: 397–405; DOI: 10.1007/s00280-011-1706-9
[40] Marquardt P, Kaft K, Nieber K. Clinical trials with herbal medicinal products in children: a literature analysis. **Wiener Medizinische Wochenschrift 2015; 165: 236–242; DOI: 10.1007/s10354-015-0373-6**
[41] Farrington R, Musgrave I, Byard RW. Potential adverse outcomes of herbal preparation use in childhood. Acta Paediatrica 2019; 108: 419–422; DOI: 10.1111/apa.14595
[42] Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonatal Ed 1999; 80: F142-4; discussion F144-5; DOI: 10.1136/fn.80.2.F142
[43] Zipursky J, Juurlink DN. Studying Drug Safety in the Real World. JAMA Intern Med 2018; 178: 1533–1534; DOI: 10.1001/jamainternmed.2018.5766
[44] Zuzak TJ, Rauber-Lüthy C, Simões-Wüst AP. Accidental intakes of remedies from complementary and alternative medicine in children--analysis of data from the Swiss Toxicological Information Centre. European Journal of Paediatrcics 2010; 169: 681–688; DOI: 10.1007/s00431-009-1087-9
[45] Bie S de, Ferrajolo C, Straus SMJM, Verhamme KMC, Bonhoeffer J, Wong ICK, Sturkenboom MCJM. Pediatric Drug Safety Surveillance in FDA-AERS: A Description of Adverse Events from GRiP Project. PLoS One 2015; 10: e0130399; DOI: 10.1371/journal.pone.0130399
[46] Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry 2007; 4: 28–37
[47] Nieber K, Raskopf E, Möller J, Kelber O, Fürst R, Shah-Hosseini K, Singh J, Kraft K, Mösgens R. Pharmaco-epidemiological research on herbal medicinal products in the paediatric population: data from the PhytoVIS study. Eur J Pediatr 2020; 179: 507–512; DOI: 10.1007/s00431-019-03532-3

[i] https://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Zulassung/zulassungsarten/besTherap/amPflanz/mono.pdf;jsessionid=E680AF1A34D2AD0CBB38220D80538559.1_cid354?__blob=publicationFile&v=3
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Most case reports and herbs have been poorly documented (Gardiner et al. 2013)”. Please give the reference number.	Thanks for this advice. Has been inserted as number, strange that CITAVI at 2 points add authors and in the rest numbers… Not understandable these programs…
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Planta Medica
Editorial Board
Prof.- Dr. E. Heiss

Dear Prof. Heiss,

please find enclosed the revised manuscript for consideration in Planta Medica entitled

Rationalizing optimal dosing of phytotherapeutics for use in children: Current status - potential solutions - actions needed

Many thanks for the quick and careful review process and the competent suggestions. We had been very happy about the quick was Planta Medica and your editorial team works on the submission – many thanks!
We have carefully considered all issues raised and attach to this revision a clean version of the MS, the MS with changes marked and a detailed action list on the different points.

All authors concur with the submission. The work has not been submitted to any other journal.

We would be happy if the MS is acceptable in the present form.

Sincerely, yours Andreas Hensel