ChildFriendlyMedicines

Diana van Riet-Nales

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ChildFriendlyMedicines

Availability, pharmaceutical design, usability and patient outcomes

Kindvriendelijke geneesmiddelen
Beschikbaarheid, farmaceutisch ontwerp, bruikbaarheid en patiënten uitkomsten
(met een samenvatting in het Nederlands)

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Prof. dr. A.F.A.M. Schobben
Prof. dr. A.C.G. Egberts

Copromotor:
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An angel in the book of life
Wrote down the babies' births
Then whispered as she turned the page
That they may (healthy) live on earth

unknown author, revised

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Chapter 1

General Introduction

Background

Child mortality rates during birth and early childhood are an important factor in determining average life expectancy, whereas paediatric diseases may have a lifelong effect on quality of life (1-3). As a consequence, there is an urgent need for medicines that save the lives and protect the health of (unborn) children (4-6).



Obviously, the applied medicines must be safe and effective, meaning that adequate pre-marketing clinical and non-clinical studies are necessary. However, and despite the introduction of medicines to cure (antibiotics) or prevent (vaccines) serious child diseases over the last fifty years, paediatric clinical trials were generally considered as unethical, too difficult or not worth the money (7-10). As a consequence, the commercial availability of authorised medicines for children is lagging behind those for adults and there is a general lack of formulations that children are able and willing to take (11-16).

All this implies that health care professionals may often have no other choice than to prescribe a medicine outside the approved conditions for the type of disease, dose and/or target age group (off-label drug use); to modify the characteristics of an authorised preparation to adjust its dose or dosage form (unlicensed drug use) or to ask the pharmacy to compound a medicine from the active substance and suitable excipients (unlicensed drug use) (17, 18). In addition, parents and caregivers may modify preparations in a different way as recommended by the prescriber in order to make sure that the child swallows the medicine i.e. to assure adequate child acceptability (unlicensed drug use) (19-22). However, off-label and unlicensed drug use imply that the medicine's safety and efficacy have not been investigated at all or not according to the standards applied for (regional) marketing authorisation, or that the acquired data were simply not submitted to the regulatory authorities for assessment and subsequent approval (23). All this may put the health of (unborn) children at (an avoidable) risk (24, 25).

Paediatric Pharmacotherapy

Over time, pharmacotherapy has evolved from the instinctive use of medicinal plants to feel good, through the more anecdotal use of plants and other remedies that were considered beneficial to certain symptoms, into the rational use of safe and effective medicines (26). These "rational" medicines merely include synthetic and bio(technologically) derived active substances that were specifically developed to prevent or cure a certain disease or condition on the basis of pharmacological principles, mechanistic disease understanding, and extensive pre-marketing clinical and non-clinical testing (27). Although, without doubt, (modern) pharmacotherapy has substantially contributed to increased average life expectancies, it has also become clear that the benefits of a medicine seldom come without harm and that children are one of the most vulnerable patient populations (8, 28, 29). In fact, many serious events have been reported during the last century e.g. by Sutherland et al. who reported in 1959 that three neonates had died from high doses of chloramphenicol due to the lack of glucuronidation reactions in the liver ultimately resulting in the accumulation of toxic metabolites (grey baby syndrome) (30).

Besides the active substance, the harmful effect of medicines may also be caused by the excipients in the formulation (10, 31). For example, in 1937 the solvent diethylene glycol was used to prepare an oral liquid preparation containing the antibiotic sulphanilamide. The manufacturer neither consulted the company's chief pharmacist when selecting diethylene glycol as the excipient to dissolve sulphanilamide nor conducted any pre-marketing animal testing on the final preparation. As a consequence, the toxic effect of diethylene glycol (multi organ and acute renal failure) was not observed until the preparation was actually taken by patients, causing over 100 deaths, mostly children (32). Unfortunately, children are still dying because of diethylene glycol, most often because the solvent has deliberately been added to liquid paracetamol preparations or cough syrups to save costs (33-35). The harmful effect of excipients may also be due to a lack of understanding of paediatric physiology. For example, Gershanik et al. reported that the repeated use of sodium chloride and water ampoules preserved with low concentrations of benzyl alcohol for the flushing of catheters and reconstitution of medicines had caused toxic concentrations of benzyl alcohol in preterm neonates (36).

At birth, the human body weight and dimensions are only fractions of those of adults, especially in case of extremely premature babies weighing well below 1 kg, however, adult values may be reached at young age, especially when children are extremely obese (37, 38). Moreover, the human organ and body functions

each develop at their own speed implying that these functions have a different and non-linear function with age, body weight or dimensions and other physical or physiological aspects such as the amount of body fat (39). Given that the efficacy of a medicine commonly depends on the fraction of the medicine that is available at the site of action and of the medicine's receptor interaction, and given that these two aspects are determined by a wide range of human organ and body functions, unfortunately, paediatric dosing recommendations often cannot be based on discrete age points or on standardised calculations based on body weight or dimensions (40). Therefore, children cannot be considered as miniature adults (39, 41).

In fact, paediatric dosing recommendations require proper understanding of how growth affects the medicine's absorption, distribution, metabolism, elimination i.e. pharmacokinetics (PK) as well as its receptor or organ interaction i.e. pharmacodynamics (PD) (39). For example, in neonates, the pH of the gastric contents is elevated i.e. greater than 4. As a consequence, a larger proportion of medicines that are sensitive to acid conditions e.g. penicillin G will remain available for absorption (39). Moreover, the anticoagulant effect of warfarin is based on competitive inhibition of vitamin K epoxide reductase, resulting in evidence that it is better to base the dose of the medicine on human liver weight than on human body weight (42, 43). Also, the occurrence of de novo suicidality in children following antidepressant pharmacotherapy (e.g. fluoxetine), has raised questions about the pharmacodynamic responsiveness of children to this (class of) medicine(s) (43, 44). Aspects other than growth may have an impact on PKPD as well, e.g. genetic variability, certain diseases or conditions, hypothermic treatment procedures (45, 46).

Adequate child acceptability i.e. the willingness and ability of a child to take a medicine as intended is an important condition of adequate drug adherence and therewith effective pharmacotherapy (31, 47, 48).

However, besides its effect on PKPD, growth also affects the physical, psychological and social-emotional aspects associated with child acceptability, such as swallowability e.g. a baby cannot swallow a commonly sized tablet; eye-



hand coordination e.g. a toddler cannot take a liquid on a spoon without spoiling; social-emotional development e.g. "I am two and I say no" and caregiver's dependence (39, 47). To a certain extent, child acceptability and behaviour can be derived from the age of the child or from observational or experimental (clinical) studies in the paediatric population e.g. babies could swallow 2 mm mini-tablets and French children considered that generic amoxicillin clavulanate antibiotics generally tasted worse than the innovator product respectively (49, 50). However, clinical studies are normally based on a carefully selected patient group, thereby frequently excluding patients with special characteristics such as hospitalization, obesity, mental retardation, behavioural problems, polypharmacy or a different cultural background (51). All this implies that the safety, efficacy and acceptability of a medicinal product by the actual patient population needs to be further explored and confirmed in daily practice (52). Nevertheless, many studies in the paediatric population have already shown great differences in child acceptability (53, 54).

Especially in young children, the administration of medicines relies on parental support and supervision, yet parents may be unable or unwilling to administer medicines to their children as intended e.g. because of difficulties overcoming child resistance, difficulties measuring the correct dose, language barriers, low health literacy or the need to rely on other caregivers such as a baby sitter or school teacher (55-59). In order to make sure that the child takes its medicine, parents and caregivers may also rely on handlings that were not foreseen by the manufacturer of the medicine such as crushing modified release tablets and that, consequently, may have a negative effect on the medicine's safety and efficacy profile (20, 60). Parents may also have their own preferences for the administration of a medicine to their child e.g. the application of mini-tablets rather than a syrup as an anti HIV remedy (54). All this supports the conclusion that the development of safe and effective paediatric medicines requires adequate understanding of the relationship between the medicine's pharmaceutical design and its efficacy, safety and usability in daily practice.

Availability of child friendly medicines

In 1997, the European Commission and European Medicines Agency met to discuss problems related to paediatric pharmacotherapy. They concluded that market forces alone had proven to be insufficient to stimulate adequate clinical trials in children, that there was a general lack of dosage forms that children were able and willing to take and that there was a need to learn lessons from the legal incentives already adopted by the US government to increase

the information in the drug label on the use of the medicine in children i.e. the 1997 US Food and Drug Administration Modernization Act (FDAMA), the 2002 Best Pharmaceuticals for Children Act (BPCA) and the 2003 Paediatric Research Equity Act (10, 32, 61-64). As a result, in 2007 the so-called European Paediatric Regulation was installed. This Regulation aims to improve the health of the children of Europe by a system of obligations and rewards facilitating the development and availability of medicines for children between birth and 18 years of age; by ensuring that medicines for use in children are of high quality, ethically researched and appropriately authorised and by improving the availability of information on the actual use of medicines in children (65, 66).

The Regulation requires companies to develop a so-called Paediatric Investigation Plan (PIP) at an early phase in the development of a new medicine, new route of administration or new indication. This PIP describes the plan for the paediatric development of the medicine, including the pharmaceutical design of the preparation(s) to be developed for each of the indicated target age groups (66, 67). The PIP is subject to agreement by the European Medicine Agency's (EMA) Paediatric Committee (PDCO) and the agreed conditions are binding at the time of marketing authorisation. This implies that companies can only apply for marketing authorisation of the (adult) medicine when compliance to the PIP has been confirmed by the EMA (68, 69). In order to evaluate whether the Paediatric Regulation meets its key goals, it is essential to carefully monitor whether the children of Europe gain increased access to well-developed i.e. age-appropriate medicines and whether this will ultimately result in reduced off-label and unlicensed prescription rates (70-72). Acknowledging that the majority of children live in neither Europe nor the US, the limited availability of well-developed medicines for children is also a key concern to the World Health Organization (35, 71).

The Paediatric Regulation is expected to result in an increased number of authorised paediatric medicines (65, 68, 71). Acknowledging on the one hand an urgent need to assure the development by industry of safe, effective, good quality and usable i.e. age-appropriate medicines and on the other hand consistent assessment of the acquired data by the European regulatory authorities, guidance on the pharmaceutical development of medicines for paediatric use was required (35, 66, 73). However, as knowledge of the relationship between pharmaceutical aspects and the efficacy and safety of medicines was scarce and fragmented, this also implied an urgent need to combine forces (74-79).

Even before the Paediatric Regulation had come into force, the EMA had already published a reflection paper on the formulations of choice for the paediatric

population that invited stakeholders to discuss the opinions given (80, 81). In addition, the Regulation allocated funds for essential research in the paediatric domain, and a paediatric research network was installed at the EMA (82). In addition, the Dutch government allocated funds for research into the aspects that are critical to the quality of medicines for use by children, while the EMA PDCO pushed for essential research in the field of patient acceptability by agreeing to some PIPs only when the company agreed to investigate this aspect during the paediatric development of the medicine (83). Moreover, at the level of health care professionals and academia, national paediatric formularia and medicines research networks were installed, and industry and academia combined forces to form research groups such as the European Paediatric Formulation Initiatives and the American Association of Pharmaceutical Scientists Paediatric Taskforce (16, 74, 84-86). Finally, taking advantage of close interaction with stakeholders and gradually increasing knowledge on the pharmaceutical development of medicines for paediatric use, the EMA has recently adopted a guideline on this subject (68, 87, 88).

As the use of medicines in daily practice outside Europe may greatly differ from within Europe e.g. with respect to temperature conditions, health literacy, the availability of clean water to reconstitute medicines or the availability of a refrigerator to keep medicines cooled, the World Health Organization has developed its own guidance on the manufacture and use of paediatric medicines (89-91).

In conclusion, the pharmaceutical development of a paediatric medicine involves a holistic approach to the selection of the pharmaceutical design aspects that assure the safety, efficacy, good quality and usability of the medicine by children (and parents, caregivers and health care professionals where appropriate) i.e. age-appropriate or child friendly medicines. These pharmaceutical aspects mainly relate to the choice of the route of administration, dosage form, dosing frequency, excipients in the formulation, container closure system, dosing device and/or user instruction. For example, the oral route of administration implies the need for a sufficiently palatable medicine, which may necessitate the inclusion of flavours and sweeteners in the formulation. Also, the need to administer the medicine to children from birth into adulthood may necessitate the development of liquid formulations in different strengths i.e. different preparations that should be measured with a co-dispensed dosing device (87). In addition, the ultimate selection of the pharmaceutical design aspects should best take account of any other aspect that may have an impact on the availability and usability of the medicine in daily practice such as any barriers to the necessary clinical studies, child and parent behaviour, reimbursement policies, return on company investment, and the risk for medical errors (78, 91).

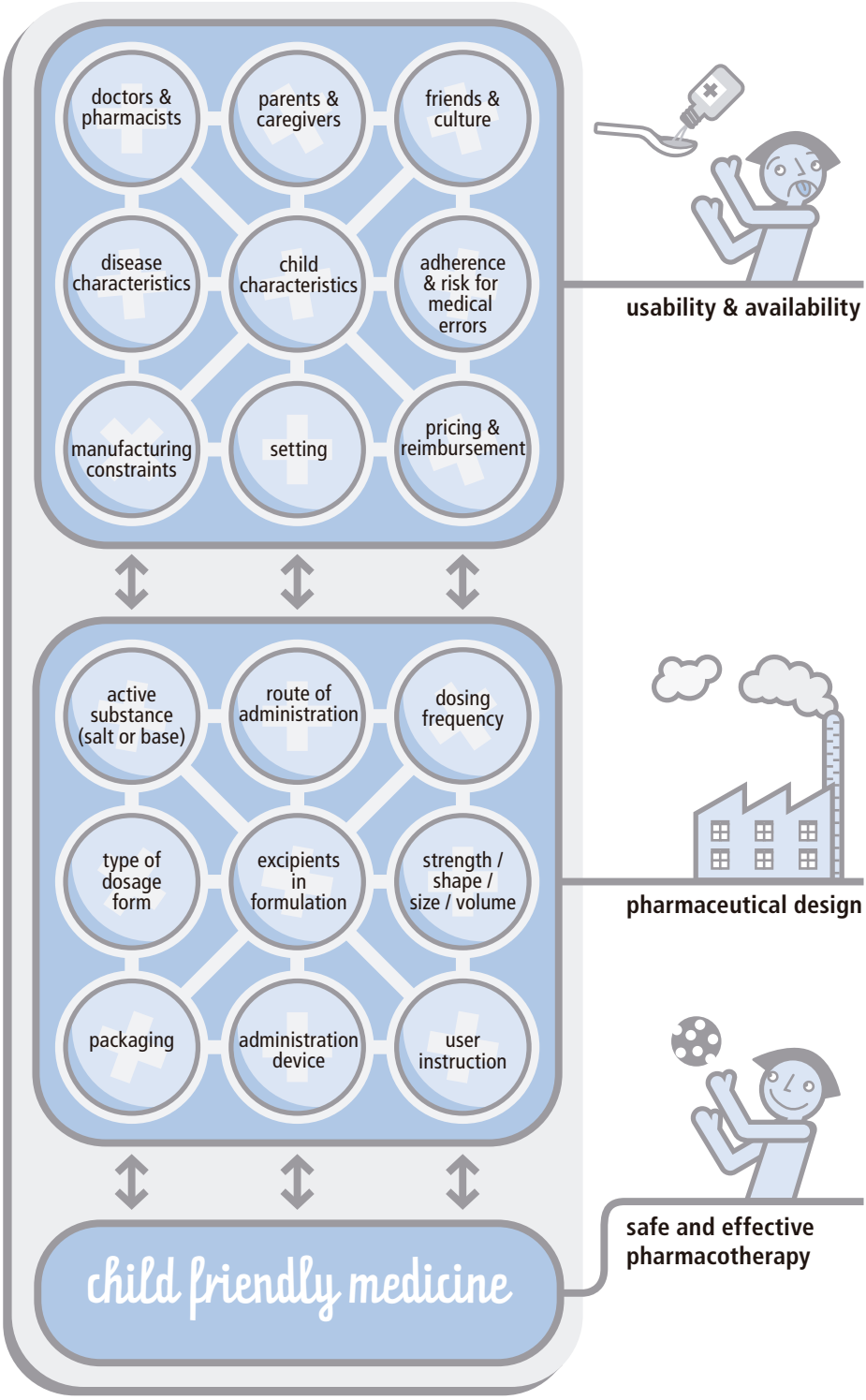

Figure 1 Holistic approach to the development of medicines for paediatric use

In view of the aforementioned, it can be concluded that the use of medicines in daily practice may be different from the use in the clinical trials on which the authorisation of the medicine was based, for example with respect to child behaviour, caregivers' attitudes, health care systems or cultural background. When focusing on the usability of tablets, it is clear that these are commonly subdivided to lower the dose, either within dosing instructions or off-label. (92-95). However, it is known from current practice, that children, parents and caregivers may have difficulties with breaking tablets by hand (96-98). As a consequence, they may rely on the use of a tablet splitter. However, it is questioned whether the application of such tablet splitters is sufficiently accurate in insuring the recommended doses (99). If not, one may argue that the design of tablets that cannot be broken by hands by a relevant part of the indicated target patient population is to be regarded as age inappropriate, implying a need for improvement of the tablets' pharmaceutical design or for the development of an additional oral flexible dosage form (87).

Conclusions

Children are not miniature adults as the human organ, body, psychological and societal functions all develop at their own speed from birth into adulthood (39, 41). As a consequence, there is an urgent need to understand how growth affects the medicine's absorption, distribution, metabolism, elimination, organ and receptor interaction, as well as how growth and child characteristics relate to the ability and willingness of the child to swallow a medicine as intended (29, 47). Yet for long periods of time, clinical studies to acquire the essential knowledge were generally considered as unethical, too difficult or not worth the money (7-10). As a result, the availability of authorised paediatric medicines is lagging behind that of adults and high paediatric off label and unlicensed prescription rates have been identified (12, 23, 72, 100). Recent incentives by the USA, Europe and WHO have tried to improve this situation by means of several incentives including obligatory studies in the paediatric population, more emphasis on the development of safe and effective preparations that children are able and willing to take, and by fostering research into essential areas where knowledge is still scarce and fragmented (32, 66).

Objective of this thesis

The overall aim of this thesis was to investigate the availability, pharmaceutical design, usability and patient outcomes of medicines for children. The first objective was to study the availability of well-designed i.e. age-appropriate medicines for children; the second objective was to study the pharmaceutical

design of medicines for children and the third objective was to study the usability of medicines for children in the domiciliary setting.

Outline of this thesis

Each study objective is described in a separate chapter. In **chapter 2.1**, the availability and age-appropriateness of paediatric medicines on the Dutch market was investigated with help of a national electronic Medicines Compendium (Informatorium Medicamentorum), a Dutch Medicines Database (Z-index) and the medicine's scientific user information (Summary of Product Characteristics).

In **chapter 2.2** the availability and age-appropriateness of future medicines for children was investigated by evaluating the proposals for the paediatric development of a new medicine as outlined by industry in the Paediatric Investigation Plans (PIPs) as well as the conditions that were agreed for such development by the European Medicines Agency and its Paediatric Committee (EMA/PDCO).

In **chapter 3.1** the Cochrane, Embase and Medline databases were systematically searched for studies on the relationship between the pharmaceutical design aspects of oral medicines for children and patient outcomes. The pharmaceutical aspects investigated were categorized in three areas (formulation and dosage form; route of administration and dosing frequency; packaging, administration device, and user instruction) and the patient outcomes in six areas (clinical efficacy, side effects and tolerability, patient preference, patient acceptance, administration errors and/or patient adherence). The number of publications in each of the 18 combinations of categories was determined in order to evaluate where knowledge on the pharmaceutical development of medicines for children was readily available and where it was scarce and fragmented.

In **chapter 3.2** the acceptability of four different types of oral placebo formulations (4 mm tablet, powder, suspension, syrup) was investigated in young children in a domiciliary setting in the Netherlands. Parents were instructed to administer each formulation twice in the same way as they would administer a prescribed medicine. They were asked to report on the child and family characteristics in a participant diary, and for each of the eight administrations, also on the method of administration, the child and parent acceptability and the child and parent preference. The relationship between the type of formulation and the overall child and parent acceptability and preference was investigated.

In **chapter 4.1** the data acquired for the study described in chapter 3.1. were analysed with respect to the method of administration, namely on its own,

co-administered i.e. with a small quantity of food or drinks or mixed i.e. with a larger quantity of food or drink. The relationship between the method of administration, type of formulation and child acceptability was investigated. Another investigation examined the increased likelihood of parents administering a formulation with food or drinks when child acceptability was low, and whether changes in the method from the first to the second administration of the same formulation were associated with changes in child acceptability.

In **chapter 4.2** the suitability of tablet splitters as an alternative to breaking tablets by hand was investigated. The accuracy and precision of tablets broken by hand (best case tablet type and operator) was compared to tablets subdivided by several tablet splitters obtained from the Dutch market, and a kitchen knife. In addition, the sustainability of the tablet splitter and kitchen knife was investigated over 100-fold use.

Finally, in **chapter 5** the results of the studies are presented in a broader perspective focusing on the medicine's pharmaceutical development, the Paediatric Regulation and Paediatric Investigation Plans (PIPs), and Child Parent relations and medication acceptability.

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Chapter 2

Availability of age-appropriate medicines for children

Chapter 2.1

The availability and age-appropriateness of medicines authorised for children in The Netherlands

Diana A. van Riet-Nales
Karin E. de Jager
Alfred F.A.M. Schobben
Toine C.G. Egberts
Carin M.A. Rademaker

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Abstract

Introduction

Physicians often have to treat children with unauthorised medicines because the necessary medicine is not authorised for children at all, not for children of the relevant age, or not in a form that the child is able and willing to take. In 2007, the European Paediatric Regulation was installed with the aim to facilitate the development and accessibility of well-developed and authorised medicines for the children of Europe. In order to evaluate the effectiveness of this Regulation, there is a need for baseline information from several European member states on the number and characteristics of the authorised paediatric medicines that are available on their market. The first objective of this study was to investigate the number of medicines and active chemical entities that are authorised and commercially available for children in the Netherlands. The second objective was to evaluate the age-appropriateness of the available paediatric medicines.

Methods

The availability of medicines and active chemical entities for use in humans as well as for use in children was studied with help of a Dutch medicines database and the medicines' Summary of Product Characteristics. The (paediatric) medicines were categorized with respect to their route of administration, type of oral dosage form and therapeutic area. The age-appropriateness of a sample of the paediatric medicines was assessed on three aspects: dose capability, suitability of the dosage form and inclusion of potentially harmful excipients.

Results

3542 paediatric medicines containing 703 different active chemical entities were identified. This equalled half of all the medicines and active chemical entities that were present in medicines for human use. The percentage of paediatric medicines increased with age and varied for the route of administration from 22% (dermal) to 81% (inhalation), and for the therapeutic category from 11% (uro-genital, sex hormones) to 89% (anti-parasites). The appropriateness of the paediatric medicines with respect to their authorisation status, dose capability and type of dosage form increased with age from 27 to 88%. Fifty-two percent of all oral paediatric liquid formulations contained a potentially harmful excipient.

Conclusions

This study confirms the limited availability of paediatric medicines for a broad range of therapeutic areas and shows that paediatric medicines may not be age-appropriate, even if authorised. The results of this study confirm the need for the European Paediatric Regulation and also provide essential baseline information for an estimation of the effectiveness of the Regulation in the near future.

Introduction

In order to provide children with essential medical care, physicians often have to resort to a prescription for an off-label or pharmacy compounded i.e. unauthorised medicine because an authorised medicine that the child is able and willing to take is not available (1–8). However, in January 2007, the European Paediatric Regulation came into force (9). This regulation aims to facilitate the development and accessibility of well-developed and authorised medicines for the children of Europe by the application of multiple strategies. One of these strategies obliges industry to plan clinical trials in children at an early stage of the development of a medicine containing a new active substance, unless a waiver or deferral would apply. The same requirement applies to the development of a new indication or a new route of administration for an existing medicine. However, as clinical trials and marketing authorisations take a substantial amount of time but the Regulation has come into force for a few years only, the real effect of the Paediatric Regulation on both the availability of authorised, paediatric medicines as well as on off-label and unauthorised paediatric prescription rates is still awaited (10, 11).

Recent studies in Australia, New Zealand, the USA and the UK showed a limited availability of medicines for children, thereby emphasizing the need for legislative incentives like the European Paediatric Regulation (1–5, 8, 12, 13). The information from the UK study can, moreover, be used as baseline information for an estimation of the effectiveness of this Regulation in the near future. However, it would be better if such an evaluation would be based on baseline information from several European countries. In order to adjust for the availability of generic medicines that may add little to covering children's therapeutic needs, such an evaluation would preferably also include a review of the availability active chemical entities that are present in authorised, paediatric medicines.

The design of the currently authorised paediatric medicines is not always optimal (9, 14, 15). This is understandable as scientific evidence on the impact of pharmaceutical technology aspects of medicines for children on child patient outcomes is scarce (16). In fact, it is well known that some medicines for children contain potentially harmful excipients (17, 18). Moreover, tablets have been authorised for children below the age of 6 years, even though they may be unable to swallow normally sized tablets (19). Thus, it is vital to study to what extent authorised medicines are really adequate for use in children. Therefore, the first objective of this study was to identify the availability of medicines and active chemical entities authorised for children in the Netherlands. The second

objective was to evaluate the age-appropriateness of the identified paediatric medicines towards their ability to provide for the recommended dose (dose capability); the suitability of their dosage form for the indicated target age group(s); and finally the inclusion of potentially harmful excipients.

Methods

Availability of paediatric medicines

All authorised medicines for human use that were commercially available in the Netherlands as well as all types of active chemical entities that were included in these medicines were identified with help of the Z-index on 6 May 2009. The Z-index is a monthly updated national database containing information on all medicines for sale on the Dutch market. Each entry in the Z-index (in this chapter further referred to as each medicine) corresponds with a unique medicinal drug product. These drug products relate to a single strength or dosage form; to all filling volumes of liquid preparations in the same concentration; or to all filling weights of powders for reconstitution for solution of the same composition (17). Homeopathic medicines, herbal preparations and radionuclide generators were excluded. In addition, parallel import products were excluded because they do not add any new treatment possibilities to the related reference products.

For each of the included medicines, the relevant characteristics were extracted. The medicines were then categorized according to their route of administration, e.g. oral, rectal. Then, oral medicines were further categorized into the different types of oral dosage forms, e.g. tablet, capsule. Finally, tablets and capsules were categorized into their different types as well, e.g. chewing tablet, effervescent tablet, soft capsule.

The Z-index did not allow direct extraction of the commercially available medicines and active chemical entities intended for use in children. Therefore, a national electronic Medicines Compendium compiled by the Scientific Institute of Dutch Pharmacists (Informatorium Medicamentorum) was examined to identify all active substances where the sections 'dosing information' or 'method of administration' contained a word suggesting use in children (18). Thereafter, the related medicines were selected in the Z-index and the child authorisation status of the selected medicines was manually verified with help of the medicines' Summary of Product Characteristics (SmPC) by examination of section 4.1 'therapeutic indications' and section 4.2 'posology and method of administration' (20). The information in these SmPC sections was examined according to newly developed criteria (Appendix 1). The selection methodology

was verified by evaluation of the SmPCs of a random sample of 400 medicines in the Z-index for which the Informatorium Medicamentorum did not suggest the use of the active substance in children. The evaluation showed that 96% of these medicines were indeed for adults only i.e. 4% misclassification. This value was considered acceptable; moreover, half of the misclassified medicines (2%) was indicated for children from the age of 15 or 16 years i.e. adolescents only.

Age-appropriateness

The age-appropriateness of the included paediatric medicines was evaluated by investigating three key aspects. The first aspect investigated was whether the recommended doses of the sampled medicine (as per its SmPC) could be given to children, i.e. if the medicine was dose capable (Appendix 1). The dose capability was studied in a sample of 400 authorised, paediatric medicines for each of the five target age-categories: term new born infants (0 to 27 days), infants and toddlers (28 days to 23 months), children 2 to 5 years, children 6 to 11 years and children 12 to 17 years (21). The sample was stratified for the type of marketing authorisation (European or national). If the recommended dose(s) could not be given with the sampled medicine (e.g. a 375 mg amoxicillin tablet cannot be used to deliver a 125 mg dose), it was verified whether this dose could be given by another paediatric medicine containing the same active chemical entity and applying the same route of administration (e.g. 5 ml of an amoxicillin 125 mg/5 ml oral liquid suspension can be used instead).

The second aspect investigated was whether the dosage form of the sampled medicine was suitable for use in children. The same sample of 400 paediatric medicines and the same age-categories were studied. If the dosage form was considered as 'not suitable' (e.g. a 250 mg capsule for a 1 year old child), then it was verified whether an alternative dosage form that was suitable to the age of the child and that was intended for the same route of administration could be identified instead (e.g. a 250 mg/5 ml oral liquid).

The suitability of the dosage forms was evaluated according Table 3.1 of the 'Reflection paper on formulations of choice for the paediatric population' applying the criterion that a value of 4 or 5 represented sufficient suitability and applying the additional criteria as described in Appendix 1 (15). Medicines were considered age-appropriate with respect to their dose and dosage form when either the medicine itself or any of its alternatives fulfilled the applied criteria. Otherwise, the medicines were considered age-inappropriate.

The third aspect examined related to the inclusion of potentially harmful excipients in medicines for children. These excipients were selected on the

basis of the aforementioned reflection paper: benzyl alcohol, benzoic acid/ sodium benzoate, methylparahydroxybenzoate, butylparahydroxybenzoate, propylparahydroxybenzoate, ethanol, propylene glycol and synthetic colouring agents. In view of the nature of these excipients, their inclusion in medicines for paediatric use was studied in two other samples, namely a sample consisting of all oral liquid paediatric medicines and a sample consisting of all parenteral paediatric medicines.

In case the preparations contained a potentially harmful excipient, it was verified whether the use of this excipient could be avoided by using another oral liquid or parenteral medicine containing the same active chemical entity. The age-appropriateness of medicines containing a potentially harmful excipient was considered questionable, especially when alternative medicines showed that their inclusion could be avoided.

Data analysis

Descriptive statistics were performed through Microsoft Excel XP and SPSS version 17.

Results

Availability

The availability of medicines and active chemical entities for use in humans and children is described in Table 1.

Evaluation of the SmPCs of medicines suggesting use in children revealed that 3542 (48%) of the 7410 medicines for human use and 703 (47%) of the 1490 active substances for human use were authorised for one or more paediatric age groups. In 51 (7%) SmPCs the child authorisation status could not be deducted due to unclear or conflicting information.

Most of the medicines for children were for oral (n = 2247 of 3542, 63%) or parenteral use (n = 788 of 3542, 22%). The percentage of oral medicines for children versus all oral medicines is 46% (n = 2247 of 4933) and the percentage of parenteral medicines for children versus all parenteral medicines 55% (n = 788 of 1439). The largest percentage of medicines for children versus all medicines was identified for medicines for inhalation (81%), nasal use (80%) and rectal use (77%). The smallest percentage was identified for medicines for dermal use (22%).

Table 1 Availability of medicines and active chemical entities for children

	authorised medicines			authorised active chemical entities		
	paediatric medicines (n)	all medicines for human use (n)	percentage paediatric versus all medicines (%)	children (n)	all chemical entities for human use (n)	percentage paediatric versus all chemical entities (%)
route of administration						
oral	2247	4933	46%	357	726	49%
parenteral	788	1439	55%	339	623	54%
dermal	71	317	22%	23	144	16%
ear/eye	52	190	27%	28	79	35%
inhalation	138	170	81%	28	34	82%
iectal	135	180	77%	20	47	43%
nasal	101	127	80%	13	19	68%
other	10	54	19%	15	39	38%
all	3542	7410	48%	703‡	1490‡	47%
type of oral dosage form						
tablets	1422	3620	39%	237	592	40%
capsules	334	633	53%	78	162	48%
oral liquid preparations*	400	495	81%	133	167	80%
powder/ granules	65	93	70%	22	31	71%
oral drops	11	17	65%	9	15	60%
others	15	75	20%	9	44	20%
all	2247	4933	46%	357‡	726‡	49%

* oral liquid preparations consisted of all medicines that are liquid when applied e.g. effervescent tablets were also considered as oral liquid preparations

‡ some active chemical entities were available in more than a single dosage form

The most frequently available type of oral dosage form in children were tablets (n = 1422 of 2247, 63%). Oral liquid preparations (n = 400 of 2247, 18%) and capsules (n = 334 of 2247, 15%) were available to a lesser extent, whereas powder/granules were the least available type of oral dosage form (n = 65 of 2247, 3%).

The percentage of tablets for children versus all tablets for human use was 39% (n = 1422 of 3620); the percentage of capsules for children versus all capsules for human use 53% (n = 334 of 633); and the percentage of oral liquid

preparations for children versus all oral liquid preparations for human use 81% (n = 400 of 495).

The majority of tablets for children were uncoated (n = 1005, 71%). Film-coated (n = 250, 18%) and modified release tablets (n = 120, 8%) were available to a lesser extent. Tablets were least often available as melting tablets (n = 16, 1%) and chewing tablets (n = 15, 1%). The majority of capsules were hard and immediate release (n = 276, 83%). Hard and modified release capsules (n = 37, 11%) and soft capsules (n = 21, 6%) were more scarce.

The percentage of the different types of tablets for children versus all tablets for human use varied between 36% (melting tablets) and 45% (chewing tablets) and for capsules between 28% (hard, modified release) and 91% (soft capsules).

Data on the anatomical therapeutic chemical classification (ATC) code of the included medicines and active chemical entities for children are described in Table 2. The percentage of medicines for children versus all medicines for human use varied from 11% for the genito-urinary system and sex hormones (ATC = G), 19% for the dermatologicals (ATC = D) and 19% for the cardiovasculair system (ATC = C) to 86% for the respiratory system (ATC = R), 86% for the antiinfectives for systemic use (ATC = J) and 89% for the antiparasitic products, insecticides and repellents (ATC = P). Evaluation on the basis of the active chemical entities showed a similar pattern.

Age-appropriateness

The random sample of 400 medicines studied for this purpose equalled 11% of all paediatric medicines. Ninety per cent of the sampled medicines were granted a Dutch Marketing Authorisation and 10% a European Marketing Authorisation. The sample contained 83 unique chemical entities, which equalled 23% of all the active chemical entities identified in paediatric medicines. Detailed analysis showed that the sample was representative concerning the route of administration and the type of oral dosage form (data not shown).

Data on the child authorisation status per target age group, the ability to provide for the recommended dose (dose capability) and the suitability of the dosage form are depicted in Figure 1. Using this first sample of 400 paediatric medicines, the percentage of authorised medicines in the population is estimated as 37% (95% CI 32.2%-41.6%) in the age group 0–27 days and as 96% (95% CI 93.3%-97.5%) in the age group 12–17 years. In addition, the percentage of authorised and dose capable medicines in the population is estimated as 30% (95% CI 25.5%-34.4%) in the age group 0–27 days and as 88% (95% CI 84.3%-

Table 2 Medicines and active chemical entities for children per therapeutic category

	authorised medicines			authorised active chemical entities		
therapeutic category	paediatric medicines (n)	all medicines for human use (n)	percentage paediatric versus all medicines (%)	paediatric medicines (n)	all medicines for human use (n)	percentage paediatric versus all chemical entities (%)
alimentary tract and metabolism (A)	470	806	59%	106	170	62%
blood and blood forming organs (B)	228	521	44%	106	174	62%
cardiovascular system (C)	240	1267	19%	32	135	24%
dermatologicals (D)	53	273	19%	17	83	20%
systemic hormonal preparations (H)	111	162	69%	22	42	52%
anti-invectives for systemic use (J)	647	760	86%	147	185	79%
antineoplastic and immuno-modulating agents (L)	108	363	30%	39	127	31%
muscoskeletal system (M)	212	413	51%	24	69	35%
nervous system (N)	842	1660	51%	90	215	42%
others (O)	72	173	42%	42	153	27%
antiparasitic products, insecticides and repellents (P)	40	45	89%	20	22	91%
respiratory system (R)	437	508	86%	84	96	88%
sensory organs (S)	56	202	28%	30	86	35%
all*	3542	7410	49%	703	1490	47%

* one chemical entity may relate to several ATC codes

90.7%) in the age group 12–17 years. Finally, the percentage of authorised and dose capable medicines with a suitable dosage form in the population was estimated as 27% (95% CI 22.7%-1.3%) in the age group 0–27 days and as 88% (95% CI 84.3%-90.7%) in the age group 12–17 years.

The percentage of medicines authorised for children has gradually increased over time since 1980. However, the age-appropriateness of the paediatric medicines towards their authorisation status, dose capability and suitability of the dosage form gradually improved with more recent dates of marketing authorisation only (Figure 2, example for the age group 1–23 months; other age groups gave similar results).

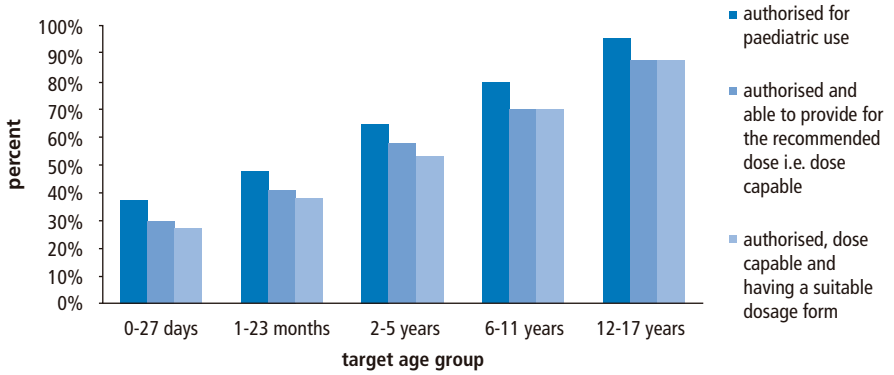

Figure 1 Age-appropriateness of medicines for children (n = 400, 100%)

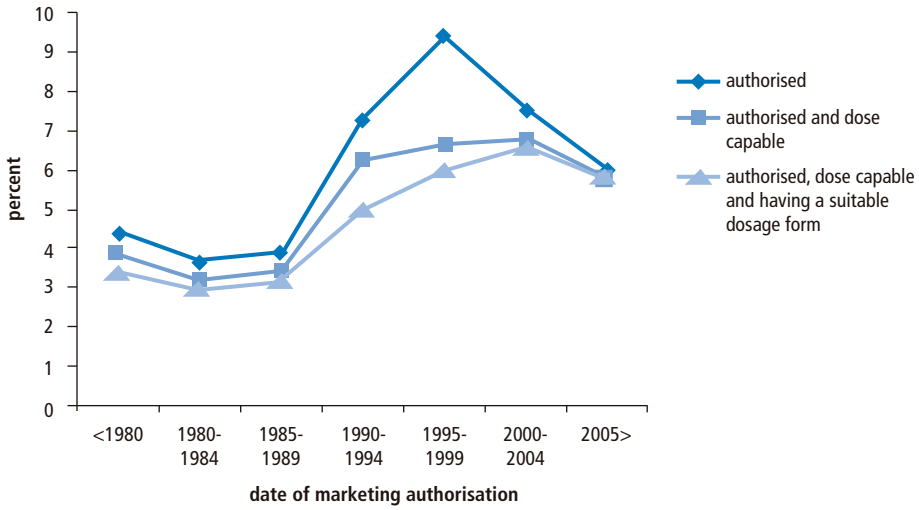

Figure 2 Percent of paediatric medicines in the sample (n = 400) for children 1–23 months

Data on the potential harmfulness of the excipients are described in Table 3. Fifty-two percent of all oral liquid paediatric preparations contained one or several of the investigated and potentially harmful excipients. For 22% an alternative liquid was available with the same active chemical entity, but not the potentially harmful substance. For 17% of the oral liquid preparations an alternative liquid with a lower number of potentially harmful substances could be identified. Seven percent of all parenteral preparations contained one or several of the investigated potentially harmful excipients.

Table 3 Potentially harmful excipients in medicines for children

potentially harmful excipient	oral liquid preparations (sample n = 400)		parenteral preparations (sample n = 788)	
	n	%	n	%
benzyl alcohol	1	0.3%	29	4%
benzoic acid/sodium benzoate	70	17%	0	0%
methylparahydroxybenzoate	77	19%	9	1%
butylparahydroxybenzoate	1	0.3%	0	0%
propylparahydroxybenzoate	45	11%	1	0.1%
ethanol	47	12%	15	2%
propylene glycol	43	11%	11	1%
synthetic colouring agents	31	8%	0	0%
natural colouring agents	48	12%	0	0%
all*	208	52%	51	7%

* total amount of oral liquid preparations and parenteral preparations containing one or more potentially harmful excipients

Discussion

This study showed that 3542 medicines containing 703 active chemical entities were authorised and commercially available for some paediatric age groups. This equalled half of all the medicines and active chemical entities that were available for human use. Paediatric medicines were mostly intended for the oral and parenteral route of administration. The percentage of medicines for children was largest for anti-infectives, respiratory medicines and anti-parasitic products, insecticides and repellents and smallest for genito-urinary medicines and sex hormones, dermal preparations and cardiovasculair agents. The percentage of authorised and dose capable medicines with a suitable dosage form increased with age.

Authorised medicines that are not available on the market do not bring any benefit to a child. Therefore, this study was conducted in a database containing information on the commercial availability of medicines in the Netherlands, the Z-index (17). The Z-index does not allow electronic identification of medicines for children. Moreover, it is not freely available. As these aspects are considered to hinder public access to actual and relevant medical information, competent authorities are encouraged to enable easy and public access to the commercial availability and characteristics of medicines that are authorised for use in children.

The percentage of medicines for children as found in this study (48%) deviates slightly from the percentages found in the UK (59%), Australia (38%), New Zealand (35%) and the USA (54%) (1, 2, 4, 5, 8). This confirms that the limited availability of medicines for children is a global rather than regional problem. However, when comparing the data of these studies, the methodological differences should be considered. First, all studies were conducted in national databases applying tailored inclusion and exclusion criteria resulting in a potentially different output. Second, in all studies the child authorisation status was determined on the basis of information on the marketing authorisation details. However, it was not clear how this determination was actually operationalized in the other studies. The criteria as employed in this study can be used as a basis for the establishment of international consensus on the criteria to be employed for the assessment of the child authorisation status of (existing) medicines.

An overall 48% relative availability of medicines for children might theoretically still be sufficient to cover most of their common therapeutic needs. However, in view of our findings as well as the EMA priority list for studies into off-patent medicinal products (22), there is a lack of age-appropriate paediatric medicines in a considerable number of therapeutic areas.

This study showed that the relative availability of tablets (39%) and capsules (53%) is limited when compared with oral liquid preparations (81%) and powders or granules (70%). This is likely due to the fact that tablets and capsules are generally considered suitable for older children only. Melting and chewing tablets are more likely to be taken at a younger age than uncoated, film-coated and modified release tablets (15). However, their availability for children appears to be limited.

The development of medicines tailored for use in children implies that a specific active substance may need to be available in a different dosage form and/or strength and sometimes even as a different active chemical entity in order to allow the manufacture of a particular formulation e.g. salt rather than base to improve dissolution. Thus, several medicinal drug products may be needed in order to treat a broad patient population from birth into adulthood or old age. Although some of the available strengths and dosage forms are only intended for a specific age group or dose, existing SmPCs may relate to all patient groups and all dosing recommendations. Therefore, the dose capability and the suitability of the dosage form were considered taking account of any alternative, authorised, paediatric medicine.

The dose capability was considered a binominal criterion. A medicine is either dose capable or it is not. However, the suitability of the dosage form is not as absolute. First of all, the table in the European reflection paper was not developed as a decision tree for the age-appropriateness of paediatric medicines as it was based on a limited number of data and as it could only be used for an evaluation of the age-appropriateness of paediatric medicines by defining additional criteria (Appendix 1). Second, according to this table, tablets and capsules are only suitable from the age of 6 years. However, recent studies have shown that small tablets can be swallowed by young children (23). Also, some capsules can be opened and their contents given as such.

The age-appropriateness of medicines with respect to their excipient composition is even less absolute; first, because this study related to a limited number of potentially harmful excipients, and second, because a final evaluation of the harmfulness of an excipient in a paediatric medicine for a specific target age group would require additional information on the concentration and maximum daily intake. However, this information is not publicly available through the medicine's SmPC.

In SmPCs referring to a range of strengths and dosage forms, it often remains unclear which of these strengths and dosage forms can be used to deliver a particular dose to children of a particular age. Such information may be relevant when choosing the most appropriate dosage form for a child, to avoid the intake of potentially harmful excipients by young children or to avoid the intake of an excessive amounts of excipients by older children that may result in side effects e.g. a laxative effect by high doses of sorbitol. Therefore, pharmaceutical companies are encouraged to provide clear information on the applicability of the types of dosage forms and strengths for the different paediatric age-groups.

Sturkenboom et al. investigated the paediatric prescription rates by therapeutic area (24). Combination of their data and ours showed that anti-infectives and respiratory medicines were frequently prescribed and also readily available, that dermal preparations were frequently prescribed, but not readily available, and that anti-parasitic products were rarely prescribed, but widely available. Future studies should evaluate whether the low availability of paediatric medicines in some of the therapeutic areas is a problem in clinical practice. This evaluation should take account of the seriousness of the disorder (unpleasant versus life-threatening) and the availability of other treatment possibilities. It is interesting to see if the real therapeutic needs of the children of Europe will be better covered after the introduction of the European Paediatric Regulation, especially as this is still doubtful in the USA where incentives have been implemented to

increase the number of commercially available paediatric medicines since 1997 (25–29).

It is not realistic to expect that all medicines for adults will also become available for children. The authors consider that in exceptional cases, industry-verified instructions for pharmacy compounded medicines together with public information on the dose–response relationships in children could also be considered sufficient. Such pharmacy compounded medicines could take the active chemical entity or the adult medicine as the starting point. Where relevant, the availability of an appropriate quality of the active substance should be guaranteed. In addition, the impact of pharmaceutical handling on the stability and bio-availability of the pharmacy compounded medicines should be understood and controlled.

This study showed that medicines authorised for children may differ with respect to their ability to provide the recommended dose, the suitability of the dosage form and the inclusion of potentially harmful excipients. Because innovator products have at least been authorised 10 years prior to their generic competitors, and because the age-appropriateness of paediatric medicines is only gaining increased attention over the last decade, there is little reason to believe that the age-appropriateness of innovative medicines will generally be better than that of its generic competitors. Thus, the different trademarks of a medicine i.e. generics may provide some additional value to children.

Clinicians and pharmacists should consider age-inappropriate formulations as a cause for administration errors, lack of therapeutic compliance, suboptimal clinical outcomes and unexpected side effects. In order to reduce the risk of any such problems, they are encouraged to compare the different trademarks of a particular medicine when prescribing or dispensing a medicine for use in children.

In view of the aforementioned, paediatric medicines may not be interchangeable with adult medicines. Even the different trademarks of a paediatric medicine may not be interchangeable themselves when they are authorised for a different age range. This fact should be acknowledged by pharmacists when substituting medicines for children and by health technology assessment bodies in reimbursement decisions.

The review of the marketing authorisation information in this study revealed that SmPCs do not necessarily meet the current regulatory requirements, which have gradually increased over the last decades in order to provide health care

professionals and patients with more extensive information. Therefore, industry and competent authorities are encouraged to update any outdated SmPC and to undertake measures resulting in a reformulation of medicines that are authorised but clearly age-inappropriate.

This study has some limitations. First, the results are determined by the selection date, the inclusion criteria, the exclusion criteria and the criteria for the evaluation of the child authorisation status. However, it is rather unlikely that alternative criteria would have a major impact on the main conclusions of this study. Second, this study evaluates the age-appropriateness of paediatric medicines with respect to three of its key pharmaceutical technology aspects. However, other pharmaceutical aspects, such as palatability, the availability and suitability of a measuring device or the comprehensibility of the user instruction may be of equal importance to the child and its parent. Third, the impact of the design of the paediatric medicine on the medicine's actual efficacy and safety profile could not be evaluated. Finally, this study did not evaluate whether the available paediatric medicines were also reimbursed. However, lack of (full) reimbursement may also hinder the actual access of children to age-appropriate medicines.

Conclusions

In conclusion, about half of all commercially available medicines and active chemical entities in the Netherlands are authorised for one or more paediatric age groups. However, in several therapeutic areas the commercial availability of medicines for children is lower, especially when focussing on young children, infants and neonates. Moreover, authorised paediatric medicines cannot be considered as age-appropriate per definition. Thus, the pharmacotherapeutic treatment options of children are lagging behind those for adults. In order to limit the application of off-label and unauthorised medicines that may not be safe and efficacious, it is necessary that the number of age-appropriate and authorised paediatric medicines and active chemical entities will increase. The effectiveness of the European Paediatric Regulation is to be closely followed towards this goal. The results of this study can be considered as baseline information for this purpose.

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Appendix 1 Interpretation of information in section 4.1 and 4.2 of the Summary of Product Characteristics (SmPC)

SmPC	comment
child authorisation status	
general statement referring to children	target age group: 0 – 18 years
general statement "juvenile"	target age group: 0 – 18 years
"zuigeling" (sucking child)	target age group: 0 – 1 year
"jong volwassene" (young adult)	target age group: 16 – 18 years
"adolescent"	target age group: 12 – 18 years
a recommended dose for a specific age range	target age group: the specific age range for dosing
a recommended dose for children from 0 until the age of 12 to 17 and a recommended dose for adults	target age group: 0 – 18 years
a recommended dose in mg kg^{-1} without any further information	target age group: 0 – 18 years
the medicine can be used from a specific minimum weight	the minimum weight is used to calculate the equivalent minimum age according the Dutch growing curve for girls, lower line
a minimum age between 0 and 18 years and a minimum weight	the target age groups are only based on the information towards age
the medicine is discouraged for use in children or a specific target age group, nevertheless a recommended dose is given	the child classification according the dosing instruction is applied
a reference to several medicines (e.g. different strengths and dosage forms) and several target age groups, but it is clearly stated which medicine is suitable for which of the target age groups.	each medicine: only those target age groups which are specific for that medicine; otherwise each medicine all target age groups
the lower target age is not consistent with the lower ranges of the adapted ICH criteria (e.g. 2.5 years)	the lower age range of the next modified ich group is applied
ability to follow the authorised posology ("dose capable")	
the dosage instruction refers to mg kg^{-1}, however, the medicine contains a fixed quantity of the active chemical entity	the medicine is not considered dose capable
suitability of the dosage form ("suitable")	
tablets	• a single dose may involve 2 tablets at the maximum • a single dose may involve a halved tablet, if 1) the tablet contains a score line; 2) the SmPC does not state that the scoring line is for esthetical reasons only; 3) the SmPC does not state that the tablet may only be broken to facilitate the intake of the full dose. • if the SmPC reads that the tablet may be pulverized, than the tablet is considered suitable for children from 1 month

(continued)

Appendix 1 (continued)

SmPC	comment
suitability of the dosage form ("suitable")	
capsules	• if the SmPC states that the capsule may be opened, then the capsule is considered suitable for children from 1 month
suppositories	• a single dose involves one suppository (no halves)
enema's	• the minimum dosing volume is 5 ml, whereas the maximum dosing volume is 150 ml
oral liquid preparations	• the maximum dosing volume is 5 ml for children aged below 5 years • the maximum dosing volume is 10 ml for children aged from 5 to 10 years • the minimum single dosing is 0.2 ml

Chapter 2.2

Oral medicines for children in the European Paediatric Investigation Plans

Diana A. van Riet-Nales
Erwin G.A.W. Römkens
Agnes Saint-Raymond
Piotr Kozarewicz
Alfred F.A.M. Schobben
Toine C.G. Egberts
Carin M.A. Rademaker

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Abstract

Introduction

Pharmaceutical industry is no longer allowed to develop new medicines for use in adults only, as the 2007 Paediatric Regulation requires children to be considered also. The plans for such paediatric development called Paediatric Investigation Plans (PIPs) are subject to agreement by the European Medicines Agency (EMA) and its Paediatric Committee (PDCO). The objective of this study was to evaluate the key characteristics of oral paediatric medicines in the PIPs and the changes implemented as a result of the EMA/PDCO review.

Methods

All PIPs agreed by 31 December 2011 were identified with help of a proprietary EMA-database. PIPs were included if they contained an agreed proposal to develop an oral medicine for children from 0 to 11 years old. Information on the therapeutic area (EMA classification system); target age range (as defined by industry) and pharmaceutical characteristics (active chemical substance, dosage form(s) as listed in the PIP, strength of each dosage form, excipients in each strength of each dosage form) was extracted from the EMA website or the EMA/PDCO assessment reports.

Results

A hundred and fifty PIPs were included corresponding to 16 therapeutic areas and 220 oral dosage forms in 431 strengths/compositions. Eighty-two (37%) PIPs included tablets, 44 (20%) oral liquid preparations and 35 (16%) dosage forms with a specific composition/strength that were stored as a solid but swallowed as a liquid e.g. dispersible tablets. The EMA/PDCO review resulted in an increase of 13 (207 to 220) oral paediatric dosage forms and 44 (387 to 431) dosage forms with a specific composition/strength. For many PIPs, the target age range was widened and the excipient composition and usability aspects modified.

Conclusions

The EMA/PDCO review realized an increase in the number of requirements for the development of oral dosage forms and a larger increase in the number of dosage forms with a specific composition/strength, both targeting younger children. Changes to their pharmaceutical design were less profound.

Introduction

On 26 January 2007, the Paediatric Regulation came into force with the aim to improve the information on medicines for children, to increase ethical drug research in paediatrics and to increase the availability of appropriately authorised medicines for the children of Europe (1–4). The Regulation requires the submission of a Paediatric Investigation Plan (PIP) to the European Medicines Agency (EMA) for agreement by its Paediatric Committee (PDCO). The PIP defines the studies, measures and timelines necessary to ensure that data are collected that are supporting the authorisation of the medicine in children, and that such studies are safe to conduct. In addition, the PIP should include a description of the pharmaceutical development of the medicine proposed for future marketing (2, 3, 5). The EMA/PDCO PIP decisions have a binding character and industry can only apply for marketing authorisation of the (adult) medicine when the EMA has confirmed that the PIP was followed or a deferral was obtained (2, 6).

Estimation of the extent to which the Paediatric Regulation will meet one of its goals to enhance the availability of appropriately authorised paediatric medicines would necessitate an analysis of the trends observed over time in the availability of medicines for children of a particular age as authorised in each of the European member states. However, only few medicines with a PIP have reached marketing authorisation already as the development of a new medicine may cost many years whereas the Regulation has only existed for a few years (7, 8). It is anticipated that a comparison of the paediatric medicines as originally proposed by industry in the PIPs and as finally agreed by the EMA/PDCO may provide a valuable prognostic estimate of the extent to which the Regulation will be able to achieve this goal.

Based on an analysis carried out on data covering one year (2009), the EMA's 5-year PIP evaluation report to the Commission stated that the EMA/PDCO raised many questions with respect to the pharmaceutical characteristics and the dosing of the medicines that were initially proposed by industry in the PIP (7, 9). This study further expands on this analysis by an evaluation of the key characteristics of oral paediatric medicines in the PIPs and the changes implemented as a result of the EMA/PDCO review.

Methods

Study design

This retrospective study evaluated the characteristics of oral paediatric medicines in the PIPs. As the study did not contain human subjects, it was not subject to ethical approval according to the Dutch Medical Research Involving Human Subjects Act (WMO) (10). The study protocol was approved by the EMA as part of the Memorandum of Understanding with the National Institute for Public Health and the Environment (RIVM). The data were retrieved from the EMA internet and supplemented with data from two proprietary EMA repositories. Protection of the proprietary data was assured by the RIVM and Medicines Evaluation Board (MEB) confidentiality rules for regulatory information. Only researchers that had signed a RIVM or MEB confidentiality agreement were allowed to extract and analyse the data. Data were anonymized after the data analysis.

PIP selection

Original PIPs that successfully passed the EMA/PDCO review between 1 July 2007 and 31 December 2011 (agreed PIPs) were identified by a single researcher (ER) in a proprietary repository, the Paediatric Records Application database (PedRA). This database captures the main administrative, pre-clinical, clinical and (since October 2011) quality details of all PIPs submitted to and assessed by the EMA/PDCO. PIPs were included in this study if they contained an oral medicine for children between birth and 12 years of age (0 to 11 years old; 0–11 years) or a subset thereof. PIPs for oral vaccines and oral allergens were excluded. Oral medicines were defined as medicines that should be taken by mouth to be swallowed (11).

Data extraction

A proposal for the development of a medicine for children in a specific age range does not assure that the medicine will be available in a dosage form(s) that is (are) sufficiently adapted to the age of the child from the minimum to the maximum of this age range, that the excipients in the dosage form(s) are safe for all the proposed ages, or that the proposed strength(s) allow(s) the administration of all doses required (12, 13). Therefore, the following data were extracted by the same researcher for each of the included PIPs:

– administrative data: PIP-number, PIP-applicant, date of start of the procedure, date of final opinion/end of procedure.
– therapeutic area (EMA classification system) (3, 7).
– target age range (as defined by industry).

– pharmaceutical characteristics: active substance, dosage form(s) as listed in the PIP, strength(s) of (each of the) dosage form(s), excipients in each strength of a dosage form.
– aspects that are relevant to the practical use and/or acceptability of a paediatric medicine by health care professionals, caregivers or patients. Such aspects will be further referred to as usability aspects. Attention was put to the correct use of tablets and information was extracted on tablet size, tablet shape and the presence of break marks.

Data were extracted from the EMA website, its original source the proprietary PeDRA database or from the PIP assessment summary reports as downloaded from a second proprietary repository, the EMA Document Records and e-Archive Management database (DREAM). The extracted data comprised information from the PIP as submitted by industry at the start of the procedure (initial PIP) and as agreed with the EMA/PDCO at the end of the procedure (agreed PIP). All data were recorded and interpreted as outlined in Annex S1.

Data analysis

For each PIP, the target age range was categorized in the following groups: 0–5 months, 6–23 months, 2–5 years, 6–8 years, 9–11 years. In addition, data were categorized per type and subtype(s) of the dosage form(s) and the type(s) of the preparation(s). A separate category further referred to as solid-liquid was created for dosage forms that were manufactured as a solid dosage form, but administered to the child as a liquid dosage form e.g. dispersible tablets. An oral preparation was defined as a subtype of an oral dosage form with a particular strength/concentration and with a particular excipient composition; e.g. a PIP containing film-coated tablets 50 mg and chewable tablets 5, 10 and 20 mg included one type of dosage form (tablets), two subtypes (film-coated and chewable tablets) and four preparations (13).

Descriptive analyses were conducted to evaluate the changes between the initial and agreed PIPs with respect to the number, therapeutic area, target age range and pharmaceutical characteristics of the oral, paediatric medicines. The analysis of the pharmaceutical aspects was conducted pair wise per PIP and group wise for all PIPs. A change in a dosage form subtype was defined as the addition, deletion or replacement of a subtype or as a proposal for a defined subtype in cases where this information was initially lacking e.g. age-appropriate formulation into oral suspension.

Results

On 31 December 2011, the EMA/PDCO had agreed on 720 PIP applications and requests for a full waiver. A hundred fifty PIPs were included in this study (Annex S2, Annex S3).

Therapeutic area

The agreed PIPs related to 165 indications in 16 of the 21 EMA therapeutic areas (3, 7). A 137 (91%) PIPs related to one, 10 (7%) PIPs to two and 3 (2%) PIPs to three areas. The main areas were infectious diseases (n = 28 PIPs, 19%), endocrinology/gynaecology/fertility/metabolism (n = 24 PIPs, 16%), cardiovascular diseases (n = 21 PIPs, 14%), oncology (n = 20 PIPs, 13%) and neurology (n = 13 PIPs, 9%). These areas were not changed as a result of the EMA/PDCO review.

Target age range

The availability of authorised paediatric medicines on the European market largely varies with age with fewer medicines for younger children (14). In order to promote the availability of authorised paediatric medicines in especially the youngest age groups, special attention is warranted to the target age range of medicines proposed for future marketing. Sixty (40%) of the agreed PIPs included at least one oral dosage form for children 0–5 months compared to 140 (93%) PIPs for children 9–11 years (Figure 1).

As a result of the EMA/PDCO review, for 60 (40%) PIPs the lower age limit was extended to a younger age group, whereas for 6 (4%) PIPs it was set at an older age. For 2 (1%) PIPs the upper age limit was agreed at a younger age whereas for 3 (2%) PIPs it was set at an older age. Five (3%) PIPs were included for which initially a full waiver was requested i.e. these PIPs related to medicines for which industry had no initial intention to market a paediatric medicine. Nowadays,

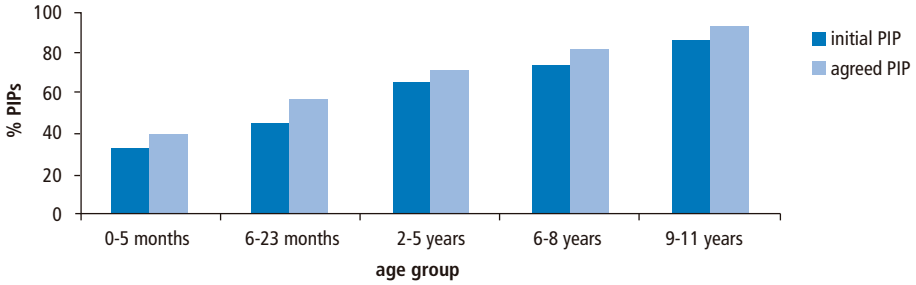

Figure 1 PIPs including at least one oral medicine for children 0–11 years

such waiver requests will be refused meaning industry has to submit a new PIP application.

Pharmaceutical characteristics: pairwise comparison

Eighty-eight (59%) of the agreed PIPs included one, 54 (36%) PIPs two and 8 (5%) PIPs three or more types of an oral dosage form. Following the EMA/PDCO review, for 13 (9%) PIPs for which initially no oral dosage form was proposed, such a form was agreed; for 8 (5%) PIPs a dosage form other than initially proposed was agreed; for 8 (5%) PIPs one or several dosage forms were added and for 8 (5%) PIPs one or several dosage forms were deleted.

As a result of the EMA/PDCO review, for 60 (40%) PIPs changes were implemented with respect to the subtype, strength and/or excipient composition of the paediatric medicine. For 44 (29%) PIPs changes were implemented with respect to the subtype of the initially proposed dosage form. For 38 (25%) PIPs the medicine could be given in a wider range of strengths than initially proposed. Comparing the same subtypes of a dosage form in the initial and agreed PIP only, for 14 (9%) PIPs the number of strengths was increased and for 12 (8%) PIPs a strength was proposed whereas it was not before. Sixteen (11%) PIPs were changed with respect to the excipient composition.

Pharmaceutical characteristics: group wise comparison

Information on the type(s) and subtype(s) of the dosage form(s) and preparations in the PIPs and the changes realized by the EMA/PDCO is provided in Table 1. Overall, the EMA/PDCO review led to a 6% increase in requirements for industry to market an oral paediatric dosage form and a more pronounced increase (11%) in requirements to market a specific oral preparation.

In the agreed PIPs, oral medicines for younger children were most commonly proposed as solid-liquid preparations (32% for children 0 – 5 months, 31% 6 – 23 months, 25% 2 – 5 years) and for older children as tablets (52% 6 – 8 years, 57% 9 – 11 years) (Figure 2).

Detailed information on a selection of excipients with a potential cause for concern and their alternatives is provided in Table 2. Propylene glycol, that may be relatively harmful for young children, was included in three preparations agreed for children 0 - 23 months (15–17). Only two of these preparations were proposed in the initial PIP. In all three preparations propylene glycol was included to dissolve the preservatives and/or active substance and the need for the inclusion of propyleneglycol was debated with the pharmaceutical company that submitted the PIP.

Table 1 Oral medicines in the Paediatric Investigation Plans (n = 150 PIPs); group wise comparison

	oral dosage forms		oral preparations*	
	initial PIP n (%)	agreed PIP n (%)	initial PIP n (%)	agreed PIP n (%)
all	207 (100)	220 (100)	387 (100)	431 (100)
tablets (all types)	72	82	183	218
uncoated, immediate release	14	14	30	31
(film-)coated, immediate release	46	52	117	146
modified release, prolonged release or gastro-resistant	8	8	17	19
orodispersible/lyophilisate	3	3	7	7
chewable	6	6	11	14
capsules	23	27	57	70
hard, immediate release	20	24	53	62
soft, immediate release	2	3	4	8
others	0	0	0	0
powders/granules	9	13	10	16
liquids	43	44	52	51
solution	25	24	29	27
suspension	14	11	16	12
unspecified liquids	4	9	7	11
solid-liquids	32	35	57	57
dispersible tablets	9	8	18	17
powder/granules for suspension	19	21	32	34
powder/granules for solution	6	6	6	6
others/unspecified	29	19	28	20

* A preparation is a subtype of a dosage form in a particular strength and with a particular excipient composition e.g. a PIP containing film-coated tablets 50 mg and chewable tablets 5, 10 and 20 mg represents one overall dosage form (tablets), two tablet subtype dosage forms (film-coated tablets and chewable tablets) and four preparations (film-coated tablets 50 mg, chewable tablets 5 mg, chewable tablets 10 mg, chewable tablets 20 mg).

The colourants tartrazine (E102), quinolone yellow (E104), sunset yellow (E110), carmoisine (E122), ponceau 4R (E124) and allura red (E129) were investigated because of their allergic potential. It is noted that, in 2007, these colourants were also associated with an increased risk on hyperactivity in children by McCann et al. (18). However, in 2008 the study was re-viewed and re-analysed by the European Food Safety Agency (EFSA). They concluded that the findings

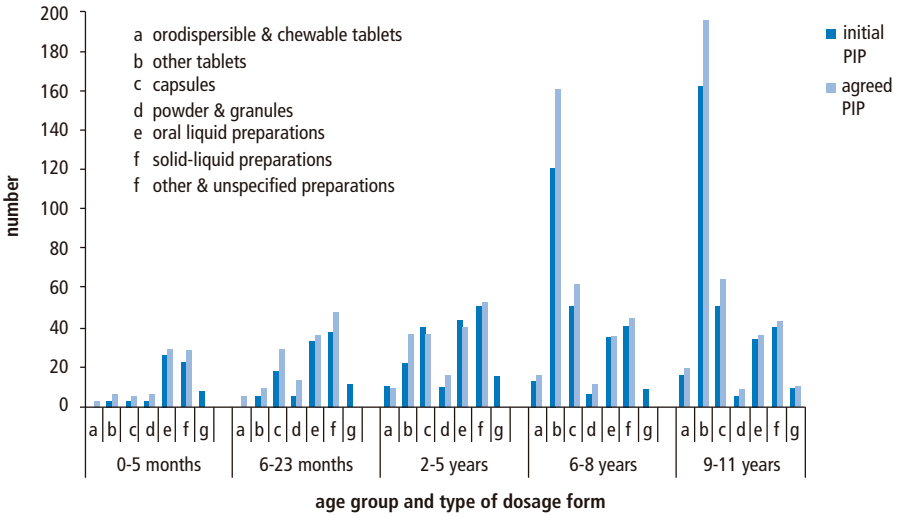

Figure 2 Oral preparations in the PIPs per target age group

could not be used as a basis to change the acceptable daily intake of any of these colourants (19). The colourants E110, E102, E122 and E124 were not included in any of the agreed PIPs; E104 was included in one preparation in one agreed PIP and E129 in two preparations in another PIP. Prior to the EMA/PDCO review these colourants were proposed in six preparations in three PIPs; E104 in an oral solution for children 2–11 years old, E110 in three film-coated tablets for children older than six years as well as in two oral solutions for children 2-11 years.

Usability

For children 2–5 years old, two agreed PIPs included each one small sized tablet (0–4 mm). Seven other PIPs included 17 medium sized tablets (5–9 mm) in a single strength/composition (4 uncoated, 6 film-coated, 5 modified release, 2 chewable in a single strength), whereas two of these seven PIPs also included 5 tablets in a single strength/composition sized 10 mm or larger (2 uncoated tablets, 2 modified release tablets and 1 chewable tablet). For six PIPs for which a tablet sized 5 mm or larger was agreed, there was no smaller tablet, oral liquid or other age-appropriate formulation required. Four of these PIPs were submitted in 2008; the other two in 2009 (Table 3).

Table 2 Excipients in the Paediatric Investigation Plans (n = 150); group wise comparison

		oral preparations* in the PIPs	
		initial PIP n (%)	agreed PIP n (%)
all preparations		387	431
preparations with excipient information		292 (100)	354 (100)
solvents	propylene glycol	17	14
	ethanol	7	8
preservatives	methylparahydroxybenzoate	5	4
	methyl/propylparahydroxybenzoate‡	9	11
	benzoates (e211)&	20	19
antioxidants	alpha-tocopherol	5	5
	butylhydroxyanisole (bha)	2	5
	butylated hydroxytoluene (bht)	3	2
	sodium phosphates	6	6
	potassium phosphates	2	2
colourants/opacifier	sunset yellow (e110)&	5	0
	tartrazine (e102)&	0	0
	carmoisine (e122)&	0	0
	ponceau 4r (e124)&	0	0
	quinoline yellow (e104)&	1	1
	allura red (e129)&	4	2
	iron oxide#	58	64
	opadry (any type)#	49	62
	titanium dioxide#	56	78
taste optimizers	sugars (incl. lactose)	107	117
	sugar alcohols	72	100
	sweeteners	27	44
	flavours	37	44

* a preparation is a subtype of a dosage form in a particular strength and with a particular excipient composition

‡ excipient that has raised special attention by regulators in recent years due to a non-confirmed safety signal

& studied by McCann et al. in the Southampton study and considered as potentially harmful [18]. The study conclusion was questioned by EFSA [19].

may be used as a safe(r) alternative to the colourants studied by McCann et al. [18].

Table 3 Tablet size and shape (n = 150 PIPs); group wise comparison children aged between 2 and 6 years.

	oral preparations in the PIPs					
	initial PIP n			agreed PIP n		
all preparations	193 (100)			210 (100)		
tablets* intended to be swallowed in their solid form	32			46		
immediate release	8			7		
film-coated	10			22		
modified release	4			8		
chewable	8			7		
oro-dispersible	2			2		
tablets* with information on size	11			24		
small/medium/large	*S*	*M*	*L*	*S*	*M*	*L*
immediate release	2	4	0	1	4	2
film-coated	1	1	0	1	6	0
modified release	0	3	0	0	5	2
chewable	0	0	0	0	2	1
oro-dispersible	0	0	0	0	0	0
tablets* with information on shape	16			25		
round/oval/specified others	*R*	*O*	*S*	*R*	*O*	*S*
immediate release	4	1	1	4	1	1
film-coated	2	0	1	3	5	0
modified release	3	0	0	5	2	0
chewable	3	1	0	3	1	0
oro-dispersible	0	0	0	0	0	0
tablets* with a break mark	3			9		
immediate release	1			2‡		
film-coated	0			5		
modified release	0			0		
chewable	0			0		
oro-dispersible	2			2		

* tablets counted as the number of oral preparations i.e. differentiated to excipient composition and strength. A small tablet was defined as 0-4 mm, medium sized 5-9 mm and large 10 mm or larger [21]. Oval tablets included those that were oblong or capsule shaped.

‡ related to the two tablets sized 10 mm or larger.

Discussion

On 31 December 2011, the EMA/PDCO had agreed with 150 PIPs including an oral medicine for children 0–11 years. The EMA/PDCO review resulted in requirements for the future marketing of paediatric medicines in a wider age range than initially proposed by the pharmaceutical companies and with an increased number of oral dosage forms and strengths. The review also resulted in an increase in information on the medicines' excipients composition and usability aspects.

The Paediatric Regulation covers medicines administered through all routes of administration for children between birth and 18 years of age (2). This study focused on oral medicines in order to allow an in-depth evaluation of their pharmaceutical characteristics. It was limited to children 0–11 years as older children can often be treated with the same oral medicines as adults. Although pharmaceutical characteristics of oral medicines for (pre-)term neonates require specific attention with respect to e.g. dosing volumes and compatibility with feeding tubes, all children 0–5 months were evaluated as a single group as essential dosing information was often not yet available in the PIP.

Changes in the target age range of a PIP as a result of the EMA/PDCO review often initiated a change in the (sub)types of the dosage forms and their characteristics. As the frequency of changes in the target age range hindered an age-specific evaluation of the achievements reached by the EMA/PDCO towards the pharmaceutical design of the proposed medicines, the pharmaceutical characteristics were evaluated per individual PIP as well as for all PIPs as a group.

The EMA's 5-year PIP evaluation report to the Commission indicated that pharmaceutical companies insufficiently justified the choice of the excipients in relation to age, maximum daily dose and the possibility to replace potentially harmful excipients with those that are generally considered safer (7). Our study showed that changes in the use of potentially harmful excipients were limited. This outcome does not contradict the above statement as the additional information that was requested by the EMA/PDCO may have justified the use of the proposed excipients on an overall positive benefit to risk evaluation of the medicine.

For three potentially harmful excipients their inclusion in oral medicines proposed for future marketing in children 0–11 years (PIPs) was compared to medicines currently authorised and commercially available for children between birth and 18 years of age (0–17 years) in the Netherlands (marketed products) (14). First,

propylparahydroxybenzoate was related to a single safety signal. Its use i.e. proposed inclusion in liquid or solid-liquid preparations in the PIPs (10%) was comparable to its use in marketed products (11%). Second, propylene glycol may cause hyperosmolarity and lactic acidosis in young children (15–17). Its use in oral medicines in the PIPs was less frequent (4%) than in marketed products (11%). Third, the use of ethanol in the PIPs was less extensive (2%) than in marketed products (12%).

The EMA PIP evaluation report identified that patient acceptability should require better attention by industry. This aspect was not evaluated in this study because in the early PIPs, the need for acceptability studies was often discussed with the pharmaceutical company during the assessment procedure, however, if such studies were considered necessary this was not clearly stated in the list of binding terms of the PIP agreement. Instead in this study, a surrogate of patient acceptability was included by the analysis of excipients generally considered improving taste (20). As a result of the EMA/PDCO review process, changes with respect to sugars, sugar alcohols, sweeteners and flavouring agents were generally uncommon.

In addition, a surrogate of child safety, patient usability and therewith patient acceptability was included by the analysis of tablet size. It is now increasingly accepted that small tablets may be applicable in young children (21–26). However, the use of medium sized tablets is still discouraged, whereas the use of large sized tablets is generally considered unacceptable because of swallowing difficulties and the risk of choking (21, 27). As a result of the EMA/PDCO review, companies had to provide more information on tablet size.

This study showed that tablets larger than 5 mm were agreed for children 2–5 years and tablets larger than 10 mm for children 6–11 years. Such tablets may be difficult to swallow by these age groups, unless they are taken as smaller parts (13,21). The majority of these "outsized" tablets were immediate release and film-coated tablets that may be broken, crushed or chewed, unless bio-availability or patient acceptability are affected (13). Industry can justify the absence of changes to either of these aspects by several means including a scientific discussion or additional studies during paediatric development. However, such studies were not included in the list of binding terms of the PIP agreement.

The EMA also stressed that industry had to pay better attention to the practical aspects of administration, dosing accuracy and dosing flexibility (7). Generally, smaller tablets may be easier to swallow and they may provide some dosing

flexibility. However, they may be more difficult to grip and hold by the patient hands. Tablets may also bear a break mark to ease swallowing or to adjust the dose (13). Although commonly applied, the use of break marks has not been universally accepted. First, the accuracy and ease of tablet breaking may have been demonstrated by companies, but not achieved by actual patients. This is because the accuracy and ease of breaking depend on hand function and the method of breaking (28). Second, the use of tablet splitters is often inaccurate (29). Tablets may also be broken, split or crushed and mixed with food or drinks to ease swallowing. However, these handlings may have an impact on the medicine's dosing accuracy, chemical stability and/or bio-availability (13). All this favours the development of lower dosed tablets or alternative dosage forms. As a result of the EMA/PDCO review, changes in the number of liquid preparations, solid-liquid preparations or tablets with a break mark were generally uncommon.

Rather than discussing pharmaceutical issues on their own merit as has been done in this study, Sam et al. considered that the pharmaceutical development of paediatric medicines should be based on a multidisciplinary approach including safety, efficacy, manufacturability and patient access (30). This opinion is consistent with the EMA/CHMP and EMA/PDCO overall benefit to risk approach for medicines entering the market (3, 31). Thus, the oral preparations in the agreed PIPs may nevertheless contain some undesirable aspects that are either unavoidable (e.g. ethanol to dissolve the active substances) or that are open to further product optimization (e.g. taste).

This study has some limitations. First, agreed PIPs may be modified on request of the pharmaceutical company when information gained during the development of the paediatric medicine would make it necessary to revise the agreed plan. As a consequence, the target age range and pharmaceutical characteristics of the preparations in the agreed PIPs may vary to those actually proposed at the time of marketing authorisation. In this study, the evaluation of PIP modifications was excluded because earlier PIPs would generally have undergone a higher number of modifications at 31 December 2011, hindering a fair comparison of all PIPs in the study period and putting overemphasis on earlier PIPs when industry and the EMA/PDCO were still learning (7).

Second, the summary report may not contain all details from the PIP that were relevant to this study. Moreover, the data in the summary report may have been interpreted slightly differently by the PDCO as intended by the EMA author or the pharmaceutical company, as the data were not fully reported. It was anticipated that the percentage error would be low.

Overall, this study confirms the likelihood that the children of Europe will gain better access to appropriately developed and authorised medicines. However, a group wise effect on the availability of medicines that are better tailored to children's needs could not (yet) be confirmed. In view of both the ongoing learning process by pharmaceutical companies and the EMA/PDCO as well as the anticipated increase in the number of medicines licensed with a PIP, it is recommended that this study will be repeated in 5 to 10 years.

Conclusions

The studies that were agreed by the EMA/PDCO to support the future marketing of a paediatric medicine were targeted at children of a younger age than those proposed by the pharmaceutical companies at the time of initial submission. For children 0–11 years old, there was also an increase in the number of oral dosage forms and an even larger increase in the number of oral dosage forms with a particular strength or composition. The changes to the pharmaceutical characteristics of these dosage forms were less profound.

Acknowledgements

The authors wish to acknowledge Dr. Siri Wang for her valuable comments.

The data on which this study is based can be obtained from the authors of from the EMA following a case by case approach. Please note that the EMA has published the agreed PIP opinions at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp&mid=WC0b01ac058001d129.

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Annex S1 Definitions and interpretation of information in the PIP

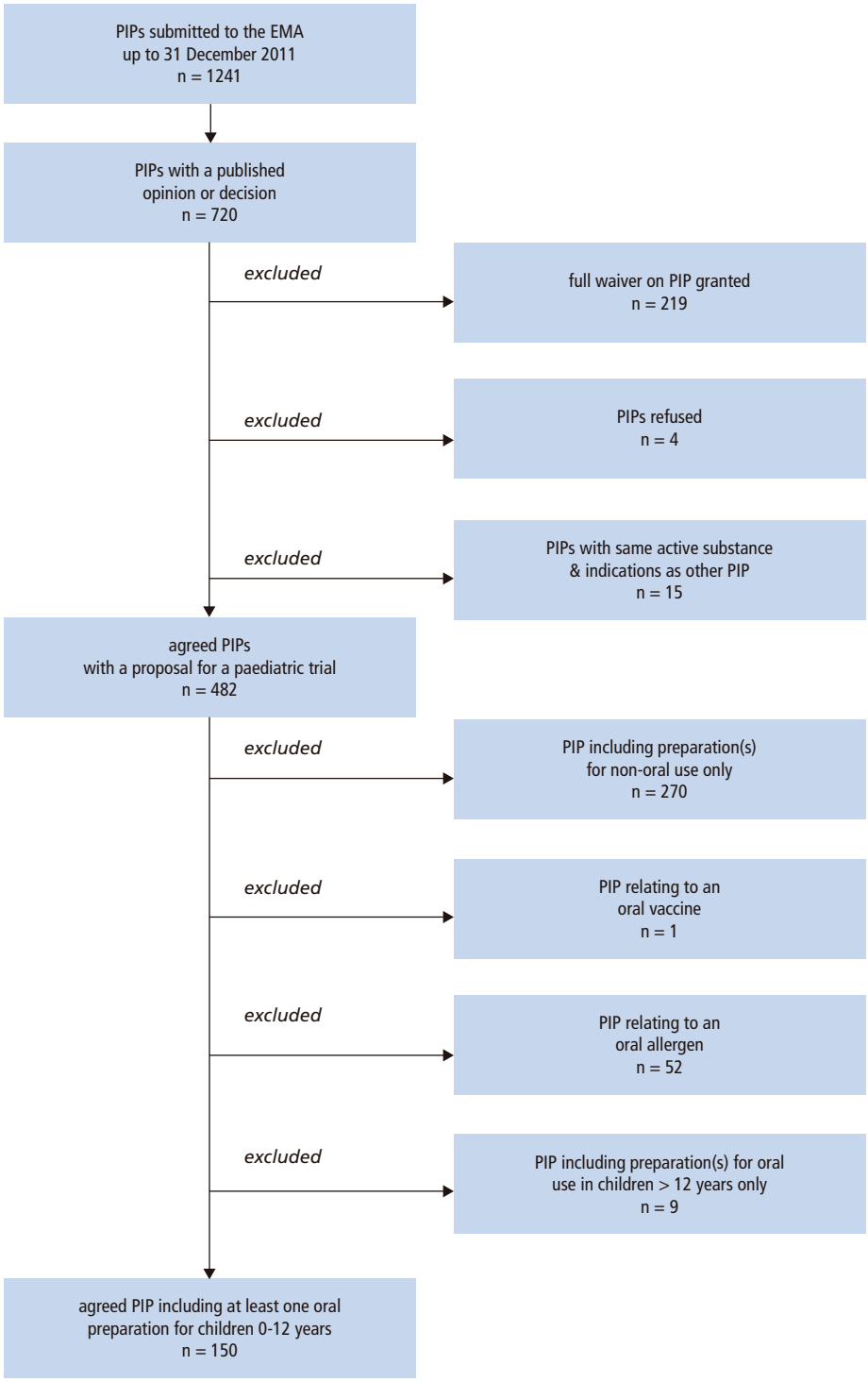
target age group	
1	When the selected target age group was specified in weight, then the corresponding age range was determined using the Dutch Denekamp scale (1). If there was a difference between boys and girls, then the youngest age was reported.
2	If the term "pubertal and post-pubertal boys" was mentioned, then an age of 11 years was reported as the lower age limit (2).
3	If the term "Tanner stage II" was mentioned, then a lower age limit of 9 years was reported for boys and 8 years for girls (3).
4	If the term "preterm children" was mentioned, then an age range of 0 to 28 days was reported.
5	If the term "preschool children" was mentioned, then an age range of 2 to 6 years was reported.
6	If the term "school children" was mentioned, then an age range of 6 to 12 years was reported.
7	If the term "older children" was mentioned, then an age range of 9 to 12 years was reported.
8	If the term "adolescents" was mentioned, then an age range of 12 to 18 years was reported.
9	PIPs only indicated for girls after menarche were excluded (the mean age of menarche is above 12 years of age (4)).
tablets	
1	Tablets were considered to be immediate release tablets, unless otherwise indicated.
2	Extended release, prolonged release and other modified release tablets may not be chewed or pulverized, unless otherwise indicated.
3	Small sized tablets (also referred to as mini-tablets) were considered to be smaller than 5 mm, unless otherwise indicated (5,6).
4	Medium sized tablets were considered to be 5 to 10 mm, unless otherwise indicated (5).
5	Large sized tablets were considered to be 10 to 15 mm, unless otherwise indicated (5).
6	Very large sized tablets were considered to be larger than 15 mm, unless otherwise indicated (5).
7	If the tablet size was not provided in the PIP, then it was considered that the tablets were large.
8	Coated tablets were considered to be neutral in taste, unless otherwise indicated.
capsules	
1	Capsules were considered to be immediate release hard gelatin capsules, unless otherwise indicated.
2	Immediate release capsules were considered to be suitable for opening, unless otherwise indicated.
3	Modified release capsules were not considered to be suitable for opening, unless otherwise indicated.
4	Capsules were considered to be neutral in taste, unless otherwise indicated.
5	Small sized capsules were considered to be smaller than capsule size 3, unless otherwise indicated.
6	Medium sized capsules were considered to be size 2 or 3, unless otherwise indicated.
7	Large sized capsules were considered to be capsules size 0 and 1, unless otherwise indicated.
8	Very large sized capsules were considered to be larger than size 0, unless otherwise indicated.
9	If the capsule size was not provided in the PIP, then the capsules were considered to be large.
multiparticulate formulations	
1	Pellets were considered as granules.
dosage forms	
1	Dosage forms which were proposed for children 12 - 18 years of age only were excluded.
2	If the applicant proposed several possible dosage forms from which eventually one would be chosen for marketing, then all proposed dosage forms were considered.

(continued)

Annex S1 (continued)

dosage forms and age	
1	Tablets smaller than 5 mm were considered to be for children from 2 years of age, unless otherwise indicated (5,6).
2	Tablets from 5 to 10 mm were considered to be for children from 6 years of age, unless otherwise indicated (5,6)
3	Tablets from 10 up to 15 mm were considered to be for children from 12 years of age, unless otherwise indicated(5).
4	Tablets from 15 mm were considered to be for adults from 18 years of age only, unless otherwise indicated (5).
5	Chewable tablets were considered to be for children from 2 years, unless otherwise indicated (7).
6	Orodispersible tablets were considered to be for children from 1 month, unless otherwise indicated (7).
7	Capsules smaller than size 3 that must be swallowed intact are considered to be for children from 6 years of age.
8	Capsules size 2 and 3 that must be swallowed intact are considered to be for children from 9 years of age.
9	Capsules size 0 and 1 that must be swallowed intact are considered to be for children from 12 years of age.
10	Capsules that may be opened prior to use in order to give their contents (powder, granules, liquid) as such are considered to be for children from 6 months.
11	Liquid preparations (solutions, suspensions, emulsions, drops) are considered to be for children from birth, unless otherwise indicated (8).
12	Powders, granules, pellets for solution, dispersion or suspension are considered to be for children from birth, unless otherwise indicated (8).
13	Powder, granules and pellets that are smaller than 2 mm and that are to be administered in their solid form are considered to be for children from 6 months, unless otherwise indicated (8).
excipients	
1	Trade-marketed coloring agents and flavorings were considered as a single excipient.
2	Printing ink was not considered as an excipient in this study.
3	The excipient composition of the capsule shell was not considered.
4	If the composition of a preparation was not provided in the summary report but it was clear from the summary report that the pharmaceutical information was identical to that of a licensed product, then the data were extracted from the product's SmPC at the EMA or MEB website.
8	If the applicant provided several possible options for one type of excipient (e.g. preservative, sweetening agent) of which one ultimately would be selected for the marketed product, then all proposed excipients were considered.
strength	
1	If a range of doses were proposed but no specific doses were mentioned, then the nature and pharmaceutical characteristics were only reported for the lower and upper limit of the range.
2	If no strength was provided, then the nature and pharmaceutical characteristics were considered as applicable to one strength only.
3	If the applicant proposed several strengths for one subtype of a dosage form and only provided the composition for some of these strengths, then the assumption was made that the same composition would apply to the strengths for which information was missing, unless it was indicated that a change in composition would be considered.
request on a full waiver	
1	If the applicant requested a full waiver and the PDCO refused this request, then no data were reported at day 0, unless the PIP was supplemented with the requested data.

Annex S2 PIP selection process



Annex S3 PIPs included in the data analysis

EMEA-000049-PIP01-07	EMEA-000290-PIP01-08	EMEA-000582-PIP01-09	EMEA-000636-PIP01-09
EMEA-000073-PIP01-07	EMEA-000317-PIP01-08	EMEA-000583-PIP01-09	EMEA-000716-PIP01-09
EMEA-000065-PIP01-07	EMEA-000300-PIP01-08	EMEA-000601-PIP01-09	EMEA-001003-PIP01-10
EMEA-000070-PIP01-07	EMEA-000008-PIP01-07	EMEA-000617-PIP01-09	EMEA-001057-PIP01-10
EMEA-000122-PIP01-07	EMEA-000325-PIP01-08	EMEA-000627-PIP01-09	EMEA-000455-PIP02-10
EMEA-000116-PIP01-07	EMEA-000331-PIP01-08	EMEA-000651-PIP01-09	EMEA-001098-PIP01-10
EMEA-000132-PIP01-07	EMEA-000332-PIP01-08	EMEA-000019-PIP06-09	EMEA-001103-PIP01-10
EMEA-000115-PIP01-07	EMEA- 000012-PIP01-07	EMEA-000694-PIP01-09	EMEA-000499-PIP02-10
EMEA-000114-PIP01-07	EMEA-000353-PIP01-08	EMEA-000709-PIP01-09	EMEA-000832-PIP01-10
EMEA-000154-PIP01-07	EMEA-000005-PIP01-07	EMEA-000718-PIP01-09	EMEA-000170-PIP02-10
EMEA-000144-PIP01-07	EMEA-000362-PIP01-08	EMEA-000720-PIP01-09	EMEA-000969-PIP01-10
EMEA-000052-PIP01-07	EMEA-000365-PIP01-08	EMEA-000727-PIP01-09	EMEA-000696-PIP02-10
EMEA-000041-PIP01-07	EMEA-000389-PIP01-08	EMEA-000734-PIP01-09	EMEA-001005-PIP01-10
EMEA-000078-PIP01-07	EMEA-000391-PIP01-08	EMEA-000745-PIP01-09	EMEA-000726-PIP01-09
EMEA-000170-PIP01-07	EMEA-000020-PIP01-07	EMEA-000339-PIP02-09	EMEA-000671-PIP01-09
EMEA-000183-PIP01-08	EMEA-000409-PIP01-08	EMEA-000774-PIP01-09	EMEA-001094-PIP01-10
EMEA-000191-PIP01-08	EMEA-000430-PIP01-08	EMEA-000777-PIP01-09	EMEA-000580-PIP01-09
EMEA-000196-PIP01-08	EMEA-000434-PIP01-08	EMEA-000780-PIP01-09	EMEA-000115-PIP02-09
EMEA-000200-PIP01-08	EMEA-000458-PIP01-08	EMEA-000804-PIP01-09	EMEA-000970-PIP01-10
EMEA-000153-PIP01-07	EMEA-000459-PIP01-08	EMEA-000822-PIP01-09	EMEA-000452-PIP02-10
EMEA-000019-PIP02-07	EMEA-000463-PIP01-08	EMEA-000828-PIP01-09	EMEA-000816-PIP02-10
EMEA-000018-PIP01-07	EMEA-000470-PIP01-08	EMEA-000235-PIP02-10	EMEA-000360-PIP01-08
EMEA-000038-PIP01-07	EMEA-000467-PIP01-08	EMEA-000463-PIP02-10	EMEA-000093-PIP02-10
EMEA-000093-PIP01-07	EMEA-000477-PIP01-08	EMEA-000637-PIP02-10	EMEA-001078-PIP01-10
EMEA-000087-PIP01-07	EMEA-000478-PIP01-08	EMEA-000912-PIP01-10	EMEA-000982-PIP01-10
EMEA-000221-PIP01-08	EMEA-000487-PIP01-08	EMEA-000927-PIP01-10	EMEA-000997-PIP01-10
EMEA-000222-PIP01-08	EMEA-000485-PIP01-08	EMEA-000972-PIP01-10	EMEA-001113-PIP01-10
EMEA-000081-PIP01-07	EMEA-000491-PIP01-08	EMEA-000425-PIP02-10	EMEA-001061-PIP01-10
EMEA-000022-PIP01-07	EMEA-000480-PIP01-08	EMEA-000084-PIP02-10	EMEA-000440-PIP01-08
EMEA-000237-PIP01-08	EMEA-000496-PIP01-08	EMEA-000597-PIP02-10	EMEA-000637-PIP01-09
EMEA-000245-PIP01-08	EMEA-000511-PIP01-08	EMEA-001030-PIP01-10	EMEA-000816-PIP01-09
EMEA-000062-PIP01-07	EMEA-000533-PIP01-08	EMEA-001034-PIP01-10	EMEA-000342-PIP01-08
EMEA-000054-PIP01-07	EMEA-000543-PIP01-09	EMEA-000007-PIP01-07	EMEA-000315-PIP01-08
EMEA-000274-PIP01-08	EMEA-000551-PIP01-09	EMEA-000788-PIP02-11	EMEA-000335-PIP01-08
EMEA-000055-PIP01-07	EMEA-000553-PIP01-09	EMEA-000100-PIP01-07	EMEA-000347-PIP01-08
EMEA-000279-PIP01-08	EMEA-000567-PIP01-09	EMEA-000063-PIP01-07	EMEA-000350-PIP01-08
EMEA-000283-PIP01-08	EMEA-000573-PIP01-09	EMEA-000498-PIP01-08	
EMEA-000288-PIP01-08	EMEA-000576-PIP01-09	EMEA-000625-PIP01-09	

The currently agreed opinions are published at h*ttp://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp&mid=WC0b01ac058001d129*

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Chapter 3

Pharmaceutical design of medicines for children

Chapter 3.1

Effects of the pharmaceutical technologic aspects of oral paediatric drugs on patient-related outcomes: a systematic literature review

Diana A. van Riet-Nales
Alfred F.A.M. Schobben
Toine C.G. Egberts
Carin M.A. Rademaker
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Abstract

Introduction

In view of high off-label and unauthorised prescription rates of medicines in children, the US Food and Drug Administration and the European Union have implemented legislative regulations for the pharmaceutical industry to increase the number of authorised paediatric medicines. However, the extent to which the effects of pharmaceutical technologic (design) aspects of oral paediatric medicines (e.g., taste, route and frequency of administration, user instructions) on patient-related outcomes (e.g., efficacy, tolerability, preference, adherence) can be based on clinical evidence from the available literature is unknown.

The objective of this study was to identify the nature, volume, and quality of comparative studies that assessed the effects of pharmaceutical design aspects of oral paediatric medicines on patient-related outcomes.

Methods

The Cochrane, Embase, and Medline databases were searched from their start through December 31, 2009. Studies were eligible for inclusion if they were published in English; included search terms for child, study design, medicine, formulation aspects, dosage form, routes of administration, patient acceptance, adherence, side effects and tolerability, and/or efficacy; reported on ≥10 children aged 0 to <18 years; and described the effects of ≥1 of 3 pharmaceutical design aspects of an oral paediatric medicine (formulation and dosage form; route and frequency of administration; and/or packaging, administration device, and user instruction) on ≥1 of 6 patient-related outcomes (clinical efficacy, side effects and tolerability, patient preference, patient acceptance, administration errors, and/or adherence). Studies were excluded if they concerned a non-allopathic medicine (i.e., homeopathic remedy, anthroposophic medicine, herbal supplement, or food supplement); related to asthma (because modern asthma treatment protocols strongly favour the use of medicines for inhalation above oral medication); and/or related to analgesics. The characteristics of each of the included publications were assessed with respect to pharmaceutical design aspect studied; patient-related outcomes studied; pharmacotherapeutic indication; year of publication; geographic location; number and age of the included subjects; and sponsorship by industry and/or author affiliation with the pharmaceutical industry. The electronic search was supplemented with a manual search of the cited references.

Results

Ninety-four publications were identified as eligible for inclusion. These publications reported on 176 assessments of the effects of ≥1 pharmaceutical design aspect on ≥1 patient-related outcome. Fifty-five percent of the studies were conducted in children aged 2 or 3 years, and 69% in children aged 4 or 5 years. Forty-three percent of the publications included ≥100 patients. Fifty-one percent of the studies were conducted in the United States or Canada, and 29% in Europe. Antibacterials for systemic use were the subject of 30% of the included publications. Two of the 94 publications were of appropriate methodological quality (Jadad score ≥4). Forty-nine percent of the studies were sponsored by the pharmaceutical industry or were written by ≥1 author affiliated with the industry. Sixty-eight percent of the included studies had Jadad scores of 0 or 1 (poor quality). The proportion of industry-sponsored or industry authorised studies with a Jadad score ≥2 or in ≥100 children was not significantly different from that of non–industry sponsored or -authored studies. The proportion of industry-sponsored or industry-authored studies conducted in the United States/Canada (n=48, 51%) was not significantly different from that of studies conducted elsewhere (n=46, 49%). The distribution of design aspects assessed in the included studies were formulation and dosage form, 48%; route and frequency of administration, 44%; and packaging, administration device, and user instruction, 8%. Seventy-six assessments included ≥100 patients. Twenty-one of these assessments addressed patient acceptance or patient preference; n=17 clinical efficacy; and n=14 side effects and tolerability.

Conclusions

This systematic review identified 94 articles on oral medicines for use in children between birth and 18 years of age, which reported on a total 176 assessments of the effects of 3 pharmaceutical design aspects (formulation and dosage form; route and frequency of administration; and packaging, administration device, and user instruction) on 6 patient-related outcomes (clinical efficacy, side effects and tolerability, patient preference, patient acceptance, administration errors, and adherence). Only 2 of the 94 publications were of appropriate methodological quality. These results suggest that the published clinical evidence to support pharmaceutical development programs is limited.

Introduction

The number of medicines that have been authorised by the US Food and Drug Administration (FDA) for use in children is limited compared with those approved for use in adults. In 2002, Balakrishnan et al. found that after 3 years of marketing in the United States, 27% of the new medical entities were authorised for use in children in a suitable formulation (1). In 2007, Young et al. showed that only 14% of the prescription entities in the Physicians' Desk Reference related to a suitable oral paediatric formulation (2). Consequently, high paediatric off-label and unlicensed prescription rates have been observed. For example, Shah et al. found that up to 78% of children discharged from a tertiary hospital were prescribed ≥1 medicine prescribed off-label during hospitalization (3). Also, Kumar et al. found that 45% of 61 parenteral medicines were prescribed off-label in neonates (4). To enhance the availability of approved paediatric medicines, the FDA has undertaken several regulations (FDA Modernization Act of 1997, Pediatric Research Equity Act of 2003, Best Pharmaceuticals for Children Act, and the FDA Amendments Act of 2007) over the past 10 years (5-8). On the basis of the evaluation of 79 medicines that were granted paediatric exclusivity, Grieve et al. concluded that the US regulation indeed resulted in the authorisation medicines for children (9). Also, Milne and Bruss reported that the initiative is generally considered as successful in the United States (10).

The limited availability of medicines approved for use in children between birth and 18 years of age and the consequential high rates of off-label and unlicensed prescribing of medicines in this patient population are a worldwide concern (11–19). In 2007, the European Union (EU) launched a Paediatric Regulation modelled on the FDA regulations (20). However, the effects of this Regulation on the availability of authorised, paediatric medicines in Europe are still awaited (21). Both the FDA and EU regulations require the pharmaceutical industry to develop and test a suitable formulation of the medicine for use in children. To promote this development, the European Medicines Agency (EMA) developed a "reflection paper", titled "Formulations of Choice for the Paediatric Population", to be used as a source of information while a more directive guideline is being drafted (22-23). The reflection paper indicates that the availability of published information is limited, suggesting that the extent to which paediatric pharmaceutical development programs can be based on clinical evidence from the available literature is not known. Thus, the aim of the present systematic literature review was to determine the nature, volume, and methodological quality of comparative studies that have assessed the effects of the pharmaceutical design aspects of oral paediatric medicines on patient-related outcomes.

Methods

Data sources

Indexed publications were identified by searching the Cochrane, EMBASE, and MEDLINE databases from their start through November 2008. Studies were included if they were published in English and included search terms for child, study design, medicine, formulation aspects, dosage form, routes of administration, patient acceptance, adherence, side effects and tolerability, and/or efficacy. The electronic search was complemented by a manual search of the references and was updated through December 31, 2009.

Study selection

Duplicate publications and those with a non-English title or abstract were manually omitted from the combined electronic search result by one of the authors (DVR). A 2-step review process of the title and abstract was conducted by the same reviewer. If there was the slightest doubt about the eligibility of a publication for inclusion, it remained to be included. The full texts of the potentially eligible publications were independently reviewed by 2 of the authors (DVR and CR). Differences were discussed until a consensus was reached. When necessary, consensus involved 2 additional authors (AS and TE).

Studies were included if they were comparative (e.g., randomized controlled clinical trials, cohort studies that compared subgroups); included ≥10 children (and where appropriate adolescents) aged between 0 and 18 years; assessed the effects of ≥1 oral (including sublingual, buccal, and antibiotic) medicine in children; and described the effects of ≥1 of 3 pharmaceutical design aspects (formulation and dosage form; route and frequency of administration; and/or packaging, administration device, and user instruction) on ≥1 of 6 patient-related outcomes (clinical efficacy, side effects and tolerability, patient preference, patient acceptance, administration errors, and/or adherence). Taste studies using an adult panel were excluded because adult preferences may not be representative of those of children (24). Studies were excluded if they concerned a non-allopathic medicine (i.e., homeopathic remedy, anthroposophic medicine, herbal supplement, or food supplement); related to asthma (because modern asthma treatment protocols strongly favour the use of medicines for inhalation over oral medication); related to analgesics; investigated the treatment of a disease or condition that was peculiar to an adult lifestyle (e.g., smoking, contraception); compared effects in adolescents even if aged below 18 years of age versus adults; had a main study topic that was user instruction involving personalized types of paediatric health care, such as the demonstration of study medicine administration or telephone reminders,

because such interventions cannot be linked to the design and presentation of the medicine product; and/or had results that did not allow the evaluation of the effect of the pharmaceutical design aspect on the patient-related outcome because this effect was likely to be due to a difference in the type of active substance as well. Studies of only pharmacodynamic or pharmacokinetic end points were excluded.

Definitions

Pharmaceutical Design Aspects: Formulation and dosage form included aspects related to the composition of the formulation (e.g., citrus vs peppermint flavoured) or to the selection of the dosage form (e.g., oral drops vs an oral powder to be sprinkled onto food) (25-26). Route and frequency of administration included aspects related to the route of administration (e.g., oral vs intranasal) or to the number of times a medicine was administered within a certain period of time (e.g., once vs twice daily) (27-28). Packaging, administration device, and user instruction included aspects related to the presentation of the medicine to the patient (e.g., packaging, the presence or absence of an administration device and/or written user instructions provided at the time of dispensation).

Patient-Related Outcomes: Clinical efficacy referred to the intended effects of the medicine. Side effects and tolerability referred to the unintended adverse events associated with the use of the medication. Patient preference referred to a choice between several medicines made by children or their caregivers, whereas patient acceptance referred to the willingness of children to receive the medicine, irrespective of whether this outcome was studied during the initiation, the execution, or the discontinuation of pharmacotherapy. Administration errors related to the ability of children or their caregivers to receive or administer, respectively, the medicine according to the user instructions when they had the intention to do so correctly. Adherence (compliance) was defined as the extent to which children and/or their caregivers used or administered the medicine as prescribed.

Data extraction

The following data were extracted from the included publications: study characteristics (year of publication, impact factor of the journal of publication, geographic location, sample size, objective, and the 5 characteristics used to calculate the Jadad score: randomized (yes = 1, no = 0), method of randomization appropriately described (yes = 1, no = –1), double blinding (yes = 1, no = 0), method of double blinding appropriately described (yes = 1, no = –1) and the description of withdrawals (described = 1, not described = 0)); characteristics of the included patients (age, number); treatment characteristics; Anatomical

Therapeutic Chemical (ATC) code for disease, active ingredient (yes = 1, no = 0); study sponsorship by the pharmaceutical industry and industry affiliation of the author(s) (yes = 1, no = 0); pharmaceutical aspects (medicine formulation as detailed as possible); characteristics of the included subjects (sick vs healthy, age number); and data on the 6 patient-related outcomes (29-30).

Data analysis

The electronic search results were imported into, and were further managed using, Endnote 9 (Thomson Reuters, New York, New York). Data from the included studies were summarised and analysed using Excel 2007 (Microsoft Corporation, Redmond, Washington).

Results

Study selection

In November 2008, the electronic search identified 2074 publications that were potentially eligible for inclusion. A total of 2005 publications were excluded, most of which did not report on an oral medicine or because the assessment of the effects of the pharmaceutical design aspect on patient-related outcomes was ambiguous. The 69 remaining publications included 1492 references. Of these, 21 were eligible for inclusion. An updated search for papers published through December 31, 2009, identified 4 additional publications, resulting in 94 publications included for data extraction (Figure 1).

Characteristics of the included publications

The characteristics of the 94 included studies are described in Table 1 (24–28,31–119). Fifty-two of the studies (55%) were conducted in children aged 2 or 3 years, and 65 (69%), in children aged 4 or 5 years. Forty-eight (51%) of the studies were conducted in the United States/Canada, and 27 (29%), in Europe. Antibacterials for systemic use were the subject of 28 of the included publications (30%). Medicines used to treat other types of diseases (e.g., psycholeptics, psychoanaleptics) were emerging when comparing the number of publications since 2000 with those published earlier (Figure 2).

Sixty-four (68%) of the included studies had a Jadad score of 0 or 1 (poor quality). The proportion of studies published in 2000 or later with a Jadad score ≥2 was significantly greater than those published before 2000 (P = 0.006), suggesting a general improvement in the quality of methodology over time. The studies published in 2000 or later were not more often conducted in ≥100 children. The first study of patient preference was published in 1990, and 14 of the 23 studies

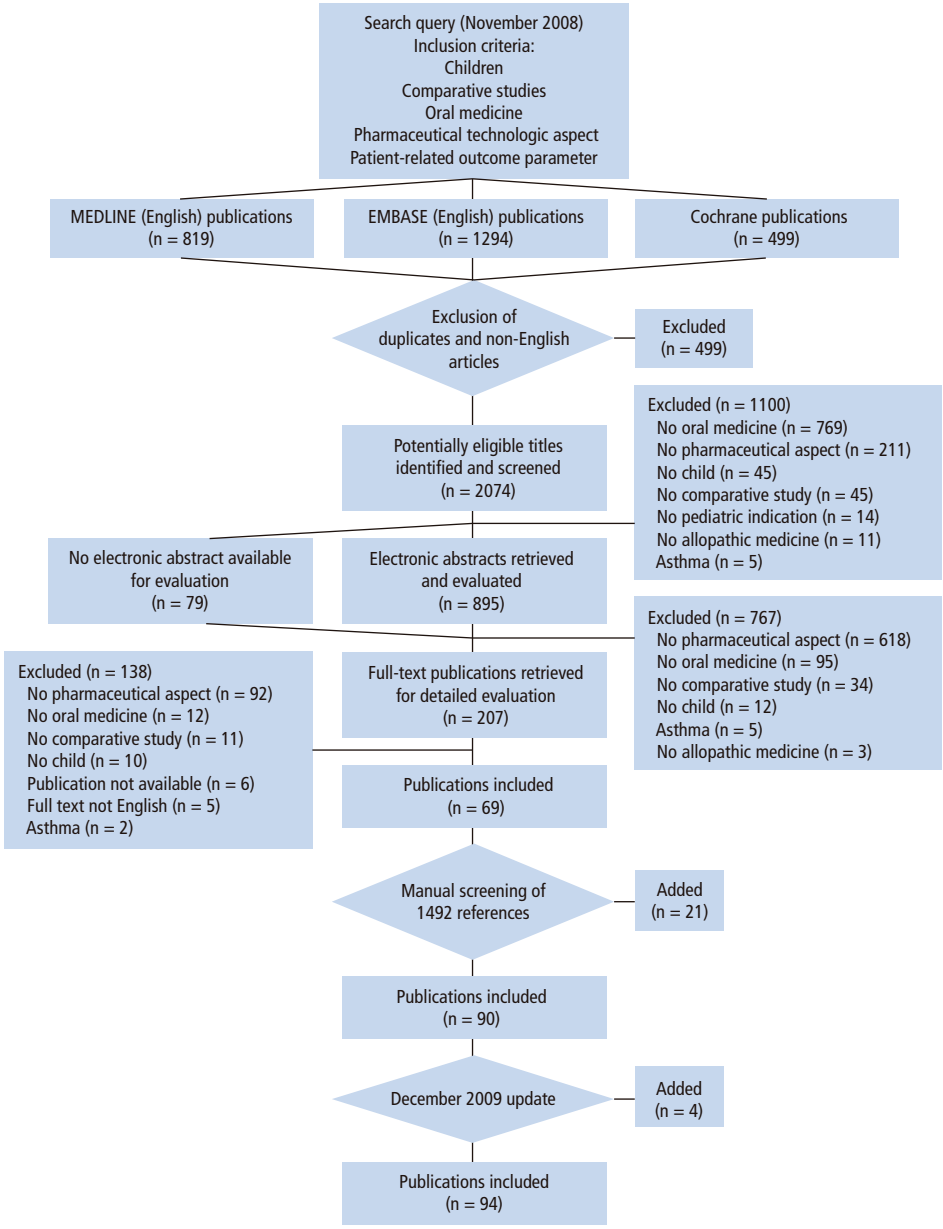

Figure 1 Literature search results

of patient preference (61%) were published in 2000 or later. This finding shows that this patient-related outcome parameter is gaining importance. Forty-six of the included studies (49%) were sponsored by the pharmaceutical industry or were authored by someone affiliated with the industry. The proportion of industry-sponsored or industry-authored studies with a Jadad score of 0 or 1 was

Table 1 Characteristics of the included publications (24-28, 31-119)

	pharmaceutical design aspect			
	formulation and dosage form n (%)	route and frequency of administration n (%)	packaging, administration device, use instruction n (%)	all studies n (%)
number of studies	51 (100%)	36 (100%)	9 (100%)	94† (100%)
STUDY CHARACTERISTICS				
year of publication				
1966 –1989	7 (14)	3 (8)	2 (22)	12 (13)
1990 –1999	16 (31)	11 (31)	1 (11)	26 (28)
2000 – 2009	28 (55)	22 (61)	6 (67)	56 (60)
journal impact factor				
0 – <1	12 (24)	3 (8)	1 (11)	16 (17)
1 – <5	31 (63)	28 (78)	5 (56)	63 (67)
≥5	2 (4)	2 (6)	0	4 (4)
unknown	5 (10)	3 (8)	3 (33)	11 (12)
geographical location‡				
United States/Canada	30 (59)	15 (42)	4 (44)	48 (51)
Europe	15 (29)	11 (31)	1 (11)	27 (29)
Africa	2 (4)	5 (14)	4 (44)	10 (11)
other	4 (8)	5 (14)	0	9 (10)
sample size				
10 –49	14 (27)	12 (33)	1 (11)	27 (29)
50 –99	17 (33)	8 (22)	3 (33)	27 (29)
100 –499	19 (37)	12 (33)	4 (44)	34 (36)
≥500	1 (2)	4 (11)	1 (11)	6 (6)
pharmaceutical design aspect as primary objective	45 (88)	32 (89)	8 (89)	83 (88)
quality (Jadad score)				
0 or 1	34 (67)	24 (67)	8 (89)	64 (68)
2 or 3	15 (29)	12 (33)	1 (11)	28 (30)
4 or 5	2 (4)	0	0	2 (2)
funded by pharmaceutical industry or author affiliated to industry	27 (53)	18 (50)	2 (22)	46 (49)

(continued)

Table 1 (continued)

	pharmaceutical design aspect			
	formulation and dosage form n (%)	route and frequency of administration n (%)	packaging, administration device, use instruction n (%)	all studies n (%)
PATIENT CHARACTERISTICS				
population				
patients	38 (75)	36 (100)	9 (100)	81 (86)
healthy volunteers	13 (25)	0	0	13 (14)
age group[‡]				
< 1 month	1 (2)	1 (3)	1 (11)	3 (3)
1 month – <23 months	19 (37)	18 (50)	9 (100)	44 (47)
2 –3 years	24 (47)	18 (50)	7 (88)	47 (52)
4 –5 years	42 (84)	12 (35)	7 (88)	60 (67)
6 –8 years	44 (88)	10 (29)	2 (25)	62 (69)
9 –11 years	26 (52)	9 (10)	2 (25)	49 (54)
12 –17 years	11 (22)	11 (26)	0	22 (24)
unknown	1 (2)	0	0	1 (1)
treatment (ATC[#]**)**				
J01 (antibacterials for systemic use)	20 (39)	7 (19)	2 (22)	28 (30)
N05 (psycholeptics)	6 (12)	8 (22)	0	13 (14)
N06 (psychoanaleptics)	1 (2)	9 (25)	0	10 (11)
other[$]	24 (47)	12 (33)	6 (78)	43 (46)

* percentage may not total 100 due to rounding
† two studies assessed >1 pharmaceutical design aspect
‡ some studies assessed > 1 age group or geographic location
$ other ATCs with <5 studies per ATC
# ATC = Anatomical Therapeutic Chemical classification code

not significantly different from that of the non– industry-sponsored studies, and the proportion of studies in ≥100 children was also not significantly different. The proportion of industry-sponsored or industry authorised studies conducted in the United States/Canada was not significantly different from the proportion conducted elsewhere.

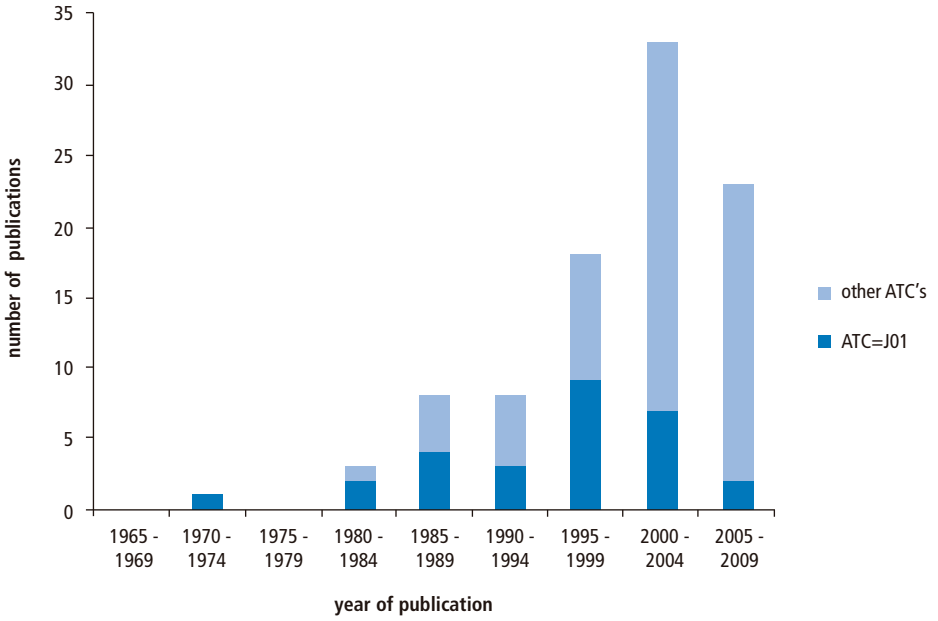

Figure 2 Included publications (n=94), total and related to antibacterials for systemic use (ATC=J01)
* ATC=Anatomical Therapeutic Chemical classification code

Assessment of the effects of pharmaceutical design aspects on patient-related outcomes

The 94 publications included a total of 176 assessments of the effects of ≥1 pharmaceutical design aspect on ≥1 patient-related outcome. Eighty-five of the assessments (48%) analysed formulation and dosage form; 77 (44%) analysed route and frequency of administration; and 14 (8%) analysed packaging, administration device, and user instruction.

Forty-four of the assessments (25%) addressed patient acceptance; 41 (23%) analysed clinical efficacy; and 23 (13%) analysed patient preference. Side effects and tolerability, and administration errors, both of which related to tolerability, were addressed in 30 (17%) and 6 (3%) of the assessments, respectively.

The main patient-related outcome parameters differed substantially between the 3 categories of pharmaceutical aspects. In studies that investigated formulation and dosage form, the most common outcomes were patient acceptance (n = 38 of all assessments, 22%) and patient preference (n = 19 of all assessments, 11%), whereas clinical efficacy, side effects and tolerability, and administration errors were each analysed in ≤5% of the assessments. In contrast, route and frequency of administration, patient acceptance, and patient preference

each were analysed in ≤5% of the assessments, whereas the most common outcomes were clinical efficacy (n = 31 of all assessments, 18%), side effects and tolerability (n = 22 of all assessments, 13%), and adherence (n = 15 of all assessments, 9%).

Six studies assessed administration errors as the outcome parameter, 5 of which (83%) studied packaging, administration device, and user instruction (Table 2). Seventy-six assessments included ≥100 patients. Twenty-one of these assessments with a large sample size (28%) addressed patient acceptance or patient preference; 17 (22%), clinical efficacy; and 14 (18%), side effects and tolerability.

The proportions of studies by type of pharmaceutical design aspects studied did not significantly differ between studies from the United States/Canada and those from Europe.

Twenty-five (14%) of the studies of the effects of formulation and dosage form on patient preference or patient acceptance were industry sponsored or were authored by someone affiliated with the industry. Sixteen studies (9%) of the effects of route and frequency of administration on clinical efficacy or side effects and tolerability were industry sponsored or industry authored.

Table 2 Impact of pharmaceutical design aspects on patient-related outcome parameters (24-28, 31-119)

	pharmaceutical design aspect			
	formulation and dosage form n (%)	route and frequency of administration n (%)	packaging, administration device and user instruction n (%)	all assessments* n (%)
number of studies	85	77	14	176
patient related outcome parameter				
patient acceptance	38 (45)	5 (6)	1 (7)	44 (25)
patient preference	19 (22)	4 (5)	0	33 (13)
adherence	11 (13)	15 (19)	6 (43)	32 (18)
clinical efficacy	8 (9)	31 (40)	2 (14)	41 (23)
side effects and tolerability	8 (9)	22 (29)	0	31 (17)
administration errors	1 (1)	0	5 (36)	6 (3)

* two investigations assessed > 1 pharmaceutical design aspect

Discussion

The literature search identified 94 papers that reported on a total of 176 assessments of the effects of pharmaceutical design aspects of oral medicines for use in children between birth and 18 years of age on patient-related outcomes.

The number of indexed publications has increased over the past 15 years. In this assessment, most of the studies published between 2000 and December 31, 2009, were not conducted within the scope of applications for a marketing authorisation (variation) for a paediatric medicine.

Eighty-five (90%) of the included studies were conducted in children aged 2 to 12 years. The lack of clinical trials in neonates and infants aged <2 years might be explained by the limited market potential of medicines in this population (10). The fact that studies were excluded from this review that compared the effects in adolescents below 18 years of age with those of adults might account for the low number of studies in older children as identified in this literature search. The proportion of the assessments in ≥100 patients versus all sample sizes should be considered with particular care. The number of assessments in some of the categories was small, and the interpretation of the number of patients in a particular study should take statistical considerations into account. However, because tolerability studies generally require large sample sizes, it was expected that larger sample sizes would have been found in the tolerability studies identified, but this was not the case.

Only 2 studies yielded Jadad scores of 4 or 5 (good quality). To a certain extent, the lower Jadad scores found in the studies in this review might be explained by the inclusion of some comparative trials that were not randomized controlled trials and by the use of single blinding rather than double blinding. In pharmaceutical development studies, double blinding might not be possible (e.g., preference for the oral over the rectal route of administration). In others, double blinding using a double-dummy technique might be possible. However, children are unlikely to accept the repeated administration of paediatric medicines required in the double-dummy design, and the authors question whether the additional burden of repeated administration in a child is always justified. Thus, there is a need for an appropriate instrument for the measurement of the methodological quality of paediatric pharmaceutical development studies (22).

To differentiate areas of interest in pharmaceutical product development, 3 mutually exclusive categories of pharmaceutical design aspects and 6 patient related outcome parameters were defined and assessed. Based on the findings

from this review, side effects and tolerability and administration errors have received limited attention in the published literature. Thus, the idea that the lack of child-friendly formulations puts children at increased risk seems to be based on common knowledge and assumptions rather than on sound scientific evidence in the indexed literature (10).

One may question the generalizability of the data because uniform definitions of pharmaceutical aspects and patient-related outcomes are lacking. The authors believe that generalizability should be considered for data on (1) the route of administration (because the impact of the route of administration will normally predominate over the impact of any differences in the other pharmaceutical aspects of the medicine); (2) frequency of administration (because the impact of this aspect will not vary with the type of other pharmaceutical aspects); and (3) administration devices (because the impact of the type of the device e.g., spoon, oral syringe will normally predominate over the particular device characteristics e.g., the shape of the spoon used to administer the medicine). However, generalizability of data on formulation-specific properties requires particular caution and may be risky. For example, taste might refer not only to the taste of the active substance but also to the concentration of the active substance (in liquid medicines), the particle size of the active substance (in solid medicines), and/or the inclusion of taste maskers.

This study had some limitations. The results should be considered within the constraints of the inclusion and exclusion criteria. Thus, the study related to oral medicines, including oral vaccines and oral antibiotics. Studies that were not published in English or that were published in non-indexed practice journals, and data from unpublished work, were not included in this review. Following the approach of the ICH tripartite (European Union, USA, Japan) Q8(R2) "Guideline on Pharmaceutical Development", this review was limited to data from comparative studies. Nonetheless, a few non-comparative studies, such as the study by Thomson et al. on the acceptability of small tablets by young children, are relevant to paediatric medicine development because they have assessed an area of pharmaceutical-formulation development or have made implicit comparisons between medicines for use in children and adolescents (120-121).

This review also excluded studies of oral medicines for asthma and analgesia. Studies were excluded from this review if they compared the effects of pharmaceutical design aspects in adolescents even if aged below 18 years versus adults because of the differences across countries in the age at which a person is considered an adult (range 16–21 years) and the time restrictions

of this review. A review of such studies is left for further research. Studies in patients with conditions that are peculiar to an adult lifestyle (e.g., smoking, contraception) were excluded because adult medicines were considered suitable for use in children who followed an adult lifestyle. The categorization of the pharmaceutical aspects and the selection of the patient outcomes played a key role in the data analysis. However, it is unlikely that divergent methodologies would have altered the main conclusions of this review.

There was a lack of clear definitions of the patient related outcomes in the published literature, thereby calling for a taxonomy to contribute to the quality of the review and to facilitate the interpretation and translation of the findings by stakeholders (e.g., the pharmaceutical industry, hospital or community pharmacists, academia, regulators). Urquhart and Vrijens defined 3 phases in ambulatory pharmacotherapy: patient acceptance (of the treatment plan), execution (of the medicine regimen), and discontinuation (of dosing). Although adherence was used by Urquhart and Vrijens as a blanket term, in some cases, a child might have been reminded to take the medicine, or might have taken the medicine only because of parental enforcement (122). Thus, the definition of adherence used by Urquhart and Vrijens could not be adopted in this review, further emphasizing the need for a taxonomy suitable to paediatric medicine research.

Based on the findings from the literature search, information on the development of oral medicines for use in children between birth and 18 years of age is not extensive. To enable pharmaceutical development programs to be based on clinical evidence and to avoid duplication of research in unpublished studies, stakeholders are encouraged to enrich the published literature with relevant data. The authors also encourage the improvement of the published literature on the development of paediatric medicines in the form of a global database. Such a database might prevent the repetition of essentially similar research in children, thereby promoting research in the neglected areas of the pharmaceutical development of paediatric medicines.

Conclusions

This systematic review identified 94 articles on oral paediatric medicines, which included a total of 176 assessments of the effects of pharmaceutical design aspects (formulation and dosage form, route and frequency of administration, and packaging, administration device, and user instruction) on clinical efficacy, side effects and tolerability, preference or acceptance, administration errors, and

adherence. Only 2 of the 94 publications were of appropriate methodological quality. These results suggest that published clinical evidence to support pharmaceutical development programs is limited.

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Chapter 3.2

Acceptability of different oral formulations in infants and preschool children

Diana A. van Riet-Nales
Barbara J. de Neef
Alfred F.A.M. Schobben
José Ferreira
Toine C.G. Egberts
Carin M.A. Rademaker

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Abstract

Introduction

Liquid medicines are easy to swallow. However, they may have disadvantages, such as a bad taste or refrigerated storage conditions. These disadvantages may be avoided by the use of oral solid medicines, such as powders or tablets.
The aim of this study was to investigate the acceptability of and preference among four oral formulations in domiciliary infants and preschool children in The Netherlands.

Methods

Parents administered four oral placebo dosage forms that were aimed at a neutral taste, at home, to their child (1–4 years of age) twice on one day following a randomised cross-over design: small (4 mm) tablet, powder, suspension and syrup. They were asked to report the child's acceptability by a score on a 10 cm visual analogue scale (VAS score) and by the result of the intake. At the end of the study, they were asked to report the preference of the child and themselves.

Results

183 children were included and 148 children were evaluated. The data revealed a period/cross-over effect. The estimate of the mean VAS score was significantly higher for the tablet than for the suspension (tablet 9.39/9.01; powder 8.84/8.20; suspension 8.26/7.90; syrup 8.35/8.19; data day 1/all days). The estimate of the mean number of intakes fully swallowed was significantly higher for the tablet than for the other formulations (all p values <0.05). Children and parents preferred the tablet and syrup over the suspension and the suspension over the powder (all p values <0.05).

Conclusions

All formulations were well accepted. The tablets were the best accepted formulation; the tablets and syrup the most preferred.

Trial Registration number

ISRCTN63138435.

Introduction

For decades, oral liquid dosage forms, such as syrups and suspensions, have been considered as the favourable type of dosage form in which to administer medicines to young children (1, 2). However, oral liquid medicines may have disadvantages, such as a bad taste, portability problems or refrigerated storage conditions (3–6). Therefore, WHO currently favours that young children, particularly in developing countries, be treated with oral solid medicines (7).

Oral liquid medicines are more commonly available for use in infants and preschool children than oral solid (flexible) medicines, such as powders or orodispersible tablets (8). Small-sized tablets, also referred to as mini-tablets, have been identified as a new type of oral solid dosage form in which to administer medicines to young children. However, only few of such tablets have been authorised for children below 4 years of age (3, 6, 9–11). Nevertheless, small tablets have been widely used in this age group as food supplements, for example, 4 mm sodium fluoride tablets for caries prevention, or 4 mm vitamin AD tablets (12–16).

The selection of an oral dosage form and the pharmaceutical aspects of the formulation, such as the palatability of an oral suspension or the size of a tablet, are important factors in the overall acceptability of an oral paediatric medicine (6, 10). As adequate child and parent acceptability are prerequisites for good medicine adherence, paediatric treatment outcomes may be enhanced by a careful selection of the formulation including the type of the dosage form. Therefore, the aim of this study was to investigate the acceptability of and preference among four oral formulations in domiciliary, infants and preschool children in The Netherlands.

Methods

Study design

A randomised cross-over trial was performed in six Dutch preschool preventive healthcare clinics in Beusichem, Beesd, Culemborg (2 clinics), Maurik and Zaltbommel. Ethical approval was waived by the Central Committee on Research involving human subjects (CCMO) on basis of the Dutch Medical Research Involving Human Subjects Act (WMO). Approval was obtained from the Institutional Review Board of the Utrecht Institute for Pharmaceutical Sciences (UIPS).

Setting and study participation

The aim of the preschool preventive healthcare clinics is to monitor the mental and physical development of children between 0 and 4 years of age, to advise parents on child-raising issues and to vaccinate children (17). The response rate to the invitation for an appointment is over 99% of children below 2 years of age and over 90% of children between 2 and 4 years of age (18).

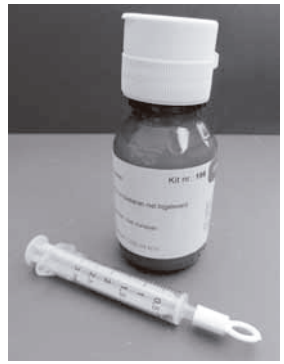
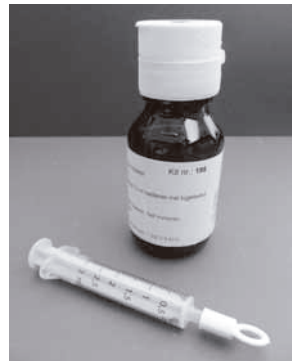
Parents were verbally approached by one of four recruiters (a licensed pharmacist and three graduate students) when attending the clinics in 2011. Parents had either received the written information by mail 2 weeks before the appointment, or this information was handed to them at the end of the face-to-face contact. Parents were asked or called by phone for written informed consent and study participation at least 2 weeks after the written information was provided. The results of the selection process were systematically gathered (date when verbally approached, healthcare clinic, recruiter, date of birth, child gender, willingness to participate, reason for exclusion if mentioned voluntarily).

Children were eligible for inclusion in this study if they were between 1 and 4 years of age and if their parents had mastery of the Dutch language. Exclusion criteria were: (1) significant developmental delay; (2) having swallowing difficulties, an eating disorder or a chronic condition requiring oral medication; (3) hypersensitive to lactose, having cow-milk allergy or having an allergy of unknown origin; (4) a member of staff of the preventive healthcare clinic considered that study participation was inappropriate in view of the family situation. During the study, the criterion added was (5) according to the parents' observation, children should not feel ill when the formulations were actually given.

Intervention

Parents were asked to administer four oral placebo formulations to their child at home during normal family routines. They were asked to administer the formulations (4 mm tablet, powder, suspension and syrup) in the same way they would administer a prescribed medicine, however, without any physical or physiological pressure (Table 1). In conformity with common Dutch dispensing procedures for immediate release formulations, chewing and co-administration/mixing with food or drinks was neither recommended nor forbidden. Parents were instructed to administer the formulations on four consecutive days; however, they were allowed to skip a day if necessary. In order to study any period or carry-over effect, the formulations should be given in a predefined, randomised order, and each formulation twice on 1 day only. The formulations were

Table 1 Characteristics of four different oral formulations

	tablet	powder	suspension	syrup
picture				
appearance	round biconvex white tablets	freely flowing powder	homogeneous and opaque liquid after shaking	clear solution
dosing recommendation	1 tablet of 4-mm (43.0 mg)	250 mg powder (1 sachet)	2.5 ml	2.5 ml
taste	aimed at neutral	aimed at neutral	aimed at neutral	aimed at neutral
dosing device	not applicable	not applicable (spoon is an example to show the powder and is not dispensed to the participant)	3-ml oral syringe with 0.1 ml graduation. the syringe can be attached to the cap of the container.	3-ml oral syringe with 0.1 ml graduation. the syringe can be attached to the cap of the container.
composition	lactose monohydrate 34.69 g maydis amylum 6.46 g maydis amylum pregelificatum 1.42 g magnesium stearate 0.43 g	lactose monohydrate 203.7 mg maydis amylum 38.0 mg maydis amylum pregelificatum 8.3 mg total 250 mg	methylparahydroxybenzoate 46.0 mg aluminiummagnesiumsilicate 484.4 mg carboxymethylcellulose 484.5 mg citric acid 36.3 mg sucrose 12.74 g purified water 37.95 g microcrystalline cellulosis 2.50 g purified water ad 50 ml	methylparahydroxybenzoate 63.1 mg propylparahydroxybenzoate 10.0 mg citric acid monohydrate 37.5 mg saccharose 8.28 g purified water ad 50 ml

specifically developed and manufactured for this study by ACE Pharmaceuticals, The Netherlands.

Outcomes

Acceptability after each administration: (1) visual analogue scale (VAS) score for child acceptability according to the parents' observation [(0–10 cm VAS scale; from 0 'heel erg vervelend' (very unpleasant/bothersome etc.), to 10 'helemaal niet vervelend' (not at all unpleasant/bothersome etc.)] and (2) result of the intake according to the parents' observation (full dose swallowed, parts of the dose swallowed, dose not swallowed). If parents indicated that they had forgotten to administer a formulation to the child, then the absent VAS scores and absent values for the result of the intake were considered 'missing values'. If parents indicated that they had not administered a formulation to the child for any other reason, then the absent VAS scores were set at '0' and the absent results of the intake at 'not swallowed'.

Preference at the end of the study: (1) the single most preferred formulation of the child according to the parents' observation; (2) the single most preferred formulation of the parents for the child.

Others: Questions concerning other family characteristics and the exact manner the formulations were administered to the child.

Sample size

The sample size for acceptability was calculated on basis of a design aimed at detecting a specified difference between the VAS scores of two treatments in a cross-over trial involving four oral formulations on four different days (19). The power was set at 0.8 and the significance level at 0.05. Due to a lack of relevant data from the literature on the acceptability of oral formulations in (young) children, the sample size calculations were based on plausible values for the mean difference and standard deviations of the VAS scores. The sample size for preference was calculated on basis of a statistical design where parents were asked to identify the single most preferred formulation. The same approach was applied as for the calculation of the acceptability. The sample size was set at 150 evaluable children, which would, in most cases, allow a maximum difference of 2 for acceptability and 0.2 for preference to be detected.

Randomisation

The study was randomised for the order of administration of the formulations by a RIVM employee who was not involved in this study. Randomisation was conducted with a random sequence obtained from http://www.random.org.

The same sequence was applied to each block of 24 children. Siblings were allocated to the same order to avoid mistakes.

Data analysis

The following analyses were conducted: (1) assessment of systematic differences between the two single VAS scores for a particular formulation (paired Z tests); (2) in case of no significant differences, calculation of the mean VAS scores per child and formulation; (3) evaluation of a potential cross-over or period effect (Z test on the order of the best accepted formulation), in case of such an effect analysis 3 and 4 were done for the administrations of the first formulation only (day 1) and for all data (all 4 days); (4) estimation of the mean VAS score per formulation and computation of the corresponding 95% confidence intervals (CIs) (Z statistics); (5) testing of differences between the mean VAS scores of two different formulations (Wilcoxon and Mann–Whitney tests); (6) estimation of the mean number of intakes that were fully swallowed by a child per formulation and computation of the corresponding 95% CIs (Z statistics); (7) computation of estimates and associated 95% CIs of the probabilities that the child and parents preferred a particular formulation, and comparison between the four probabilities (Z tests). All statistics were conducted applying Excel 2007 (Microsoft, Redmond, Washington), R V.2.13 (R development core team).

Results

Setting and study participation

Between February and July 2011, 421 children from 373 families were verbally approached; 405 children from 358 families were eligible for inclusion if their parents would pass the language check. Informed consent was obtained for 183 children from 153 families. Diaries including information on the acceptability and preference of the formulations were returned for 151 children from 124 families (recruitment success rate 45%, loss to follow-up 17%). Three diaries from two families could not be used in the data analysis because it was not clear in which order the formulations were administered (Figures 1 and 2). The recruitment success rate in the population eligible for inclusion was similar among all the participating healthcare clinics and recruiters. The age and gender of the children eligible for evaluation were not statistically different from the children eligible for inclusion.

Child and parent acceptability

The data did not indicate systematic differences between the single VAS scores of the two administrations of each formulation to a child. Therefore, the mean

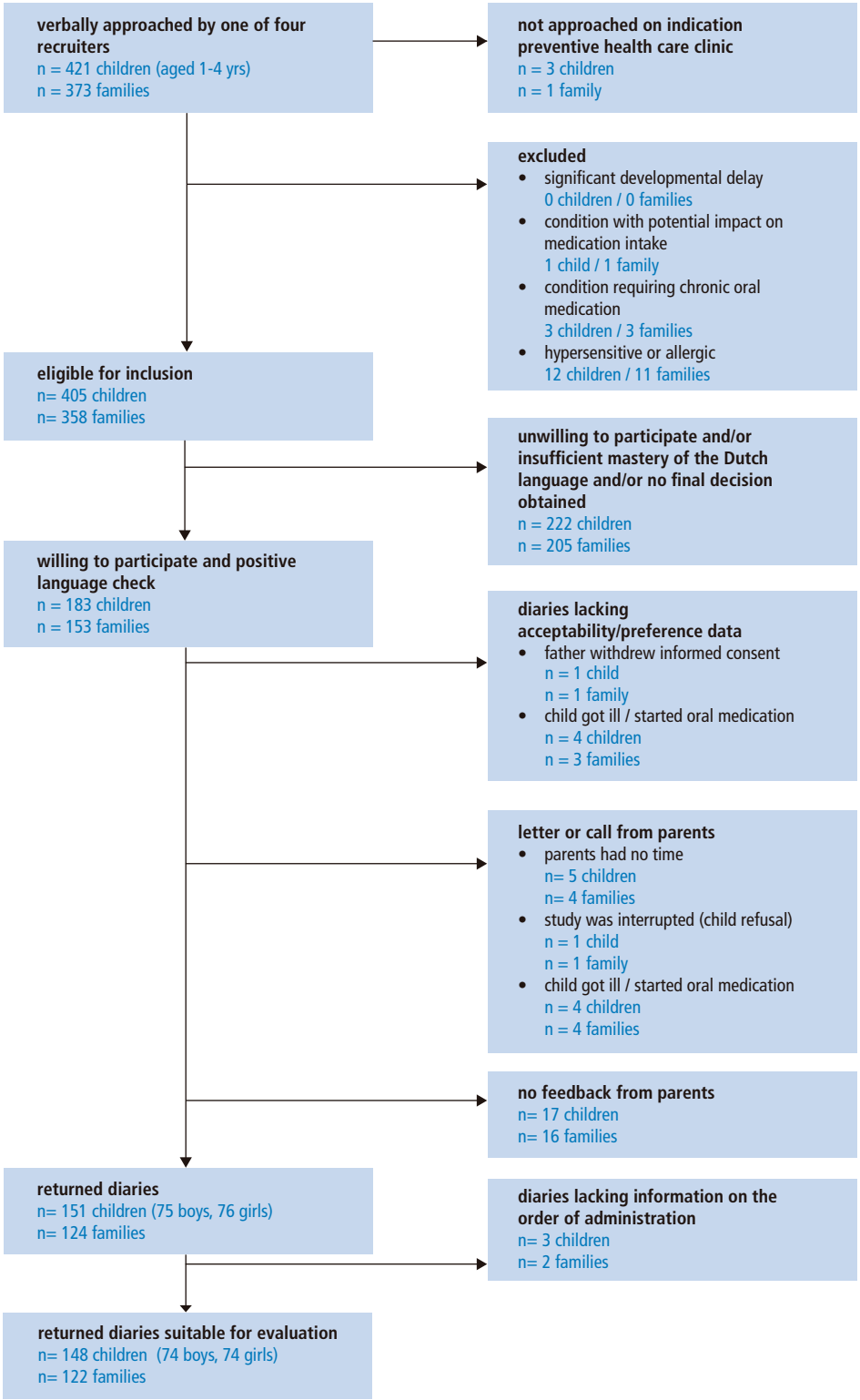


Figure 1 Participant flow through the study

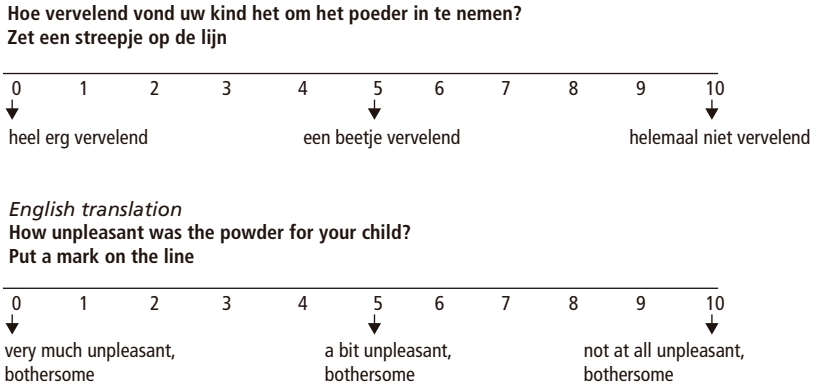


Figure 2 Visual Analogue Scale to report the Child Acceptability
Example shown for the powder

VAS scores were used for the further evaluations. The VAS score data indicated a period or cross-over effect by which formulations administered earlier tended to have somewhat higher scores (p value <0.0001). As a consequence, analysis started with the data of the first day only. The estimates of the mean VAS scores of the first day were: tablet 9.39 (32 children); powder 8.84 (45 children); suspension 8.26 (34 children) and 8.35 syrup (37 children); see Table 2 for the CIs. The tablet scored better than the suspension even when applying a Bonferroni correction (p=0.001: for correction multiply by 6). The other comparisons were less clear, but there was an indication that the tablet scored better than the syrup as well as the powder.

Using the data from all 4 days, estimates of mean scores per formulation were obtained across the 24 different orders of administrations, each order getting the same weight. Although no clear ranking was visible between the syrup, suspension and powder, the superiority of tablet over the other three forms was more evident than by considering the data from the first day only (Table 2).

The estimate of the mean number of administrations that were fully swallowed were 1.96 (tablet), 1.58 (powder), 1.70 (suspension) and 1.67 (syrup). This number was significantly higher for the tablet than for the other formulations (p value <0.05) (Table 2). The scatter-plot of the single VAS scores versus the result of the intake (data not shown) clearly illustrated that the VAS score was predictive for the result of the intake. No choking was reported.

Table 2 Acceptability of four different oral formulations (n=148 children)

	acceptability score		result of the intake
	first day (four different groups)	all four days (cross-over design)	all four days
numerical data	mean* (95%CI)	mean* (95%CI)	mean[&] (95% CI)
tablet	9.39 (8.85 – 9.93), n=32	9.01 (8.75 – 9.28)	1.96 (1.92 - 2.00)
powder	8.84 (8.19 – 9.49), n=45	8.20 (7.84 – 8.56)	1.58 (1.44 - 1.71)
suspension	8.26 (7.47 – 9.04), n=34	7.90 (7.42 – 8.38)	1.70 (1.57 - 1.83)
syrup	8.35 (7.45 – 9.25), n=37	8.19 (7.73 – 8.64)	1.67 (1.54 - 1.80)
testing for any differences	p-value[%]	p-value[%]	p-value[$]
tablet versus powder	<0,001	0.054	<0.001
tablet versus suspension	<0,001	0.001	<0.001
tablet versus syrup	<0,001	0.027	<0.001
powder versus suspension	0.378	0.060	0.081
powder versus syrup	0.869	0.611	0.168
suspension versus syrup	0.164	0.302	0.513

* estimate of the mean acceptability as expressed by the child on a 10-cm visual analogue scale (VAS-score) and as corrected for the willingness of the parents to administer a formulation to their child

[&] estimate of the mean number of administrations of a formulation that were fully swallowed by a child, maximum n=2.00

[%] p-values of the Mann-Whitney-Wilcoxon tests regarding any differences between the mean VAS-scores of two different formulations

[$] p-values of the Z-tests comparing pairs of formulations regarding the mean number of administrations that were fully swallowed by a child

Child and parent preference

Children and parents appeared to prefer the tablet and syrup over the suspension and the suspension over the powder (p values <0.001). There is also some indication (p value=0.082) that parents preferred the tablet to the syrup (Table 3).

Table 3 Preference of four different oral formulations (n=148 children)

	child		parent	
numerical data	**probability (95% CI)***		**probability (95% CI)***	
tablet	0.40 (0.32- 0.49)		0.49 (0.40-0.58)	
powder	0.07 (0.03 – 0.11)		0.07 (0.03-0.11)	
suspension	0.27 (0.19 – 0.34)		0.23 (0.17-0.30)	
syrup	0.48 (0.39 – 0.57)		0.36 (0.27-0.44)	
testing for any differences	**difference%**	**p-value%**	**difference%**	**p-value%**
tablet versus powder	0.334	<0,001	0.423	<0.001
tablet versus suspension	0.131	0.046	0.256	<0.001
tablet versus syrup	-0.080	0.306	0.137	0.082
powder versus suspension	-0.203	<0.001	-0.166	<0.001
powder versus syrup	-0.414	<0.001	-0.285	<0.001
suspension versus syrup	-0.211	<0.001	-0.256	<0.001

* estimate of the probabilities that the parent/child has indicated a preference for the formulation

% estimate of differences between the probability that one formulation is preferred and the probability that another dosage form is preferred and the corresponding p-values of the test that the two probabilities are equal.

Discussion

In this randomised cross-over trial, the four formulations investigated can all be considered well accepted by children between 1 and 4 years. The small 4 mm tablet was significantly better accepted than the suspension, and there was an indication that the tablet was also better accepted than the powder and syrup. The tablet was significantly more often fully swallowed than the other formulations. Children and parents preferred the tablet and syrup over the suspension, and the suspension over the powder.

Child acceptability of oral medicines has been studied for many years (20–22). Few studies however, have focussed on the acceptability of oral dosage forms as such. Ansah et al. (23) compared tablet with syrup formulations in 155 children from between birth and five years of age for the treatment of malaria, and Bagenda et al. (24) in 129 children between 6 months and 12 years of age in case of treatment with highly active anti-retroviral therapy (HAART). Both teams concluded that the tablet formulations resulted in better adherence. Spomer et al. (3) compared 2 mm uncoated placebo tablets with a sweet syrup in 60 inpatient children aged between 6 months and 6 years of age, and concluded

that the acceptability of the tablet was at least as good as that of the syrup. Despite key differences in the patient population and methodology, the results of our study are consistent with those of the aforementioned authors.

Three studies have been identified on the child acceptability of small tablets (3, 9, 10). Apart from the study of Spomer et al. (3), the study of Van de Vijver et al. (10) demonstrated that 2 mm medicated tablets were good to excellently swallowed by 16 outpatient Belgium or Dutch cystic fibrosis patients who were between 6 and 30 months of age. Thomson et al. (9) demonstrated that larger 3 mm tablets could be swallowed by 46 out of 100 inpatient British children who were 2 years old. Like the team of Spomer (3) and Van de Vijver (10) we found good to excellent acceptance of the tablet, even though our tablets were of a larger size. When comparing our results with those of Thomson et al. (9) we found a better acceptance of our 4 mm tablets. The reason for this difference is not known, but differences in tablet characteristics, setting, cultural and behavioural attitudes may be considered (11, 25, 26).

This study is the first randomised cross-over trial investigating the child and parent acceptability of and preference among four oral placebo formulations in infants and preschool children. It is also the first study investigating the child acceptability of oral placebo formulations in a domiciliary rather than inpatient setting, with a double rather than single administration of each formulation, a 4 mm, rather than a 2 or 3 mm tablet, and with two different measuring instruments for child acceptability.

In this study, an indication was found that the mean VAS acceptability score of the tablet was higher than that of the syrup, and that the parents preferred the tablet over the syrup. However, when parents were asked to report the child's preference, no significant difference was found between the syrup and the tablet. Results such as ours provide an argument for the fact that child and parent acceptability and preferences are different outcomes providing complementary information on the suitability of a formulation. Preferably, these outcomes are investigated in the same study.

This study has some limitations. First, the administrations were not supervised by the research team as this would bias normal family routines. Consequently, the evaluation of the child acceptability and preference relied on parental reports. This self-reporting methodology was not validated prior to the start of the study. Therefore, recruiters focused heavily on adequate verbal instructions to the method of administration and reporting.

Second, child acceptability may be influenced by taste aspects. The powder and tablet were manufactured from the same blend, so their taste was identical. However, the taste of the suspension and syrup differed due to the intrinsic nature of these dosage forms. Therefore, it cannot be excluded that any differences in the acceptability and preference among the liquid formulations were also related to taste.

Third, the recruitment was tailored to healthy domiciliary children between 1 and 4 years of age and parent with mastery of the Dutch language. Hence, the applicability of our findings to children outside this population, for example, children who are feeling ill, who are otherwise fractious or who are from a foreign ethnicity is left for future research. In view of the findings of the teams of Ansah (23), Bagenda (24), and Spomer (3) it is anticipated that our study's findings will equally hold for older children.

Fourth, chewing was not evaluated as it is common practice in The Netherlands that children may chew on immediate release tablets if they want to. Therefore, the acceptability (swallowabilty) of tablets that should be taken as a whole, for example, monolithic extended release tablets or tablets with essential taste masking, is left for future research.

Fifth, we did not systematically evaluate the parents' reasons to decline participation. However, from the voluntary reasons provided, it seemed that parents were mainly 'too busy' or having a second name suggesting a non-European ethnicity. It cannot be excluded that parents who did not participate in this study might be more reluctant to administer a particular formulation to their child than those who participated.

This study showed that the acceptability of 4 mm tablets is unlikely to be inferior as those of three currently employed types of oral dosage forms in infants and preschool children when aimed at a neutral taste. Thus, there is no reason to further question the acceptability of 4 mm immediate release tablets for children from the age of 1 year. Rather than discussing whether small tablets should be the preferred type of dosage form for the development of future paediatric medicines, pharmaceutical industries are recommended to consider the possibility of developing two essentially different dosage forms alongside each other.

Conclusions

Oral placebo 4 mm round uncoated tablets, powders, suspensions and syrups may be considered well accepted dosage forms in children between 1 and 4 years of age when aimed at a neutral taste. The tablets were significantly better accepted than the suspension, and there is an indication that they were also better accepted than the powder and syrup. Children and parents preferred the tablet and syrup over the suspension, and the suspension over the powder, but it was not clear whether they preferred the tablet over the syrup or otherwise. This study does not support the historic approach that medicines should normally be given to young children as an oral liquid formulation as other formulations may result in equivalent acceptability.

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Chapter 4

Usability of medicines for children in the domiciliary setting

Chapter 4.1

Methods of administering oral formulations and child acceptability

Diana A. van Riet-Nales
José A. Ferreira
Barbara J. de Neef
Alfred F.A.M. Schobben
Toine C.G. Egberts
Carin M.A. Rademaker

Abstract

Introduction

The administration of medicines to children poses specific challenges to parents, caregivers and health care professionals which are usually not encountered with adults, such as a lack of age-appropriate formulations in the required strength or recalcitrant children. Currently employed management strategies such as crushing tablets or mixing medicines with food or drink are intended to improve child acceptability, yet these strategies may reduce clinical efficacy or increase the risk for adverse drug reactions when dosing accuracy, stability or bio-availability are affected.

The objective of this study was to investigate how parents administer different types of oral formulations to infants and preschool children at home, and whether the methods of administration correlate with child acceptability.

Methods

The analysis is based on data from a randomized cross-over trial (RCT) on the acceptability and preference of four oral placebo formulations (4 mm tablet i.e., mini-tablet; powder; suspension; syrup) by 1 to 4 year old children in the Netherlands. The children were recruited through six preschool preventive health care clinics and the analysis had already been foreseen in the RCT protocol (ISRCTN63138435). Parents were asked to administer each formulation at home to their child twice on a single day, to report the family characteristics in a participant diary as well as details concerning the child's acceptability (VAS-score i.e., score on Visual Analogue Scale; result of the intake), eventual breaking or crushing of tablets, administration by the co-dispensed oral syringe or otherwise, and the method of administration (directly i.e. without food or drink; co-administered i.e., with a small quantity of food or drink; mixed i.e., with a larger quantity of food or drink; by syringe or spoon). First, the association between method of administration and type of formulation was investigated. Then the following associations were investigated separately for each formulation: 1) method of administration and child acceptability; 2) first VAS-score (score at the first of the two administrations) and eventual changes in method of administration (first to second administration); 3) changes in method of administration and changes in VAS-scores (first to second administration).

Results

A hundred and fifty-one children were included. Fifty-five (36%) children were 12 to 23 months old. The tablet was offered on all occasions (n=302, 100%), the powder on 295 (98%), the suspension on 296 (98%), and the syrup on 293 (97%). On 14 (5%) occasions the tablet was broken or crumbled/crushed

prior to administration. On 115 (19%) occasions the syrup or suspension were measured with the syringe, but administered with a household spoon. The most commonly applied methods of administration were: tablet directly (n = 249; 82%), powder co-administered (n = 119; 40%); suspension directly (n = 266; 90%); syrup directly (n = 271; 92%).

As expected, overwhelming evidence was found for an association between type of formulation and method of administration. Evidence was found that the method of administration is associated with the VAS (acceptability)-score for the suspension ($p=0.0146$) and tablet ($p<0.001$), but not for the powder ($p=0.701$) nor the syrup ($p=0.495$). However, evidence for an association between the method of administration and the result of the intake was found only in the case of the suspension ($p<0.001$). There was good evidence that in general the higher the first VAS-score, the less frequently the method of administration is changed (tablet: $p=0.001$; powder: $p=0.367$; suspension: $p=0.031$; syrup: $p=0.046$), and that a change in the method of administration generally results in higher VAS-scores (tablet: $p=0.005$; powder: $p<0.001$; suspension: 0.168; syrup: $p=0.001$).

Conclusions

The tablet, suspension and syrup were mainly given on their own, whereas the powder was mainly given with food or drink. This supports earlier conclusions that small tablets are well accepted by young children. However, clear instructions on the administration of powders are needed. Generally, child acceptability is improved when medicines are given with food or drink.

Introduction

In young children, the correct use of medicines, especially the oral administration, poses specific challenges to parents, caregivers and health care professionals which are usually not encountered in adults (1-5). For example, the medicine may not be commercially available in the required strength (a 2 mg tablet needs breaking or splitting to administer a 1 mg dose), the medicine may not be available in a dosage form that the child is able to take (babies cannot swallow large tablets), or the medicine may not be available in a dosage form that the child is willing to take (bad taste; adequate taste, but child does not like it; recalcitrance) (6-9).

Clear instructions on how to overcome such administration challenges are hardly available, e.g., in patient information leaflets (10). Therefore, parents and caregivers handle medicines in various ways that they consider best in a particular situation, such as breaking, crumbling or crushing tablets, mixing medicines with food or drink, or even refraining from administering them (10-12). All these strategies may reduce clinical efficacy and/or increase the risk of adverse drug reactions when the dosing accuracy, chemical stability, physical stability and/or bio-availability of the formulation are affected (13-15).

In a previous study among infants and preschool children in the domiciliary setting, we showed that the child and parent acceptability were related to the type of an oral formulation, e.g., tablet or syrup (16). In this study, we investigate how parents administer different types of oral formulations to infants and preschool children at home, and whether the applied methods correlate with child acceptability.

Methods

Study design and setting

The analysis is based on data collected for a randomized cross-over trial (RCT) that investigated the child and parent acceptability of four oral placebo formulations in infants and preschool children in the Netherlands and which has been described in detail elsewhere (16). The current analysis had already been planned in the RCT protocol (ISRCTN63138435). In brief, 151 children were recruited through six preschool preventive health care clinics in the centre of the Netherlands between February and July 2011. Children were eligible for inclusion if they were 1 to 4 years old. Children were excluded if they suffered

from a condition that might have negatively affected swallowability or if they were (potentially) hypersensitive to any of the excipients in the formulations.

The four tested formulations were a 4 mm round tablet (also referred to as mini-tablet) in blister, a 250 mg powder in sachet, a suspension (2.5 ml dose) in a brown glass container with syringe adapter that was co-dispensed with a 3-ml oral syringe, and a syrup (2.5 ml dose) in a comparable presentation. The placebo character of the formulations was known to the parents and, when appropriate, explained to the child. Parents were asked verbally and in writing to offer the formulations to their child at home in the same way as they would administer a prescribed medicine, but without any mental or physical pressure. Each formulation had to be administered twice on the same day and in a randomized order for the type of formulation i.e., at eight occasions. Parents did not receive any additional instruction on how to administer the formulations to their child other than that the suspension had to be shaken prior to use. This formally implies that the formulations were intended to be given on their own i.e., without food or drink.

Data collection

Parents were asked to write down in a participant diary, after each of the eight administrations, information on: 1) whether the formulation was offered to the child and, if not, why not; 2) by whom the formulation was offered to the child; 3) whether the tablets were broken, crumbled or crushed prior to administration; 4) whether the oral liquids (suspension and syrup) were administered with the co-dispensed oral syringe or otherwise; 5) whether the formulations were given with food or drink and, if so, which type and quantity; 6) child acceptability according to the parents' observation as measured on a 0-10 cm Visual Analogue Scale (VAS-score); 7) child acceptability as measured by the result of each intake; 8) other aspects of the administration (optional).

Practically all this information could be provided by ticking box outcomes that were based on the results of an earlier questionnaire study among Dutch parents on the problems they experienced when administering medicines to their child(ren) (17). Where appropriate, parents were given the possibility to provide an open answer. Other questions in the participant diary related to child and family characteristics and child and parent preferences.

Data analysis

The method of administration was classified as "directly" when a formulation was given on its own, as "co-administered" when a formulation was given with a small quantity of food or drink (one bite/slug), and as "mixed" when a

formulation was given with a larger quantity of food or drink (several bites/slugs). For the purpose of testing associations involving the methods of administration, we have taken the ordinal character of this variable into account by labelling its three levels as 1, 2 and 3.

The association between the method of administration and the type of formulation, which is naturally expected to exist, was checked first. Then the following associations were investigated separately for each type of formulation: 1) association between the method of administration and the VAS-score; 2) association between the method of administration and the result of the intake; 3) association between the first VAS-score (the score at the first administration) and the change in the method of administration (from the first to the second administration); 4) association between the change in the method of administration (from the first to the second administration) and the change in VAS-scores.

The analysis took account of the small effect that was observed for the order in which the four formulations were administered to a child (16). The testing of associations was based on a permutation version of Spearman's test for independence. In this test the null distribution is approximated by randomly permuting the data separately within the 24 groups pertaining to the different orders of administration of the four types of formulations.

The data were analysed by Excel 2007 (Microsoft Corporation, Redmond, Washington), SPSS version 17.0 (IBM) and R (version 2.13, R development team). Spearman's test was conducted with the R package coin (Hothorn et al, 2006) (18).

Results

A hundred and fifty-one children were included, 72 (48%) of which were boys and 79 (52%) girls. Fifty-five (36%) children were 12 to 23 months old; 32 (21%) 24 to 35 months, and 64 (42%) 36 to 51 months old.

For the first/second administration, the tablet was offered to the child on all occasions, the powder on all but two/five occasions; the suspension on all but one/five occasions and the syrup on all but four/five occasions. A one thousand and six (84.8%) of all administrations were carried out by the mother, 173 (14.6%) by the father, and 7 (0.6%) by another caregiver. The main reason (n = 17, 77%) for not offering a formulation to a child was either that the parent

considered that the child would refuse it anyway or that the child actually said so to his parent.

On 14 (4.6%) occasions the tablet was broken, crumbled or crushed prior to administration, once at the first administration only (age child 16 months), trice at the second administration only (age children 19, 31, 45 months) and five times at both administrations (the children being aged 12, 20, 33, 31, 48 months). On 58 (20%) occasions the suspension was emptied into a spoon prior to administration and so was the syrup on 57 (19%) occasions.

The tablet, suspension and syrup were given mainly directly (tablet n = 249, 82%; suspension n=266, 90%; syrup n=271, 92%). However, the powder was mainly given with food or drink (co-administered: n=119, 40%; mixed n=71, 24%). On two occasions (first and second administration of the powder for the same child) the method of administration was unknown. As expected, the method of administration depends significantly on the type of formulation (p-value <0.001 from a chi-square test). An illustration of this dependence for children of different ages is provided in Figure 1 (children of 48-51 months are

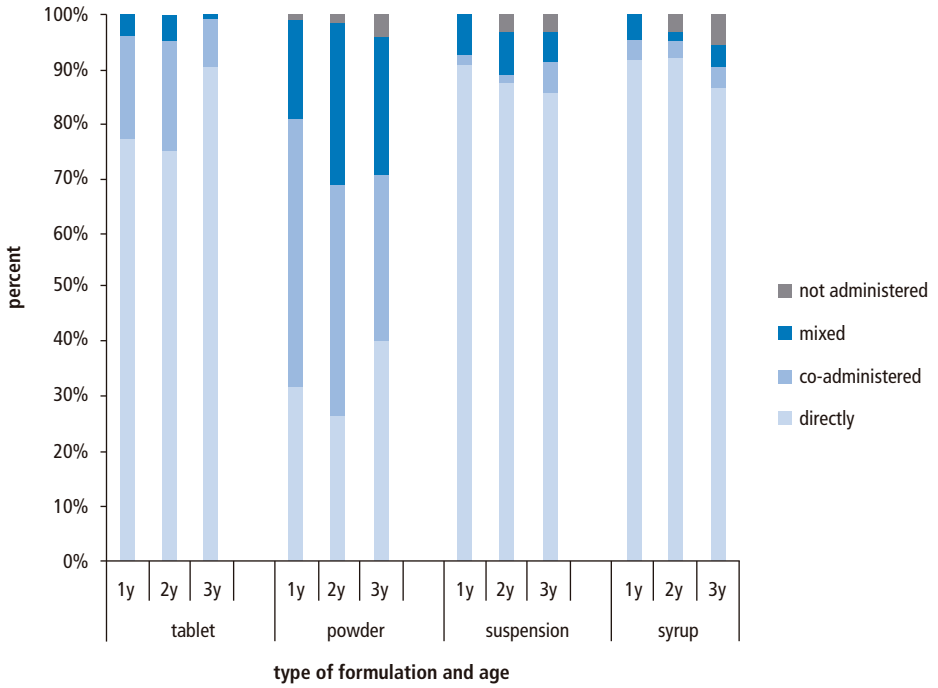

Figure 1 Illustration dependence type of formulation and method of administration for children of different ages (n=1206 administrations)

presented as 3 years). The foodstuffs most commonly used for co-administration or mixing were vanilla pudding, quark, yoghurt, porridge and fruit sauce.

For formulations fully swallowed, an illustration of the association between the method of administration and the VAS-score of each type of formulation is given in Figure 2 . The differences suggested by Figure 2 appear to be significant for the tablet and suspension even when ignoring the result of the intake i.e., considering all administrations (p-values < 0.001 and 0.0146), but not for the powder (p=0.701) nor the syrup (p=0.495).

As expected and illustrated in Figure 3, the VAS-score was related to the result of the intake. The illustration supports the categorization of VAS-scores in three groups: VAS-score 0 to 2 (bad acceptability), VAS-score 3 to 7 (moderate acceptability) and VAS-score 8 to 10 (good acceptability). Considering all intakes, a VAS-score of 8 to 10 was obtained for the tablet on 222 (74%) occasions

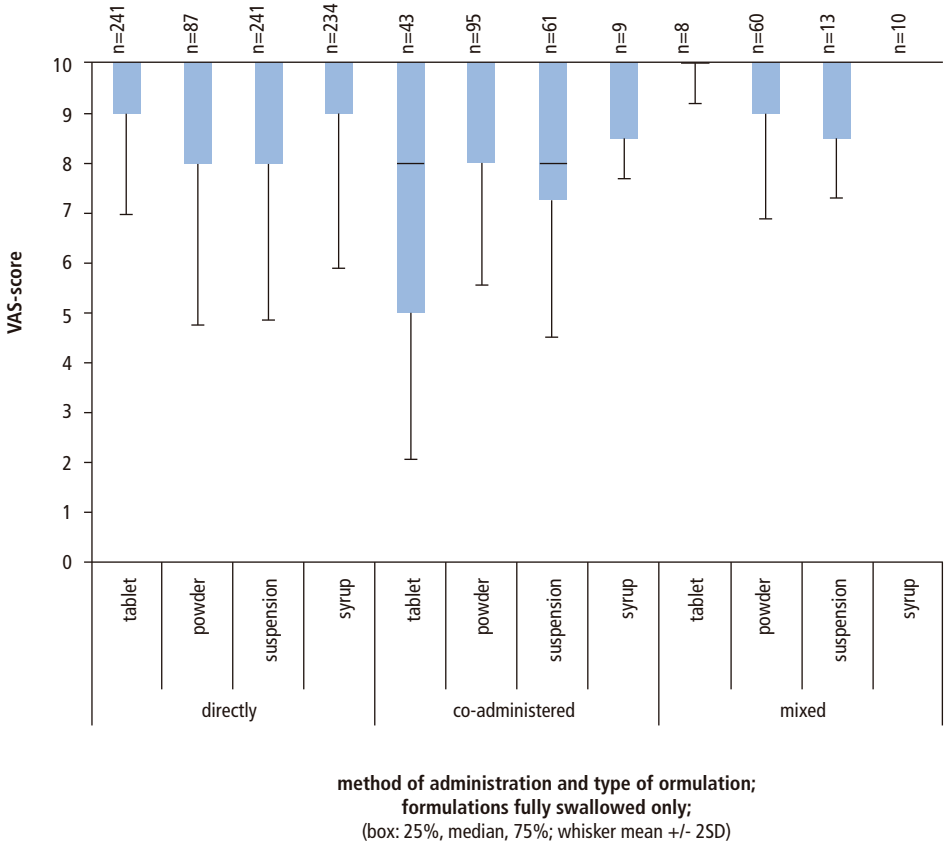

Figure 2 Illustration association method of administration and child VAS-score

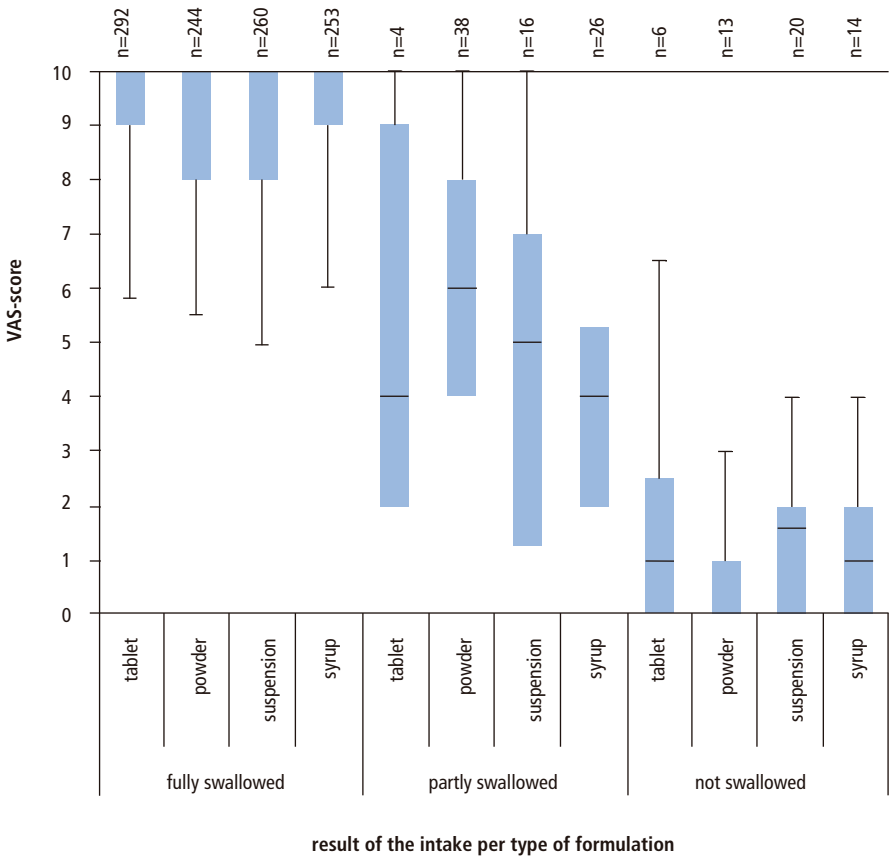

Figure 3 Illustration agreement result of the intake and child VAS-score

when given directly, on 29 (10%) when co-administered and on 8 (3%) when mixed; for the suspension, on 196 (66%) occasions when given directly, on 5 (2%) when co-administered, on 12 (4%) when mixed; for the syrup, on 201 (69%) occasions when given directly, on 9 (3%) when co-administered and on 10 (3%) when mixed. For the powder, a VAS score 8 to 10 was almost as often achieved when given directly (n=74, 25%) as when co-administered (n = 78, 26%) or mixed (n = 59, 20%).

Although, as expected, the VAS-score is in good agreement with the result of the intake, it is also clear that good acceptability did not guarantee full swallowing on all occasions, e.g., because parents stated that the formulation got spoiled during the intake or that it dropped out of the child's mouth. Similarly, bad acceptability did not always imply lack of swallowing, as parents indicated that the child only showed its disgust afterwards.

When given directly, the tablet was fully swallowed on 241 occasions (equalling 97% of all direct tablet administrations), the powder on 87 (85%), the suspension on 241 (91%) and the syrup on 234 (86%). When co-administered, the tablet was fully swallowed on 43 (95%) occasions and the powder on 95 (80%). Finally when mixed, the tablet was fully swallowed on 8 occasions (100%) and the powder on 60 (84%). Considering the youngest children only (12 to 23 months), the tablet was given directly and fully swallowed by 82 (75%) of these children.

Considering only occasions on which the formulations were given directly and fully swallowed, good acceptability (i.e., a VAS-score 8 to 10) was obtained for the tablet on 221 occasions (73%), for the powder on 70 (24%), for the suspension on 195 (66%), and for the syrup on 199 (68%).

The association between the method of administration and the result of the intake was found to be significant for the suspension ($p<0.001$), but not for the tablet ($p=0.271$), the powder ($p=0.383$) and the syrup ($p=0.105$).

There was good evidence that the higher the VAS-score of the first administration of a formulation to a child is, the less frequently the method of administration of this formulation is changed from the first to the second administration (tablet $p=0.001$, powder $p=0.367$, suspension $p=0.031$, syrup $p=0.046$). For example, when the VAS-score in the first administration was 8 to10, the method of administration was not changed in most cases (tablet 94%, powder 82%, suspension 98%, syrup 96%).

A change in the method from the first to the second administration is denoted as "more complex" when it involved a larger quantity of food or drink (going from "directly" to "co-administered", from "directly" to "mixed" or from "co-administered" to "mixed"). Conversely, it is denoted as "less complex" when it involved a smaller quantity of food or drink (going from "mixed" to "co-administered", from "mixed" to "directly" or from "co-administered" to "directly"). Generally, the method of administration changed more frequently into a more complex method when the VAS-score in the first intake was 0 to 2 (n = 11/45, 24%) than when it was 3 or higher (n = 33/552, 6%). Figure 4 provides an overall illustration of these results. Except for the suspension, strong evidence was also found for an association between changes in the method of administration and changes in the VAS-score, indicating that a change in the method of administration resulted in higher VAS-scores (tablet $p=0.005$, powder $p<0.001$, suspension $p=0.168$, syrup $p=0.001$).

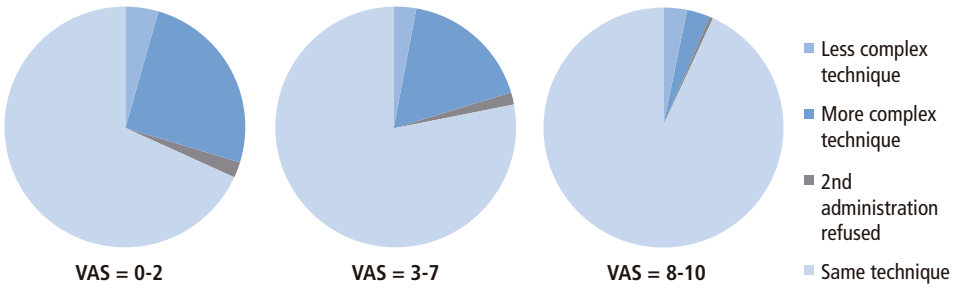

Figure 4 Association VAS-score first administration of a formulation and changes in method of administration from first to second administration

Discussion

This study showed that oral placebo formulations in the forms of a 4 mm tablet, a suspension and a syrup were mostly administered to infants and preschool children as intended i.e., without food or drink. On the contrary, the placebo powder was mostly given with food or drink, even though this was not recommended. As expected, the method of administration was clearly associated with the type of formulation. For the tablet and suspension, the method also appears to be associated with child acceptability as measured on a 1 to 10 cm Visual Analogue scale i.e., the VAS-score, and for the suspension with the result of the intake. Parents were more likely to administer a formulation with (a larger quantity of) food or drink when the child acceptability of the earlier administration of the same formulation was low than when it was high(er). Changes in the method from the first to the second administration of the same formulation generally resulted in better child acceptability.

The limited availability and age-appropriateness of medicines for children has resulted in a globally emerging effort towards an improvement of paediatric medicines (8, 19, 20). As suggested by Kozarewicz (21), this requires the collection of pre-marketing data on the acceptability of medicines by children. However, a suitable methodology for collecting and making sense of such data is yet to be developed. Therefore, the selection of the test methods and the proposals for data assessment are currently left to researchers (19, 21). According to Ranmal et al. (19), researchers should, among other things, consider the variability in child acceptability in typical and atypical populations, acknowledge that acceptability testing based on small samples may lead to inconsistent and limited findings, and realize that parents may be more likely to participate in a study when they feel positive about the formulation being investigated.

Kozarewicz and Ranmal's et al. remarks were considered in the design of our RCT. Following discussions with Dutch health care professionals and taking data from the palatability and pain literature into account, we measured child acceptability by two instruments, namely the child VAS-score and the result of the intake. For the VAS-scale, the commonly applied facial expressions below the line indicating "like" and "dislike" were replaced with words relating as to whether the child considered the intake unpleasant or not.

The variability in child characteristics was addressed by focusing on generally healthy domiciliary children who did not have any difficulties swallowing food or drink. In addition, the variability in parents' attitudes to study participation was acknowledged by two means. First, recruitment was conducted through national preventive health care clinics in view of the high response to invitation of the overall population of parents. Second, the likelihood that parents were more willing to participate in a study when they were positive to a certain formulation was avoided by studying four types of oral placebo formulations and allowing parents not to administer a particular formulation if they rather did not like to do so (22).

The increasing global focus on better medicines for children has also resulted in an increased focus on mini-tablets. Whereas our study related to 4 mm tablets, other authors tend to study smaller sizes, e.g., 3 mm by Thomson et al. and 2 mm by Klingmann et al. (23, 24). Such smaller tablet sizes entail an increased need to swallow several mini-tablets to arrive at the recommended dose as the maximum amount of active substance per mini-tablet is limited. However, at the same time this would allow more dosing flexibility. In any case it should be acknowledged that a larger number of smaller tablets may make the administration more "powder like" and that the more "suspension like" when applying a novel approach by which the addition of some water to several mini-tablets results in a semi-solid mass. In both cases, this may have an impact on the child acceptability. Thus, the acceptability of larger numbers of mini-tablets by children in the domiciliary setting remains subject to further investigations. In any case, 4 mm mini-tablets do not seem "too big" for 1 to 4 year old children.

Current studies on medication adherence focus mainly on the ability of parents to calculate and measure the recommended dose, on the eventual relationship between health literacy and deviations from the written user instruction, and on the effectiveness of verbal, written or pictogram interventions designed to encourage adequate administration practices (25-27). Studies on the associations that were investigated in this study are more scarce. Akram et al. (28) investigated the prevalence and nature of, and the reasons for, mixing medicines with soft

foods by nurses working in a national health service, and Richey et al. (11) studied which dosage forms and drugs were routinely modified in paediatric clinical practice. Both studies were conducted in the United Kingdom among nurses, in relation to any type of prescribed medicine and to a wide variety of children. These studies as well as our study share the conclusion that medicines may be given with food or drink or otherwise be modified to guarantee adequate child acceptability and/or medication intake.

Generally, parents and caregivers will have less experience in administering medicines to children than nurses working on paediatric wards. However, Akram et al. indicated that parents often advised staff as to whether their child's medication needed to be co-administered or mixed with food or drink or otherwise modified in order to enable swallowing (29). Also Alsulami et al. indicated that the most frequent type of deviations from hospital policy on the administration of medicines was that the formulation was given by the parents without the nurse being present (30). Thus, it is likely that the findings of our study will also have some relevance to children that are hospitalized for short stay.

Akram et al. (29) indicated that nurses rather added the medications to the foodstuff instead of adding the foodstuff to the medicine. This aspect was not investigated in our study as we considered that it is the quantity of the food or drink that is being used that is most important. We had several reasons for this. First, the contact time and area will be significantly smaller when a formulation is given with a small quantity of food or drink (one bite/slug) than when it is mixed with a larger quantity (several bites/slugs). This considerably reduces chemical or physical interactions, which may have an effect on the bio-availability and stability of the formulation and therewith on its clinical efficacy and risk for adverse drug reactions. Second, children may not be willing to swallow larger quantities of medicated food or drink fully. Depending on the criticality of the disease and the type of medicine, this may put the child at an immediate risk. Third, verbal reports from Dutch health care professionals stated that feeding problems may be due to negative experiences involving medicated food. Consequently, they argued that it is important that medicines be given only with a small quantity of food or drink, and that the remaining quantity of the non-medicated food or drink should be given immediately after so that the child will remind the non-medicated experience. However, this opinion was not confirmed by other authors (31).

This study has several strengths. It is, to the best of our knowledge, the first study comparing the method of administration and child acceptability of different types

of oral formulations involving infants and preschool children. Child acceptability was investigated in a domiciliary rather than in the more commonly applied hospital setting, because oral formulations are frequently taken by children who are not and also have not been hospitalized, whereas hospitalized children may need to take oral formulations at home for long periods of time after they are discharged from hospital. The choice for the domiciliary setting implied that the study outcomes take account of any impact on the method of administration and child acceptability caused by child-parent relations, child-sibling relations, parents' understanding of the user instruction and the absence of a supervising health care professional (23, 24).

In this study, the method of administration was investigated for three types of oral paediatric formulations commonly administered to infants and preschool children, namely a powder, a syrup and a suspension, as well as for a less commonly used (and by some even considered as new) type, namely a small 4 mm tablet. The method of administration was also evaluated in relation to other aspects that potentially might have affected it, namely child acceptability and earlier administration experiences. In addition, it was investigated whether changes in the method of administration improved child acceptability.

Besides the aforementioned strengths, this study has some weaknesses also. The participant diary included tick-box outcomes that were supplemented with the possibility to provide an open answer. However, it cannot be excluded that the pre-printed administration possibilities might have influenced the applied method. Also, the sample size was based on the primary aim of the former RCT rather than this analysis itself. Moreover, the current analysis did not consider the 22 occasions where the syrup, suspension and powder were not offered to the child for anticipated child refusal i.e., when the patient acceptability was expected to be bad. This weakness must be considered when disputing the suitability of small tablets as an alternative to powder, suspension, syrup for the reason that they were broken, crumbled or crushed in 14 occasions.

In addition, the results of this study should be considered realizing that it was limited to four types of oral formulations with defined characteristics and to Dutch parents and children living in a small region of the Netherlands ("Rivierenland"). Finally, this study showed that parents may empty the dose from the oral syringe onto a household spoon prior to administration. We consider that this handling can be accepted without any further justification as the risk for any additional loss of dose is negligible.

This study showed that the powder was mainly given with food or drink, even though this was not recommended. In view of the special characteristics of this dosage form, it may be argued that powders that were given with a small quantity of food or drink may also be considered as to be given as intended. In any case, it is recommended that parents receive clearer information on the acceptable method of administering powders, preferably on the product label or patient information leaflet. This information should preferably clarify as to whether the powder should be administered in the dry form or with water only, or if it can also be administered with small quantities of food or drink, and if so, any type or only some.

The method of administration was associated with the type of formulation. However, it was only associated with the VAS-score and the result of the intake in the case of the suspension. Overall, this suggests that it is mainly the type of formulation that made parents decide to administer a formulation with food or drink. However, when parents observed that the child acceptability of the first administration was low, they frequently chose to administer the formulation with (a larger quantity of) food or drink. This approach turned out to be effective i.e., to improve child acceptability.

It is generally acknowledged that child acceptability problems may be handled by breaking, crumbling or crushing tablets and administering the parts with food or drink (32-34). In lack of a specific warning about any of such handlings in the medicine's user instruction (product label, patient information, summary of product characteristics), parents, caregivers and health care professionals will normally not consider such handlings as a deviation from this instruction, but rather as fully acceptable. However, this opinion is not consistent with the regulatory approach, as regulators consider that the lack of a recommendation on any of such handlings in the user instruction implies that the handlings have not been justified and consequently, should not be applied.

Considering clinical practice and the fact that pharmaceutical companies are generally reluctant to conduct interaction studies between a formulation and a specific type of food or drink, regulators are considering precautionary warnings in the user instruction stating that the formulations should not be taken with food or drink unless compatibility had been demonstrated. Although these warnings are intended to protect the health of the child by avoiding any impact of food or drink on the stability and bio-availability of the formulation, they may in fact put the child at risk if the warning withholds the child from taking its medicine. Since our study points towards the latter possibility, it is recommended that regulators carefully consider the risk for reduced adherence rates when

implementing warnings. This may be especially relevant for powders, which are commonly given with food or drink. Actually, we consider that it is not at all in the interest of children to implement warnings that are solely based on the absence of data supporting adequate compatibility, and certainly not when an interaction is not to be expected on scientific grounds.

The optional remarks written by the parents on the participant diary indicate that the type of dosing device may have had an effect on child acceptability. Some parents stated that their child "wanted more" of the suspension or syrup because the child knew it would be allowed to play with the empty syringe when both doses were taken, whereas other parents indicated that they emptied the oral suspension or syrup into a spoon because the child was afraid of the syringe. Thus, the design and child acceptability of syringes for oral use should be further investigated.

Conclusions

The tablet, suspension and syrup were largely administered as intended i.e., without any foods or drink and without breaking, crumbling or crushing tablets. This shows that simple administration instructions can be adequately followed by parents who master the Dutch language. It also confirms that all three types of formulation can be considered as age-appropriate to young children and that there is no reason to dispute the acceptability of small tablets in this age group. The powder was commonly given by all three methods of administration i.e., directly, co-administered and mixed. Thus, it is recommended that clear instructions on the administration of this type of dosage form be included in the patient information leaflet and summary of the product's characteristics. Formulations that were administered with food or drink were generally so for good reason i.e., to improve child acceptability. Consequently, any warnings in the user instructions on the mixing of medicines with food or drink must be carefully balanced against the risk of reduced child acceptability and reduced adherence rates, especially when there is no clear evidence of a relevant medicine-food interaction that is likely to result in a clinically relevant effect.

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Chapter 4.2

The accuracy, precision and sustainability of different techniques for tablet subdivision: breaking by hand and the use of tablet splitters or a kitchen knife

Diana A. van Riet-Nales
Myrthe E. Doeve
Agnes E. Nicia
Steven Teerenstra
Kim Notenboom
Yechiel A. Hekster
Bart J.F. van den Bemt
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Abstract

Introduction

Tablets are frequently subdivided to lower the dose, to facilitate swallowing by e.g., children or older people or to save costs. Splitting devices are commonly used when hand breaking is difficult or painful. The primary objective of this study was to evaluate the accuracy, precision and sustainability of commercially available tablet splitters and a kitchen knife as an alternative to breaking tablets by hand. The secondary objective was to evaluate if tablets subdivided with a splitting device were likely to comply with current regulatory requirements for break marked tablets.

Methods

Three techniques for tablet subdivision were investigated: hand breaking, tablet splitter, kitchen knife. A best case drug (paracetamol), tablet (round, flat, uncoated, 500 mg) and operator (24-year student) were applied. A hundred tablets were subdivided by hand and by three devices of each of the following types: Fit&Healthy, HealthCareLogistics, Lifetime, PillAid, PillTool, Pilomat tablet splitter; Blokker kitchen knife. The intra and inter device accuracy, precision and sustainability were investigated. The compliance to (adapted) regulatory requirements was investigated also.

Results

The accuracy and precision of hand broken tablets was 104/97% resp. 2.8/3.2% (one part per tablet considered, parts right/left side operator). The right/left accuracies of the splitting devices varied between 60 - 133%, the precisions 4.0 - 29.6%. The devices did not deteriorate over 100-fold use. Only hand broken tablets complied with all regulatory requirements.

Conclusions

Health care professionals should realize that tablet splitting may result in inaccurate dosing. Authorities should undertake appropriate measures to assure good function of tablet splitters and, where feasible, to reduce the need for their use.

Introduction

Breaking or splitting tablets is common practice in inpatient and outpatient settings as it increases dosing flexibility, facilitates swallowing and allows cost savings for both patients and healthcare providers (1-4).

However, patients have indicated that it may be difficult and painful to break tablets by hand (5, 6). This is especially true for patients with impaired hand function such as (school) children and older people (patient populations who often need lower doses or dose titrations) or patients suffering from rheumatic diseases (5, 7-9). Ekedahl (5) for example concluded that 31% of Swedish adult patients experienced difficulties subdividing tablets, Mehuys et al. (8) that 29.7% of home dwelling older adults experienced difficulties when they had to subdivide tablets and Barends et al. (7) that older Dutch people were far less able to break tablets by hand than healthy adult volunteers. Wilson et al. (9) reported a mean pain score of 3.2 out of 10 for generic anti-diabetic tablets when hand broken by older American citizens.

As breaking tablets by hand is often considered problematic, the use of tablet splitters is common. This is especially true for tablets that do not have a break mark. Other splitting devices such as kitchen knives or scissors may be applied as well (5, 10, 11).

Indexed publications on the accuracy and precision of tablet splitters, kitchen knives or other devices that may be applied to subdivide tablets (all further referred to as "splitting devices") generally show limitations as e.g., uncertainties about the type of device, operator or weight measurements applied; random selection of the device and tablet types; only small numbers of tablets/devices tested and the lack of data comparison between tablets subdivided with a splitting device and those broken by hand. Consequently, it is not yet possible to draw a firm conclusion on the suitability e.g., accuracy, precision, sustainability of splitting devices as an alternative to breaking tablets by hand.

In addition, the conclusion of Freeman's review that tablet splitters may not subdivide tablets into equal doses and that the accuracy of tablet splitters may depend on the type of splitter, tablet or operator applied needs further consideration as the review shows methodological shortcomings such as no information on search profile, data extraction and data analysis and no quality evaluation of the included publications (12).

Therefore, the primary objective of this study was to evaluate the accuracy, precision and sustainability of commercially available tablet splitters and a kitchen knife as an alternative to breaking tablets by hand. The secondary objective was to evaluate if tablets subdivided with a splitting device were likely to comply with current regulatory requirements for break marked tablets (13-15).

Methods

Study design

In this experiment three techniques for tablet subdivision were compared: hand breaking, tablet splitter, kitchen knife. A hundred paracetamol tablets were hand broken by a single operator, by three devices of several types of tablets splitters or by three kitchen knives of the same type. The suitability of the techniques was compared by evaluation of the accuracy, precision, sustainability and regulatory compliance of the weight measurements. The experiment did not require ethical approval according to the Dutch Medical Research Involving Human Subjects Act (WMO). The study protocol was approved by the Committee on Clinical Practice of the Medicines Evaluation Board in the Netherlands (MEB).

Methodology

All data were collected between November 2012 and February 2013.

Splitting devices: Tablet splitters were included if these were available in the standard assortment of at least two community pharmacies or drugstores in Utrecht, the Netherlands. The pharmacies were identified via a list of the Dutch Society for the Advancement of Pharmacy (KNMP) whereas drugstores were identified via the Dutch Trading Register or the internet. Thirty five pharmacies and 59 drug stores were identified, selling 15 types of tablet splitters. Five tablet splitters were excluded because these were not in the pharmacy's standard assortment and another four because these were sold in one establishment only. Six types of tablet splitters were included. The kitchen knife was purchased at a household warehouse in Utrecht (national chain) (Figure 1).

Drug compound and tablet trade mark: Marketing authorisations for round, flat, uncoated, break marked 500 mg paracetamol tablets were identified with help of the database of the MEB. The retrieved tablet authorisations were categorized in groups with authorisations for tablets sharing the same manufacturer and excipient composition. For each group, the diameter and thickness (household vernier calliper gauge) and resistance to crushing (Heberlein

	Fit&Healthy	HealthCare Logistics	LifeTime	PillAid	PillTool	Pillomat	kitchen knife
price paid (EUR)	8.99	8.54	0.99	2.67	2.25	4.95	0.59
picture device							
picture tablet holder							

Figure 1 Characteristics splitting devices

diametral compression test apparatus; 2E/205 Schleuniger Productronic AG, Solothurn, Switserland) of the commercially available tablets was assessed (n = 10). The results from all groups were compared and a tablet with "average" characteristics i.e., Paracetamol Centrafarm RVG 53055 was selected.

Operator: A best case operator with adequate understanding of the study principles and good hand function was selected i.e., a healthy, female, 24-years old master student in her 5th year of pharmaceutical sciences at Utrecht University (Myrthe Doeve).

Weight measurements: The weight of 100 intact tablets was determined (Mettler Toledo AG64 analytical balance). The average weight (further referred to as "theoretical intact tablet weight") and standard deviation were 619.775 mg, 4.152 mg. The theoretical weight of a tablet part was calculated as half the theoretical intact tablet weight i.e., 309.888 mg.

Data collection

The key characteristics of each tablet splitter (name, appearance, shape tablet holder, position tablet holder, shape knife, price), kitchen knife (name, appearance) were extracted. The weights of both parts of each subdivided tablet were determined (Mettler Toledo AG64 analytical balance). It was recorded whether a tablet part resulted from the right or left side of the splitting device or the operator's hands.

Data analysis: accuracy, precision, sustainability

Five approaches were used to the selection of the tablet parts to be considered in the data analysis: 1) The intra device accuracy was calculated as the percent of the average weight of 100 parts obtained from the right side of a splitting device (where the parts from the left side were rejected) versus the theoretical weight of a tablet part. The inter device accuracy was calculated in the same way as the average weight of 300 parts obtained from the right side of the three devices of the same type (where the parts from the left side were rejected). The intra and inter precision were calculated likewise as the relative standard deviations of the weight measurements; 2) As approach 1, however now the left sides were considered and the right sides rejected; 3) As approach 1, however the tablet parts were no longer grouped depending on the side of the splitting device they originated from, but in those weighing the least or most following subdivision. The tablets with the lowest weight were considered (and those with the highest weight rejected); 4) As approach 3, however now the tablets with the highest weight were considered (and those with the lowest weight rejected); 5) As approach 1, however now both parts from each tablet were considered.

All results were compared with those of tablets broken by hand (multiple t-tests; analysis of variance with type of splitting device and device as factors, with the latter nested within the former, followed by Dunnett's posthoc analysis). The sustainability of the splitting devices over 100-fold use was inspected visually (integrity of the device, trends in weight variability).

Data analysis: regulatory requirements

Uniformity of weight of tablet parts as adapted from Ph. Eur. 478 subdivision of tablets: Both parts of the same tablet were considered. It was evaluated if the weight of the parts complied with the following criterion "at least 194 of 200 parts resp. 582 of 600 parts should be within 85-115% and all parts within 75-125% of the theoretical weight of a tablet part" (13).

Simulated assay as adapted from Directive 2001/83/EC: It was evaluated if the mean weight of parts obtained from the same side of the operators hands or a splitting device would be within 95.0-105.0% of the theoretical weight of a tablet part i.e., if the accuracy would be 95.0-105.0% (14) .

Loss of mass as adapted from FDA: For each tablet, the loss of mass was calculated by subtracting the weight of the right and left part of a tablet from the theoretical intact tablet weight. The loss of mass of each tablet should be smaller than 3.0% (15).

Results

Accuracy, precision, sustainability

The intra- and inter accuracies of tablets broken by hand or a splitting device are displayed in Table 1. The accuracy of hand broken tablets was 104/97% (right/left side operator i.e., R/L); 96/104% (lowest/highest weight i.e., L/H); 100% (both sides). The accuracies of the splitting devices varied between 60 - 133% (R/L); 59-133% (H/L); 94 - 100% (both). The largest difference between sampling R/L versus L/H was observed for the Fit&Healthy device 1: 96.3/93.6% (R/L) resp. 81.4/108.5% (L/H). Results for the intra and inter precision are displayed in Table 2. The precision for hand broken tablets varied between 2.4% (lowest parts considered) and 4.7% (both parts considered). The precision of tablets subdivided by a splitting device was 29.6% at the maximum when parts from one side were considered only (Fit&Healthy device 2; left parts). Overall, the accuracy and precision of three types of tablet splitters (Fit&Healthy, Lifetime, PillAid) were less favourable than the kitchen knife.

Comparing all parts derived from the same side of a splitting device with those broken by hand from the corresponding side of the operator, Dunnett's posthoc analysis showed a statistical difference in the following cases when the tablets were grouped per side of device: Lifetime (both $p<0.000$), PillTool ($p=0.032$, $p=0.001$), HealthCareLogistics ($p=0.002$, $p<0,000$), PillAid (right $p=0.001$) and Fit&Healthy splitter (left $p=<0.000$).

Visual evaluation of the splitting devices did not show any deterioration over 100-fold use and the devices still worked. In one single case (PillAid device 2) the knife detached from the device during the experiment. The knife was put back again anticipating that this approach would also be carried out by patients. No trends in weight variability of the tablet parts were observed over 100-fold use (Figure 2).

Regulatory requirements

The uniformity of weight of tablet parts broken by hand or subdivided by the HealthCareLogistics or PillTool splitter types complied with the adapted Ph. Eur. test. The other types of devices did not comply (Table 3).

The accuracy of tablet parts broken by hand or subdivided by the HealthCare Logistics, PillAid, PillTool or Pilomat tablet splitter complied with the simulated assay criteria of 95.0-105.0% when the parts were sampled from the same side of the operator and when the overall type of tablet splitter was considered (Table 3).

Table 1 Intra and inter accuracy of paracetamol tablets broken by hands (n=100), several types of tablet splitters or a kitchen knife (n=100 per device; three devices per type investigated)

splitting technique		number device tested	accuracy (%) for five different approaches to the selection of the tablet parts to be considered				
			right side only	left side only	lowest weight of both parts only	highest weight of both parts only	both sides
hand broken		nap	103.8	96.6	96.3	104.1	100.2
tablet splitter	Fit&healthy	1	96.3	93.6	81.4	108.5	95.0
		2	108.0	80.5	74.6	113.9	94.2
		3	102.5	86.9	80.2	109.2	94.7
		all	102.3	87.0	87.8	101.5	94.6
	Health Care Logistics	1	99.2	100.3	96.4	103.1	99.8
		2	95.6	103.5	95.1	104.1	99.6
		3	98.5	100.6	96.2	102.9	99.5
		all	97.8	101.5	95.9	103.4	99.6
	Lifetime	1	69.0	125.0	69.0	125.0	97.0
		2	78.3	115.6	78.3	115.7	97.0
		3	113.1	82.6	82.6	113.2	97.9
		all	86.8	107.7	86.8	107.7	97.3
	PillAid	1	59.9	132.5	59.3	133.1	96.2
		2	117.2	77.6	76.8	118.0	97.4
		3	119.6	78.3	77.2	120.7	98.9
		all	98.9	96.1	95.7	99.3	97.5
	PillTool	1	98.2	100.8	95.4	103.6	99.5
		2	100.3	99.1	94.8	104.6	99.7
		3	98.9	100.9	96.0	103.8	99.9
		all	99.1	100.3	95.4	104.0	99.7
	Pilomat	1	101.2	98.1	94.9	104.4	99.7
		2	101.5	98.0	95.3	104.2	99.8
		3	101.5	97.5	94.7	104.3	99.5
		all	101.4	97.9	97.9	101.3	99.6
kitchen knife	Blokker own brand	1	100.4	94.0	87.5	106.9	97.2
		2	98.34	94.5	83.2	109.6	96.4
		3	104.9	92.6	88.3	109.2	98.7
		all	101.2	93.7	93.3	101.6	97.5

Table 2 Intra and inter precision of paracetamol tablets broken by hands (n=100), several types of tablet splitters or a kitchen knife (n=100 per device; three devices per type investigated)

splitting technique		number device tested	precision (% RSD) for five different approaches to the selection of the tablet parts to be considered				
			right parts only	left parts only	lowest weight of both parts only	highest weight of both parts only	both parts
hand broken		nap	2.78	3.15	2.74	2.43	4.66
tablet splitter	Fit&healthy	1	20.31	20.74	21.31	8.52	20.52
		2	16.90	29.59	25.81	9.91	26.79
		3	16.69	23.14	20.58	10.04	21.33
		all	18.47	25.06	24.56	19.46	22.99
	Health Care Logistics	1	4.52	4.62	3.48	2.78	4.59
		2	4.46	3.99	3.96	3.18	5.78
		3	4.42	4.36	3.48	2.37	4.50
		all	4.73	4.54	3.70	2.85	4.98
	Lifetime	1	14.55	5.68	14.47	5.65	30.28
		2	12.84	6.06	12.75	6.00	21.28
		3	6.72	8.75	8.71	6.69	17.39
		all	24.42	18.13	24.42	18.13	23.54
	PillAid	1	25.67	11.16	24.94	9.16	40.96
		2	13.56	24.72	23.67	12.58	27.22
		3	8.76	14.24	11.13	6.63	23.60
		all	31.37	31.21	31.12	31.40	31.30
	PillTool	1	5.22	5.45	3.90	3.40	5.49
		2	5.43	6.20	3.69	2.64	5.84
		3	5.02	5.03	3.68	2.96	5.11
		all	5.29	5.61	3.80	3.05	5.48
	Pilomat	1	6.04	6.20	4.51	3.81	6.31
		2	5.99	5.99	4.70	3.92	6.24
		3	6.03	6.35	4.86	3.89	6.49
		all	6.00	6.12	6.45	5.91	6.40
kitchen knife	Blokker own brand	1	11.88	15.10	11.97	7.47	13.85
		2	18.59	19.23	18.40	8.25	18.96
		3	12.39	14.82	12.79	8.48	14.88
		all	14.70	16.50	17.71	13.24	16.03

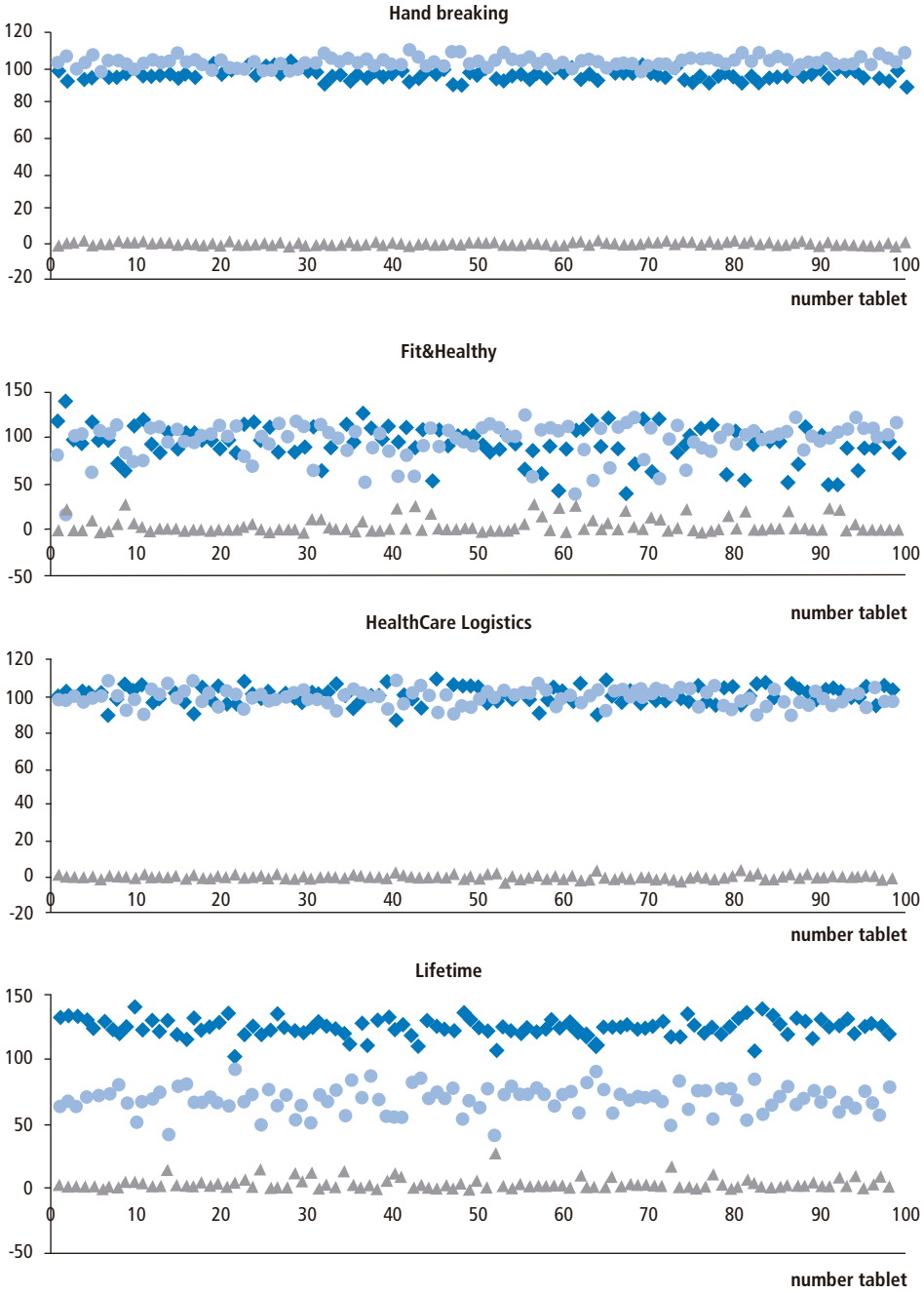

Figure 2 Percent active substance for tablets subdivided by hand and three different types of tablet splitters (red left parts, blue right parts, black loss of mass)

Table 3 Compliance to regulatory requirements of paracetamol tablets following subdivision by three techniques: hand breaking, tablet splitter and kitchen knife (100 tablets subdivided by hand; 300 tablets subdivided per type of device)

		uniformity of weight as adapted from Ph. Eur. 478 subdivision of tablets*						assay simulated as adapted from Directive 2001/83/EC&			loss of mass as adapted from FDA$	
		number of tablet parts (from both sides) in the specified range						mean weight parts from				
splitting technique		<75% (n=)	75-85% (n=)	85-115% (n=)	115-125% (n=)	>125% (n=)	complies	right side (%)	left side (%)	complies	>3.0% (n=)	complies
hand broken		0	0	200	0	0	yes	103.8	96.6	yes	0	yes
splitting devices	Fit&healthy	110	46	360	58	26	no	102.3	87.0	no	128	no
	Health Care Logistics	0	2	598	0	0	yes	97.8	101.5	yes	7	no
	Lifetime	148	91	173	126	62	no	86.8	107.7	no	88	no
	PillAid	149	91	149	88	123	no	98.9	96.1	yes	83	no
	PillTool	0	2	598	0	0	yes	99.1	100.3	yes	6	no
	Pilomat	1	8	584	7	0	no	101.4	97.9	yes	5	no
kitchen knife	Blokker own brand	48	47	460	38	7	no	101.2	93.7	no	74	no

* both parts of the same tablet were considered. Not less than 194 parts of 200 parts and 582 of 600 parts should be within 85-115% and all parts within 75-125% of the theoretical (nominal) halved tablet weight (Ph. Eur. requirements: break 30 tablets by hand; take 30 parts at random and reject the other parts; not less than 29 parts should be within 85-115% and all parts within 75-125%).

& only parts from the operators hands or the same side of the device were considered. The average weight of the 100/300 parts should be 95.0-105.0% of the theoretical halved tablet weight

$ loss of mass each tablet not more than 3.0% of the theoretical intact tablet weight.

When the 21 devices were considered separately and when all five approaches to the selection of the tablet parts were taken into consideration, then only tablets broken by hand and by the HealtCareLogistics splitter complied in every case (Table 2).

Tablets broken by hand complied with the adapted FDA test for loss on mass of maximum 3% (Table 3) whereas no of the seven types of splitting devices complied. When the 21 devices were considered separately, also tablets subdivided by the Pilomat device 1 complied (data not shown).

Discussion

The accuracy, precision and sustainability of three techniques for the subdivision of paracetamol tablets was investigated: hand breaking (n = 1 operator), tablets splitter (n = 6 types, 3 devices for each type tested), kitchen knife (n = 1 type, 3 devices tested). The results showed large differences and were generally best for hand broken tablets. It was also tested whether the tablet parts complied with three regulatory requirements adapted to the conditions of this experiment: 1) Ph. Eur. subdivision of tablets; 2) assay; 3) FDA loss of mass. Only hand broken tablets complied with all three tests. The devices did not deteriorate over 100-fold use. Any impact of the type of operator or tablet characteristics on the superiority of hand breaking over the use of a splitting device is left for future research.

The methodology was specifically developed for the aim of this experiment. In order to limit bias to the selection of the types of tablet splitters to be considered, we evaluated all splitters that were likely to be used by patients living in a specified region of the Netherlands (Utrecht) and those that could be purchased form either a community pharmacy or a drug store.

Currently, tablet splitters are not considered as a medical device. This implies that their manufacture is outside the control of a Notified Body i.e., the consistent performance between several devices of the same type may not be adequately assured. Therefore, we decided to evaluate three devices of the same type i.e., to study the intra- as well as the inter device accuracy and precision. In addition, there is also no assurance that the devices will not deteriorate over repeated use. Therefore, we decided to evaluate the performance of each device over common dispensing periods and dosing frequencies i.e., 100 tablets (equalling 3 months twice daily dosing and 2 months trice daily dosing of a half tablet).

Paracetamol was selected as the drug of choice because it is frequently used by a wide variety of patients in the Netherlands; because the dose for children and older people is often achieved by subdivision of the "standard" 500 mg immediate release tablet; because the geometry of this "standard" tablet (round, flat, uncoated) favours easy breaking and because the handling of large numbers of paracetamol tablets would not involve a risk to the operator's health (16). In order to avoid any bias due to the evaluation of a paracetamol tablet with "outlier characteristics", we carefully selected a trade mark with "average characteristics".

There is substantial evidence that tablets may not always break into two parts i.e., that tablets may break into several pieces or show grinding. In such cases the difference in the weight of one tablet part to the half of the intact tablet weight may differ from the other part and consequently, the accuracy and precision may depend on the selection of the tablet parts that are considered in the data analysis. In order to evaluate any impact of the selection of the tablet parts on the results of this experiment, we decided to evaluate five pre-defined approaches. These approaches were based on the following considerations: 1) the possibility to study any impact of the key characteristics of the splitting devices on the accuracy, precision, sustainability of the devices; 2) current clinical practices where large numbers of tablets are broken at the same time and put back into the container as if they were single dose units; 3) current clinical practices where both parts from the same tablet may not be given to the same patient.

In this experiment, the accuracies and precisions were calculated on basis of the theoretical weight of an intact tablet rather than the weight of each tablet itself prior to subdivision. This approach was considered acceptable in view of the low variability in the weight of 100 intact tablets (0.7%).

The differences in the accuracy and precision of the tablet splitters could not be explained by their design and price: although some splitters looked the same, their accuracy and precision were quite different and the most expensive tablet splitters were not always the best. One of the tablet splitters had a knife that was sharp on one side only. By visual examination, it turned out that the sharp end was at the left side for two splitters and at the right side for the third splitter. A correction for this aspect was implemented in the General Linear model and Dunnet's analysis.

This experiment showed that tablet splitters and a kitchen knife may not accurately and precisely subdivide tablets into equal parts. This result is consistent with findings from other authors (11, 12, 17). However, in contrary to their studies, this experiment tested several types of tablet splitters and a kitchen knife over 100-fold use applying a best case drug, tablet and operator, and allowing comparison of the results with those of tablets broken by hand. In addition, three devices of each type were considered as well as the impact of five different approaches to the selection of the tablet parts.

Health care professionals may consider to study the dosing accuracy and precision of a specific type of tablet splitter in relation to a specified medicine if such a medicine must be subdivided by a splitting device. However, such studies will only be of any value to the patient when the results show consistent and acceptable intra device accuracies and precisions and when the results do not depend on the selection of the tablet parts that were considered in the data analysis. This investigation showed that these conditions were only met by the HealtCareLogistics splitter when applying a range of 95.0 - 105.0 for accuracy and a maximum of 5.0% for precision, and also by the PilTool and Pilomat splitter when applying a slightly lower threshold for accuracy of 94.7% and a higher threshold of 6.5% for the precision.

This experiment has some limitations. First, only a "best case" tablet with "average" hardness was studied. It was assumed that smaller, convex, very soft or very hard tablets would be more difficult to break into two equal parts by hand than the selected paracetamol tablets and that such smaller, convex, very soft, or very hard tablets would also be more difficult to subdivide with a splitting device. The included tablet splitters were dispensed without any restrictions to the type of tablets for which the splitters could be used. Therefore, we considered that the tablet splitters and the kitchen knife should be suitable for any tablet type, especially "best case". Thus, the impact of tablet geometry and hardness on the accuracy and precision of splitting devices is left for future research for those with adequate accuracy and precision with a best case tablet only.

Second, this experiment was conducted by a "best case" operator. However, the ability to break tablets by hand and correctly use a splitting device is known to decline with certain patient characteristics such as impaired hand function, limited visibility or mental retardation. It is unlikely that the effect of such changes on the accuracy and precision of tablet subdivision will show a similar pattern between the three techniques e.g., people with trembling hands may be well able to use a tablet splitter but not a kitchen knife. The evaluated tablet splitters were dispensed without any restrictions to the operator. In the Netherlands,

tablet splitters and kitchen knives are commonly used by health care professionals and caregivers who need to subdivide large numbers of tablets. Therefore, we considered that splitting devices should be suitable for any patient population. Thus, the impact of patient characteristics on the accuracy and precision of splitting devices is left for future research for those showing adequate accuracy and precision with a best case operator only.

None of the splitting devices meet the regulatory requirements as adapted for this experiment. As our criteria are reasonable and our results cannot be explained by a poor performing operator, we consider that the device industry should develop better tablet splitters.

In view of the high potential of intended or unintended off-label breaking, we advise the pharmaceutical industry to assure precise and accurate breaking of all break marked tablets irrespective of their posology and user instruction i.e., irrespective as to whether breaking has been approved by the regulatory authorities or not. In addition, industry is recommended to assure that the majority of the indicated patient populations will be able to break tablets by hand without any relevant difficulties or discomfort.

We urge authorities to undertake measures to assure that only tablet splitters with an acceptable accuracy, precision and sustainability can enter the market. In addition, the ease, accuracy and precision of breaking tablets by hand should be evaluated during the licensing process (new applications) and appropriate measures should be considered for break mark tablets that are already on the market. The development of a standardised methodology for the ease of tablet breaking would be welcomed. Such a test may be included in the Ph. Eur. In addition, incentives may be aimed at the development and authorisation of additional dosage forms that allow flexible dosing and easy swallowing such as oral liquids, sprinkles and mini-tablets (18, 19).

The development of an international harmonized methodology for the subdivision of tablets with a tablet splitter is recommended also. As this experiment showed that the accuracy and precision may depend on the selection of the tablet parts to be considered in the data analysis, such a test preferably includes a predefined approach to the selection strategy.

Health care professionals, patients and caregivers should realize that tablet splitting may result in dosing inaccuracies, which may have an effect on clinical outcomes. They should also remember that the subdivision of tablets is likely to go with any loss of mass and that even a small loss ("dust") may be potentially

harmful to the patient's environment depending on tablet's type of active substance e.g., in case of subdivision of mercaptopurin tablets for paediatric dosing in a domestic setting (20). Thus, patients should tell their nurses, doctors and pharmacists that they have difficulties breaking or swallowing tablets. Together they should consider alternative treatment options. These considerations may result in the continuation of the tablet splitter, however if so, the best available device should be used.

Conclusions

The accuracy and precision of none of the investigated tablet splitters and kitchen knife was equivalent to hand breaking when applying a best case drug, tablet and operator. Health care professionals and patients should realize that tablet splitting may result in inaccurate dosing. Authorities should undertake measures to assure good function of tablet splitters and, where feasible, to reduce the need for their use. The devices did not deteriorate over 100-fold use.

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Chapter 5

General Discussion and Summary

Introduction

Child and maternal health are key to overall human life expectancy, implying an urgent need for medicines that keep (unborn) children and mothers healthy and alive (1, 2). Unfortunately, medicines may bring harm as well (3, 4). For example, the intake of thalidomide by pregnant mothers in the 1950/60s turned out to be the cause for the increased incidence of phocomelia in new born babies (5, 6). Also, the use of the toxic solvent diethylene glycol in a US manufactured sulphanilamide elixer in the 1930s led to renal failure and death in many children (4, 7, 8). Therefore, the safety and efficacy of medicines needs to be investigated prior to marketing (4).


U. S. Races Death to Save 700 From Elixir

Recovery of Pint Bottles Sold to Patients Goal as Deaths From Poison Reach 36

In view of a series of serious and fatal events caused by the use of medicines in the past century, most countries considered that the responsibility of bringing safe and effective medicines to the market could not be left solely to industry. An authorisation (regulatory) system was introduced, requiring that companies should obtain approval from the authorities prior to the marketing of any industrially manufactured medicine and prior to introducing any post-marketing changes to the medicine's characteristics such as its indication or composition. In order to obtain such approval, companies were required to send the clinical, preclinical and quality data to the regulatory authorities for subsequent assessment. In the Netherlands, the authority task was laid down at the "College ter Beoordeling van Geneesmiddelen" (CBG) i.e., the "Medicines Evaluation Board in the Netherlands" (MEB). Currently, companies can also seek approval at the European Medicines Agency (EMA) for the marketing of a medicine in the whole European Union. A national or European marketing authorisation is issued in case of a positive benefit to risk balance and adequate and consistent product quality (4, 5, 9).

However, clinical studies in adults may not be predictive for children. As well as body weights and dimensions, children may also differ from adults with respect to their physical, physiological and psychological characteristics as human organ and body functions each develop at their own speed. Moreover, there may also be large differences among children of the same age themselves, e.g. with respect to child behaviour. Therefore, clinical studies are needed in each of the various target age groups by which a medicine is to be used (10, 11).

For long periods of time, clinical studies in children were considered as too difficult, unethical or not worth the money (12-14). As a consequence, the availability of authorised paediatric medicines is lagging behind those for adults: there is a general lack of formulations children are able and willing to take, and there is also a lack of formulations that parents and caregivers are able or willing to administer to their child. Thus, health care professionals may have no other choice than either a) to prescribe a medicine outside the conditions that were agreed with the authorities for the age, indication, or the dose of the medicine (off label prescription); b) to adjust the dosage form of an authorised medicine to make it suitable for use by a specific child (unlicensed drug use); or c) to compound a medicine from the active substance and excipients (unlicensed drug use) (15-18). In addition, parents and caregivers may decide to use a medicine in a way other than prescribed e.g. avoiding the intake of the medicine during school hours (off-label drug use if the newly applied schedule is not recommended in the product information) or to modify the characteristics of the dosage form such as breaking or crushing tablets to make the child swallow the dose (unlicensed drug use if breaking and/or crushing is not recommended in the product information) (19-21).

Off-label and unlicensed drug use may hamper the effectiveness of pharmacotherapy and/or increase the risk of side effects in comparison to a situation where the same quantity of the same active substance would have been given by an authorised medicine. Thus, off-label and unlicensed drug use may put the health of a child at an avoidable risk (22, 23). This is no longer considered ethical and incentives by the US government, the European Union (Paediatric Regulation) and the World Health Organization have been directed at improving this situation by, among other things, stimulating the development of safe; effective; well-designed and authorised medicines for children i.e., age-appropriate or child friendly medicines (3, 24).

In order to support this goal, several research budgets for studies on the (pharmaceutical) development of medicines for children have been allocated by national, regional or global funding bodies, e.g. the 2007-2011 RIVM

strategic research program in the Netherlands (RIVM MAP SOR), the European KP7 projects and the WHO program "Make medicines child size" (25, 26). This PhD thesis is one of the products of these strategic programmes. The aim of the PhD study was to investigate the relationship between the availability, pharmaceutical design, usability and patient outcomes of medicines for children. The knowledge acquired through either this PhD study itself or any related activities was also aimed at the establishment of good regulatory guidance (regulatory science) (27).

Key results of the studies in this thesis

In 2009, we investigated the commercial availability of age-appropriate medicines for children on the Dutch market for two main reasons. First, to understand any challenges that health care professionals, parents and caregivers faced when providing children with medicines in the correct dose they are able and willing to take. Second, to provide a baseline for an evaluation of the effectiveness of the European Paediatric Regulation in increasing the availability of well-designed and authorised medicines for the children of Europe (28).



As expected, we found that the proportion of paediatric versus adult medicines was limited, increasing with age and largely dependent on the route of administration. However, we also found that marketing authorisation did not necessarily imply that the medicine was adequately designed for the age of the child as some formulations were unlikely to be swallowed by children of that age and because some doses could not be given with any of the commercially available formulations and strengths (Chapter 2.1). The reason for the latter problem has not been investigated, but might for example be explained by the fact that marketing authorisation does not necessarily assure that a medicine is also commercially available (29). Also, the problem might be explained by the fact that for long periods of time, companies were allowed to withdraw any specific formulation and/or strength of a medicine from the market without the need to consult any authority.

In view of the aforementioned, we also investigated to what extent the availability of age-appropriate paediatric (child friendly) medicines was likely to be improved by the European Paediatric Regulation. We found that the authority oversight ensured that medicines were generally developed for children of a wider age group. However, and despite the large number of questions to industry, changes to essential pharmaceutical design aspects such as the type of the oral dosage form or its composition/strength were generally fewer (Chapter 2.2).

In 2009, we also found that only 94 publications in the published scientific literature were providing information on the relationship between a pharmaceutical design aspect and a patient (related) outcome. This finding supported earlier conclusions that little is known about the pharmaceutical design aspects that are promoting the safety, efficacy and usability of medicines in clinical and domiciliary practice (24, 30). We found that information was most often available on the relationship between the type of formulation and dosage form versus patient acceptability and preference. However, rather than aiming to obtain knowledge on how fundamental design aspects would relate to patient outcomes, studies seemed merely driven by (marketing) considerations in preferring one product over the other (Chapter 3.1).

Therefore, we also studied the acceptability and preference of three commonly applied types of oral paediatric formulations, namely a powder, suspension and syrup, and a fourth less frequently applied, or by some even considered as novel, type of oral paediatric formulation, namely a 4 mm uncoated tablet (mini-tablet) (31). We found that all formulations were generally well accepted by 1 to 4 year old children and their parents, but that the small tablets were the best accepted and preferred formulation (Chapter 3.2). These results were consistent with our expectations, which were based on the wide availability of 4 mm vitamin D tablets in the Netherlands (no lower age limit); on earlier (unpublished) interviews with parents, caregivers and health care professionals on the way vitamin A/D was administered to young children and on how tablets of different sizes and oral liquid formulations were received by the child(ren) they were caring for.

In addition, we investigated how parents administered the four different formulations to their child in the domiciliary setting. As neither the written nor the verbal user information provided a recommendation that the formulations could be given with food or drink if desired, formally the formulations should have been given on their own (32). As expected, we found that the formulations were sometimes given with food or drink, and that parents were more likely to

do so when the child acceptability of the formulation was low than when it was high(er). Also, we found that the combined intake of the formulations with (a larger portion of) food or drink generally resulted in a higher child acceptability (Chapter 4.1).

Swallowing difficulties may be overcome by breaking tablets into two or more parts and swallowing all parts as a single dose. Alternatively, tablets may be broken into two or more equal parts to obtain a lower dose. As a consequence, tablets are frequently subdivided by patient populations who generally require lower doses or who are more prone to swallowing difficulties i.e., children and older people (18, 33). However, parents, (older) caregivers and health care professionals may have difficulties in breaking tablets by hand (34). In these cases, tablet splitters and kitchen knives are commonly applied as a coping strategy (35). We found that the dosing accuracy and precision of tablets broken by the hands of a best case operator was better than for each of six commonly available tablet splitters and a kitchen knife. We also found that the accuracy and precision of the tablet splitters may vary greatly among themselves (Chapter 4.2).

In this general discussion, the studies presented in this thesis will be put in a broader perspective. The discussion will focus on three main themes, namely pharmaceutical development of medicines for paediatric use, the Paediatric Regulation and Paediatric Investigation Plans (PIPs), and child-parent relations and medication acceptability.

Pharmaceutical development of medicines for paediatric use

According to international definitions, "the aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product", where quality is to be understood as "the suitability of either a drug substance or a drug product for its intended use" (36). In accordance with these definitions, it is now increasingly acknowledged that the pharmaceutical development of a (paediatric) medicine involves more than its formulation aspects. For example, the recommended dosing frequency, type of packaging, type of medical device or the comprehensibility of the user instruction may an impact on the medicine's "intended use" in clinical and/or domiciliary practice also (37, 38). In fact, child health is likely to benefit from a holistic approach to the pharmaceutical design of a paediatric medicine as will be explained below.

Formulation and Dosing frequency. In this thesis, we investigated the child and parent acceptability and child and parent preference of four different oral paediatric formulations given twice a day (Chapter 3.2). However, we did not investigate if, and if so how, the results would have changed in the case of different dosing frequencies. The potential importance of the dosing frequency to child health and thereby to the pharmaceutical design of a paediatric medicine is supported by the findings of van den Ban et al. for example (39). They found that the use of once daily methylphenidate extended release formulations for the treatment of ADHD in children resulted in less discontinuation of pharmacotherapy than the use of immediate release formulations that had to be administered three times a day.

Type of packaging. In many countries the risk of accidental medication overdosing is thought to be reduced by the use of child resistant container closure systems for certain types of active substances (40-42). However, some experts argue that the advantages and disadvantages of child resistant closures remain to be established. For example, because the application of such closures may be misleading and withhold parents and caregivers from the preferred approach to keep medicines out of the reach and sight of children; because accidental medication intake is commonly associated with medicines that were already taken from their packaging; or because the application of child resistant container closure systems may be challenging for people with impaired hand function (41, 43).

Another aspect relating of the type of packaging is the number of tablets per (over the counter) pack. On the one hand, companies may decide to market tablets in pack sizes that are small in relation to the maximum recommended daily dose e.g. 10 paracetamol 120 mg tablets. On the other hand, authorities may decide that the maximum number of tablets per pack size should be limited e.g. 50 paracetamol 500 mg tablets (44). In either case, the small pack size or the limitation to the number of tablets in the packaging may be intended to reduce the risk for missed diagnosis or intentional medication overdosing. However, we consider that for oral solid paediatric medicines, the influence of the pack size on public health needs to be further investigated. For example, because a small number of tablets per packaging may imply a higher risk of situations where parents will run out of stock and where they will modify the adult formulation to make it suitable for intake by their child. Or because the effectiveness of the limitations in the maximum number of tablets per pack size is reduced by the fact that several packs can be bought at once. Moreover, it is quite unlikely that people will use lower dosed oral solid paediatric medicines for intentional overdosing.

Type of medical device and the comprehensibility of the user instruction. In one of the studies in this thesis (Chapter 4.1), we showed that some parents did not use the syringe to administer the syrup and suspension to their child but rather chose to empty the contents of the syringe onto a spoon first, and then to administer the dose to their child. Other parents decided to administer the formulations with a small portion of food or drink on a spoon, while other parents preferred to mix the formulations in a larger quantity of the food or drink and to give the medicated food spoon by spoon or the medicated drink slug by slug. However, the joint intake of the formulations with food or drink was not recommended in the written and verbal user instruction and thus it was formally not acceptable (32, 37).

All of this handlings give rise to the question as to whether it is reasonable to expect that parents will understand that the lack of a recommendation in the user instruction to possibly administer a medicine with food or drink, should be understood as an instruction that the formulations should have been given on their own. We fully agree that there is a need to improve the comprehensibility of the user instruction on this aspect. Yet, it is also important to realize that in many cases the direct contact between the formulation and any food or drink will not result in any interaction, or not to a relevant extent when the contact time is only seconds (that is when the formulation is put onto a spoon with a small portion of food or drink and given immediately) or minutes (that is when the formulation is mixed through the whole portion of food or drink). Also, even when interactions such as impaired bio-availability occur, is may be considered either that the altered bio-availability is ultimately not clinically relevant in view of the wide therapeutic window of the medicine, or that it may be in the interest of the child to accommodate the problem by adjusting the dose rather than accepting suboptimal dosing adherence or daily quarrels between the parents and the child. Therefore, we consider that precautionary warnings on the joint intake of a medicine with food or drink should be limited to those situations where clinically relevant food-medication interactions may be expected on scientific grounds.

Pricing: According to Sam et al., the pharmaceutical development of a paediatric medicine requires a structured framework for the assessment of the comparative benefits and risks of the different pharmaceutical design options against predefined criteria for safety, efficacy and patient access, including costs (45). This opinion is supported by, for example, the aforementioned results of van den Ban et al. (46) on the use of methylphenidate by children and adults. The result of van den Ban et al. may be further considered in relation to a) the earlier Dutch health technology assessment that the added value of extended

release methylphenidate preparations for ADHD does not justify their higher price and that consequently, parents must pay the higher costs involved (47, 48); b) parental complaints on the internet that they consider their child (children) is doing much better on the extended release formulation and that they do not think it reasonable that the extended release formulation is not fully reimbursed and that they have to pay for the increased costs themselves (49).

The introduction of Clarosip to the market in 2005 also showed that pricing and reimbursement policies may have a broader impact on the availability of paediatric formulations beyond the inability of some parents to pay the increased costs. The product brought a new concept to the administration of the antibiotic clarithromycin to children, namely a drinking straw. The straw included the entire dose of clarithromycin as tasteless coated granules. It was closed at the bottom by a white controller preventing granules from leaving the straw. When sipping the straw with any cold or hot drink (but without pulp), children would taste the beverage of their choice and at the same time co-swallow the medication without delay (50).

Thus, the pharmaceutical design of Clarosip was clearly intended to favour child acceptability, however, naturally the formulation was more expensive than the commercially available alternatives. As a consequence, health insurance companies were generally unwilling to reimburse the higher price and sales were low. As a result, the product was withdrawn from the market (51).

Both examples (extended release methylphenidate, chlarithromycin straw) show that innovative approaches intended to favour the ability and willingness of a child to swallow a medicine in accordance with the recommended dosing instruction may be counteracted by reimbursement policies. However, this implies that reimbursement policies may block essential innovations to the pharmaceutical design of paediatric medicines, which can be considered against the spirit of the Paediatric Regulation. Thus, there is a need for increased collaboration between regulators, industry, health technology assessment bodies and insurance companies.

During the drafting of the protocol and the participant recruitment of two of the studies in this thesis (Chapter 3.2 and Chapter 4.1), we observed that many parents, and even some health care professionals, considered that vitamin D tablets and drops were real medicines. Acknowledging the need to arrive at formulations that children are able and willing to take and that parents are able

and willing to administer to their child, we feel that aspects of the promotion of the use and sales of vitamin and food supplements may also be of value to the use and reimbursement policies of medicines for children.

For example, (multi)vitamin supplements can be purchased from the market through a wide range of trademarks and dosage forms e.g. oral drops, 4 mm tablets, chewing tablets, coated tablets, soft capsules. Their prices may be very different, yet they are all successfully sold, implying that the advantages of some high priced trademarks are apparently "worth the money". Thus, the availability of different types of oral vitamin dosage forms could be considered to support the conclusion of one of the studies in this thesis (Chapter 3.2) that rather than discussing which formulation would be best for children of a specific age, it might be better to promote the availability of (essentially) different formulations next to each other.

Vitamin sales also show a different concept in the appearance of the formulation and design of the packaging i.e., the product presentation. Whereas medicines are normally white, round or oval and packed in simple boxes, vitamin supplements for paediatric use are commonly available in a wide range of colours, shapes and packs, e.g. bear and sun shaped chewing tablets, pink, orange or red "gummies" and packaging referring to Disney princesses or to special cars. On the one hand, one may argue that the vitamin approach to product presentation should not to be followed or even considered for paediatric medicines because it is too much directed at sales promotion through child attraction, and because child attraction may result in an increased risk for craving and/or accidental overdosing. Also, from a pedagogic perspective, one may argue that it may not be wise to give the child the message that taking a medicine is something "nice" you are allowed to do by your doctor or parents, rather than something you should do to obtain or maintain good health.

On the other hand, one may also argue that suboptimal or a complete lack of child acceptability may mean that the child will not swallow its medicine, or not fully on all occasions, and that, depending on the criticality of the disease, this can be an even more serious risk to the health of the child than the increased risk of craving or accidental overdosing. Also, one may argue that child parent and sibling relations may suffer from repeated quarrels and that it may also not be wise from a pedagogic perspective to give the child the message that he or she can only obtain or maintain good health by doing something "horrible" on a repeated basis.

Therefore, in our opinion, the pharmaceutical development of a paediatric medicine should best be based on a holistic approach to its pharmaceutical design aspects including other aspects that may have an impact on the intended and correct use of the medicine in clinical and domiciliary practice. Such aspects may e.g. involve the child and parent acceptability resp. child and parent preference of the formulation, the product presentation, the comprehensibility of the user instruction, manufacturability and cost aspects (37). All this entails a need to understand what children and parents actually want. We feel that valuable lessons may be learned from the vitamin i.e., food industry. In addition, we also feel that there is a need for a different approach to the pharmaceutical development of a paediatric medicine within the pharmaceutical industry, health technology assessment bodies, insurance companies, and regulatory authorities as novel approaches should be given a fair chance, especially when aimed at overcoming unlicensed or off-label drug use. All this necessitates bringing together the worlds of drug research (industry and academia), food industry, regulatory affairs, clinical and domiciliary practice, marketing, health technology assessment and, where applicable, politics.

The Paediatric Regulation and Paediatric Investigation Plans

By the end of the last century, high off-label and unlicensed prescription rates in children, especially in neonates, were reported (52). These reports raised concerns among stakeholders who argued that the application of off-label and unlicensed medicines in children implied a higher risk for adverse drug reactions and reduced efficacy rates, and that such higher risk could have been avoided if medicines that were authorised for use in adults or older children had been properly studied in (younger) children (53). Currently, this presumption is supported by the findings of Bellis et al. for example, who found that the risk of adverse drug reactions from the use of the off-label or unlicensed medicine use was 2.25 times greater than that from the use of an authorised medicine and who also found that the highest relative risk was associated with medicines given to children below the minimum recommended age or weight (22). The earlier reports also showed that there was a general lack of (authorised) formulations children were able and willing to take. This conclusion is consistent with the findings of one of the studies in this thesis (Chapter 2.1).

Acknowledging that the limited availability of authorised and well-designed medicines children are able and willing to take was already known to the pharmaceutical industry for many years, and acknowledging that paediatric research may present challenges from ethical, scientific and financial perspectives, there was a need for the authorities to become involved. Learning lessons from earlier incentives by the US government, in 2007 the European Paediatric Regulation was initiated (28). The Regulation aims to "facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations".

The Regulation is based on a system of obligations and rewards aiming to assure that the necessary data will be acquired to support the authorisation of the medicine for use by children. The Regulation applies to new medicines (medicines for which the active substance has not yet been authorised in any of the European Member States) and in case of a new indication, a new pharmaceutical form or a new route of administration of an existing medicine (a medicine including an active substance that had already been authorised in at least one medicinal product in at least one member state). The Regulation requires companies to develop a paediatric investigation plan (PIP) describing the studies planned to be conducted among children of different ages, the time lines to be followed and the formulations to be applied for each of the target age groups. For safety and/or ethical reasons, the PIP may also propose a deferral of the paediatric studies until the studies in adults have been completed. Moreover, companies may apply for a waiver of studies in children where the medicine is likely to be in-effective or unsafe; when the disease does not occur in children or when the medicine has no significant therapeutic benefit over existing treatments. The PIP must be sent to the European Medicines Agency (EMA) for agreement by the Paediatric Committee (PDCO) and the agreed proposals are binding at the time of marketing authorisation.

In June 2013, the European Commission published a report for the European Parliament and the Council on the experiences acquired over the first five years the Regulation had been into force (54). In the report "Better medicines for children - from concept to reality", the Commission concluded that the true impact of the Regulation on the health of the children of Europe would only become apparent over time, as paediatric studies may take many years and the Regulation has so far been into operation for only five. However, the Commission also concluded that the signs were promising. They stated that

paediatric development had become a more integral part of the development of medicines in Europe, that already a number of paediatric formulations had been authorised for which the PIP procedure had been followed and that the high number of PIP assessment applications indicated that there were many new medicines for children in the pipeline.

The Commission's report was based on an interim analysis of the experiences obtained from a wide variety of stakeholders through public consultation, including an EMA 5-years report to the Commission (55). The EMA-report included, among other things, an evaluation of the assessment of the paediatric formulations in the PIPs. The report indicated that for the majority of the PIPs, concerns had been raised about the company's proposals and that the most common issues related to the lack of justification on the use of the excipients in the proposed formulation for the anticipated target age groups; the lack of proposals to test the palatability or the overall acceptability of the proposed formulation in children and the lack of adequate information on dosing flexibility, accuracy and the practical handling of the formulations by health care professionals and patients. As one of the studies in this thesis showed (Chapter 2.1), similar issues may be present for marketed products.

The fact that the EMA/PDCO raised concerns about the majority of the formulations in the PIPs might be interpreted to mean that companies would not have been able to develop an age-appropriate paediatric formulation at the time of the application for marketing authorisation without the EMA/PDCO involvement. However, this assumption may not be correct. The concerns may simply indicate that both the EMA and the companies were still in the learning process regarding the data to be included in the PIP. Also, it should be realized that PIPs are normally submitted at the end of the human pharmacokinetic studies in adults and before the clinical efficacy of the new active substance had been shown. This implies uncertainties about the paediatric doses and the age of the children for which the medicine will ultimately turn out to be effective, and consequently, the relevant aspects in the pharmaceutical design of the paediatric medicine to be considered.

In fact, the number of modifications to agreed PIPs is now higher than the number of PIP applications. According to Winzenburg, this may be due to the need to change the timelines or study design of the agreed paediatric trials, or difficulties during the agreed paediatric formulation development (56). Winzenburg's explanation may be considered together with the results of one of the studies in this thesis (Chapter 2.2) on the changes realized by the EMA/PDCO oversight to the PIPs.

Despite the fact that concerns were raised about the majority of the formulations in the PIPs, our study indicated that the EMA/PDCO review did not result in a substantial number of changes to the pharmaceutical characteristics of the oral formulations in the original and agreed PIPs from an overall perspective (55). This difference may be explained by the fact that a) concerns were adequately explained and justified by the companies; b) concerns were to be regarded as voluntary suggestions for product improvement rather than strict requirements that had to be met prior to EMA/PDCO agreement; c) concerns were rather directed more to the best type of dosage form to be applied e.g. oral solid flexible versus oral liquid, than to the characteristics of the oral liquid or oral solid flexible dosage form itself; d) the opinion on the formulation requirements for the PIPs and marketed products was still pending.

Normally, it does not matter to children, parents or caregivers if a paediatric medicine has or has not been developed following a PIP, or as to whether the trademark dispensed has been authorised recently or many years ago. Considering that scientific knowledge has gradually evolved over time and that the design aspects of medicines which were authorised long ago do not necessarily meet current standards, it is likely to be in the interest of the health of the children of Europe to discuss the criteria that should be met by any medicine that is currently marketed for children. This is especially relevant as one of the studies in this thesis (Chapter 2.1) showed that some authorised paediatric medicines were actually age inappropriate.

The need to apply the same requirements to any paediatric formulation in the PIP where appropriate as well as any paediatric medicine newly introduced to the market (innovator as well as generic medicines; new as well as revised formulations) was clearly acknowledged in the "Guideline on pharmaceutical development of medicines for paediatric use" (37). In our view this is a very important contributor to the development of patient centric medicines. Moreover, the guideline puts high emphasis on the need to justify the choices made (36). Thus, to our opinion, the condition of the Paediatric Regulation that the agreed proposals to the formulation development of the medicine in the PIP are binding at the time of the foreseen marketing authorisation is not intended to be used as an excuse to refrain from compliance with the guideline at the time of the actual marketing authorisation.

New evidence from the scientific literature, new guidance or the knowledge acquired through the clinical and pharmaceutical development program of a paediatric medicine, may show that the formulation as proposed for marketing in the PIP is adequate, but no longer the best from an overall holistic approach.

In such cases, we feel that companies could be stimulated to propose any such better approaches in the dossier for marketing authorisation; and that it should not be necessary to pre-discuss such proposals with the EMA/PDCO in order to pass the PIP compliance check.

The "Guideline on pharmaceutical development of medicines for paediatric use" is not intended to be applied retrospectively i.e., to products that are already on the market, although this was initially (with a 5-years transitional period) considered (57). Instead, the adopted guideline now clearly states that pharmaceutical companies should respect the condition of Directive 2001/83 Article 23 stating that "After an authorisation has been issued, the authorisation holder must, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods" (37, 58). Reference to this Article was included for reasons outlined above i.e., because practical evidence and scientific knowledge may increase over the lifecycle of a product and thereby result in a need to improve the pharmaceutical design of the paediatric medicine in the interest of the health of the children of Europe.

Article 23 puts the main responsibility for applying for any necessary variations to marketed products on the shoulders of the marketing authorisation holders. When marketing authorisation holders do clearly not meet this expectation, then we believe that appropriate actions by the regulatory authorities are needed.

The Paediatric Regulation has led to a greater public availability of protocol-related information from clinical trials. Moreover, increased transparency measures by the regulatory authorities have resulted in the publication by the EMA of the PIP opinions and decisions, Public Assessment Reports and the scientific user information of any medicine for human use (SmPCs). All of this data can be used by researchers to evaluate the effectiveness of the Paediatric Regulation by means other than those presented in this thesis.

The public data already show that PIPs are being assessed on their own merit. This may imply that different companies may have been asked to conduct similar pharmaceutical studies in children, which may not bring any new information. Also, different companies may need to undertake studies in the same small patient population. In order to meet the PIP time lines, participant recruitment may become a critical aspect of company competition. The burden this may bring to patients may not only be considered unethical, it may also be argued

that the money involved could have been spent more effectively in the interest of the health of the children of Europe if forces had been combined (59, 60).

Child-parent relations and medication acceptability

Adequate drug adherence is an important precondition to the clinical safety and efficacy of a medicine: even a medicine with an optimal benefit to risk profile does not work if it is not taken. In the domiciliary practice, adequate drug adherence is to a great extent determined by the ability and willingness of a child to take the medicine as intended as well as the ability and willingness of the parents to administer the medicine to their child as recommended.

However, rather than two straightforward relationships, namely between the pharmaceutical design of the paediatric medicine and the child abilities and character, and between the pharmaceutical design of the paediatric medicine and the parents' abilities and character, the experiences from the participant recruitment of our RCT (Chapter 3.2 and Chapter 4.1) suggest that it is rather a triangular relationship. In addition, the relationship may be considered as even more complex when the impact of professional health care providers and the child's relatives and friends is included as well.

Although it must be emphasized that the verbal explanations which were part of the participant recruitment process were not designed as interviews for a qualitative study, the discussions between the interviewers and the parents provided interesting considerations and ideas for future studies. For example, the interviewers recalled that it was hard work to explain to the parents why it was so helpful to participate in the trial, regardless of the acceptability of the formulations to their child. This is because many parents simply argued that they did not have to try, but could just tell the interviewer how their child would behave.

This finding supported our belief that it was very important to explain the reason for our RCT to the parents and also to involve them actively in the conduct of the study. However, it also highlighted the importance of further scientific studies into what extent parents are able to predict their child's acceptability of the medication, or alternatively, to which extent parental ideas about their child's acceptability of medication may actually influence the acceptability of the child itself.

Other parents indicated that participation by their child in our RCT would give a bad signal to the child as if it was allowed to refuse medication. These parents were only willing to participate in the trial when they understood that the aim of the study could be explained to their child by words such as "Children may have to take medicines when they are ill. We know that some children do not like taking medicines because they are difficult to swallow and do not taste nice. Now people want to make better medicines for children, but they do not know how, as they do not know what children want. They are trying to find out. Do you want to help them by swallowing four placebo formulations and telling them if you found them unpleasant or not?" This observation supports the approach by which the participation of children in studies is discussed with them from a very young age where appropriate.

Another group of parents did not seem to understand the aim of our RCT at all, arguing that "if I say my child needs to swallow a medicine, he will do so". Parents also frequently asked questions relating to the child's siblings. "If my younger child is allowed to participate in a study where adults are interested in his opinion, then my elder child will be jealous". Or "my youngest child will swallow anything his brother does as he wants to be big as well. Can you then still trust the result?". All this supports the approach by which parents are actively involved in the design and conduct of paediatric trials.

Our observations also provide a basis for an additional approach to child medication acceptability, namely to what extent this acceptability might be improved through the child's close circle of family, relatives and friends. If such interventions appear to be possible, this may be very helpful in cases where the child acceptability of a formulation is low and where a fundamentally different alternative formulation that may accommodate the problem does not exist, e.g., a syrup if the child does not want to swallow a tablet or vice versa.

We have found some support for our observations in the scientific literature. For example, Akram et al. indicated that parents often advised nurses as to whether their child's medication needed to be co-administered or mixed with food or drink or otherwise modified in order to enable swallowing (19). Also, Dashiff et al. found that the child mother relationship (support, conflict, control, involvement, emotional expression) is an important link to diabetes outcomes in older children (61). Moreover, Iskander et al. found that adherence during a 3 year observational study in children from 9 to 11 years old could be predicted from baseline preadolescent youth and maternal positive communication (62). Finally, we found that 4 mm tablets were well accepted by children from 1 to 4 years old when given in the domiciliary setting in the Netherlands, yet Thomson

et al. found that smaller tablets were only accepted by about half of children aged 2 to 3 years when given by the parent in a quiet distraction free area of a hospital in the UK (31).

All of these findings support the conclusion that child medication acceptability is best to be considered within the context of its actual use i.e., parent versus health care professional, hospital ward versus domiciliary setting, in one country versus another and also for any special paediatric patient populations such as Attention Deficient Hyperactivity Disorder (ADHD), mentally impaired etc. We realize that all such acceptability studies may not be possible prior to the marketing of a paediatric medicine i.e., that not all such studies are already proposed in the PIP. Especially in cases where the child acceptability of a paediatric medicine has not been fully explored, we recommend that companies actively research the child acceptability of the paediatric medicine in the actual domiciliary and clinical practice i.e., post marketing. Moreover the acceptability of the paediatric medicine by parents, caregivers and health care professionals should preferably be considered as well.

Acknowledging the need for medicines that are acceptable to the majority of children within a certain population, companies are now frequently requested to propose child acceptability studies in the PIP, however the choice of the method, and the justification for each choice, is left to the companies themselves (63). We consider that such a justification could include for example a) the representativeness of the children eligible for inclusion in the test to the children in the actual patient population; b) how differences in child and parent behaviour were considered in the design of the medicine and how the impact of both aspects on drug adherence could be observed by the proposed test; c) how the potential impact of the dosing frequency and duration of therapy was addressed in the design of the test; d) in which setting(s) and countries the different formulations of the medicine are likely to be used; e) by whom the formulations are likely to be administered to the child and from what age the child is expected to take the medicine itself; f) why the selected outcome parameter in the acceptability test (e.g. VAS-score, result of the intake) was considered appropriate; g) when child acceptability was considered adequate and why the threshold was considered suitable for the specific medicine. We consider that the development of an internationally developed and harmonized method including acceptance criteria could be promoted when results of these studies are made publicly available and forces (academic, industry, regulators) combined.

Conclusions

Children are no miniature adults as human growth is not a linear process. As a consequence, the relevant differences between children and adults (and likewise between younger and older children) with respect to e.g. body weight/dimensions, physical, physiological and psychological characteristics necessitate a holistic approach towards the clinical and pharmaceutical development of medicines for use in children. However, in order to assure that children will actually be treated with safe, effective, well-designed and authorised i.e., child friendly medicines, it is important that such an holistic approach takes due account of any aspect that may influence adequate drug adherence, and thereby the usability and commercial availability of the medicine in domiciliary and clinical practice. Thus, close collaboration between formulation scientists (industry and academia), clinicians, regulators, health care professionals, and experts working in the fields of product marketing, health technology assessment, food industry, psychology/pedagogy and patient (organisations) is recommended.

In the studies presented in this thesis, we found that the commercial availability of medicines for children is lagging behind those for adults and that some authorised paediatric medicines are actually age inappropriate. We also found that the EMA/PDCO authority oversight to the proposals for the development of a new paediatric medicine in the PIP, generally resulted in a limited number of changes to the pharmaceutical design of the formulations. In addition, we found that scientific evidence on the relationship between the pharmaceutical design of paediatric medicines and patient outcomes is generally scarce. Therefore, we studied the child and parent acceptability of four different oral formulations (4 mm tablet, powder, suspension, syrup) in children from 1 to 4 years old in the domiciliary practice and found that all formulations were well accepted and that the small (4 mm) tablets were the best accepted formulation. We also observed that some parents had given the formulations in a different way as formally intended, namely with food or drink. We found that parents were more likely to do so when child acceptability was low and that the joint intake of the formulations with food or drink generally resulted in better child acceptability. Finally, we realized that (normal-sized) tablets may be subdivided in order to lower the dose or to facilitate swallowing and that tablet splitters are commonly used as a coping strategy when hand breaking is difficult. We found that the accuracy and precision of tablet subdivision was better when these were broken by the hands of a best case operator, than with any of six readily available tablet splitters. We also found that relevant differences between the different types of splitters exist.

The need to include a proposal on the pharmaceutical development of the paediatric medicine in the PIP is supported. However, it should be remembered that it is the company itself which is primarily responsible for bringing a safe, effective and well-designed i.e., age-appropriate (child friendly) medicine to the market. Thus, the final acceptability of the proposed paediatric medicine, including its pharmaceutical design, is to be assessed at the time of marketing authorisation. As a consequence, it is recommended that both companies and the EMA/PDCO avoid a system whereby the PIP frequently needs to be modified to enable the implementation of advancing knowledge. However, companies and regulatory bodies are urged to propose variations to the pharmaceutical design of any currently marketed paediatric medicine that clearly does not fulfil current expectations.

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Chapter 6

Appendices

Abbreviations

ATC	Anatomical Therapeutical Chemical (classification code).
CCMO	Centrale Commissie Mensgebonden Onderzoek (Central Committee on Research in Human Subjects)
DREAM	Document Records and e-Archive Management database of the EMA
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
MA	Marketing Authorisation (in this thesis equivalent to licensed paediatric medicine)
MEB	Medicines Evaluation Board in the Netherlands
PedRA	Paediatric Records Application database of the EMA
PIP	Paediatric Investigation Plan
PDCO	Paediatric Committee
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment)
RCT	Randomised Clinical Trial
SmPC	Summary of Product Characteristics
UIPS	Utrecht Institute for Pharmaceutical Sciences
UK	United Kingdom
USA	United States of America
VAS	Visual Analogue Scale
WMO	Wet Mensgebonden Onderzoek (Dutch Medical Research Involving Human Subjects Act)

Recommendations from this thesis

The main recommendations arising from this thesis are summarised in this Appendix.

Recommendations for future research

Availability

- This thesis confirms that the availability of authorised paediatric medicines is lagging behind that of adults. Therefore, it is recommended that there is an evaluation of the extent to which the low availability of medicines in a particular therapeutic area is causing problems in actual clinical (hospital, institutional, domiciliary) practice.
- In addition, in 5 to 10 years' time, it is recommended that there is a re-evaluation of the effectiveness of the Paediatric Regulation in increasing the availability of authorised and well-designed i.e. age-appropriate medicines for children.
- At the same time, it is also recommended that there is an evaluation of the extent to which any increase in the availability of age-appropriate medicines has been able to cover the real therapeutic needs of children.

Pharmaceutical design and usability

- Small (mini-) tablets may not be large enough to contain the recommended dose. Therefore, it is necessary to study the acceptability of several mini-tablets for the provision of a single dose in children of different ages.
- Preferably, any other (novel) strategies for the administration of medicines to children will be considered as well.
- Where there is a lack of age-appropriate formulations, conventionally sized tablets may be subdivided to lower the dose or to ease swallowing. When hand breaking tablets is difficult or painful, tablet splitters may be used as a coping strategy. In this thesis we investigated the impact of the type of tablet splitter on the dosing accuracy of the subdivided tablets. However, the actual impact of the tablet or operator characteristics on the suitability of tablet splitters is not yet clear and these are left for future research.
- We feel that the child acceptability of paediatric medicines is best investigated in conditions similar to actual use. Therefore, any impact of different cultures or settings (domiciliary, institutional, hospital) on the acceptability of oral formulations needs to be further explored.

- Preferably, children and caregivers will be involved in the testing and ultimate choice of the formulations intended for marketing, including the willingness and ability of children to accept the formulations and including the willingness and ability of parents and caregivers to adhere to the user instruction.
- Acknowledging that paediatric medicines may be used for adults with swallowing difficulties and/or in need of lower doses such as older adult patients, the appropriateness of paediatric formulations for use in other special patient populations should be investigated where feasible.

Research methodology

- We advise researchers to follow our approach in involving specialist librarians for the establishment of search profiles on the pharmaceutical design aspects of medicines for special patient populations because publications are scarce and fragmented and uniform key words yet to be established. For the same reason, any search result should be carefully validated.
- In this thesis, we have used the Jadad score to measure the methodological quality of paediatric studies. However, this instrument acknowledges neither the specific characteristics of children nor the special conditions for research in legally incapable patients. Therefore it is recommended that an appropriate instrument for measuring the methodological quality of clinical trials in children is developed.
- The following needs for uniform definitions and methodologies have been observed in this thesis.
  - First, the criteria to be employed for the assessment of the child authorisation status of medicines that are already on the market i.e. existing medicines. Such criteria are important because the Summary of Product Characteristics (SmPCs) of existing medicines may be outdated, and as a result, it may not be sufficiently clear to health care professionals and patients whether the medicine can or cannot be used in children of a specific age.
  - Second, an appropriate taxonomy for the patient outcomes in paediatric studies as e.g. paediatric adherence may be influenced by parental enforcement.
  - Third, a methodology for testing the acceptability and preference of medicines in children of different ages.
  - Fourth, a methodology for testing the suitability of splitting devices.
  - Fifth, a methodology for testing the ease of tablet breaking.
- The definitions and methodologies that have been specifically developed for the studies presented in this thesis have proven to work well. As a consequence these may be adopted and further explored by other researchers

and considered as a basis for regional or international consensus building through e.g. the European Pharmacopoeia or ISO standards.

Recommendations to industry, authorities and insurance companies

Availability

- It is recommended that pharmaceutical industries continuously assure that all dosing recommendations for children of a specific age in the medicine's SmPC can be conducted with at least one commercially available and age-appropriate formulation.
- It is further recommended that competent authorities undertake appropriate actions when the recommended doses cannot be given with any of the authorised paediatric medicines.

Pharmaceutical design and usability

- When designing (oral) medicines for children, it is recommended that pharmaceutical industries acknowledge the valuable lessons that might be learned from the promotion, sales and use of food and vitamins for children as e.g. swallowability and age-related behavioural aspects may be quite similar. These lessons could also be of use to the competent authorities for assessment or reimbursement policies.
- In order to improve child acceptability, it is recommended that pharmaceutical industries consider the marketing of several types of (oral) dosage forms and/or formulations in parallel.
- Acknowledging the limited availability of age-appropriate medicines for children, it should also be acknowledged that tablets are commonly broken for dose reductions as this may allow the off-label application of the medicine to younger children. As a consequence, it is recommended that pharmaceutical industries assure easy and accurate breakability of any tablet.
- It is recommended that authorities carefully monitor the impact of assessment and reimbursement policies on any blocking of changes that are aimed at improving the age-appropriateness of a paediatric medicine, and on any blocking of novel approaches that are intended to favour the administration of medicines to children, as such blocking can be considered against the spirit of the Paediatric Regulation.

Summary of Product Characteristics (SmPC)

- This thesis confirms that authorised medicines may not be licensed for children at all, or not in an age-appropriate form. Thus, it is essential that health care professionals have easy and immediate access to information on the availability and pharmaceutical design of medicines for children i.e. easy and immediate access to (the information in) the Summary of Product

Characteristics (SmPCs). Therefore, it is recommended that authorities are developing a publicly accessible SmPC database that can be searched for any relevant keyword, see e.g. www.cbg-meb.nl.

- In addition, it is recommended that pharmaceutical industries update any outdated SmPCs in order to provide health care professionals and patients with information currently considered relevant to adequate pharmacotherapy.
- Any precautionary warnings on the joint intake of medicines with food or drink that are based on the lack of compatibility data i.e. the fear for a potential impact of the food or drink on stability and bio-availability, should be carefully balanced against the risk for reduced child acceptability and adherence rates. This is especially true when chemical and/or physical interactions are unlikely to result in a clinically relevant effect.
- Where the marketing of an age-appropriate formulation, either new or existing, cannot be reasonably expected from industry, it is recommended that the SmPC is extended with information on the industry verified pharmacy compounding of the paediatric medicine.

Recommendations to health care professionals and patients

Pharmaceutical design and usability

- Doctors, pharmacist, parents, nurses, other caregivers and patients should realize that the safety and efficacy of an adult medicine has not been demonstrated for use in children and that, consequently, paediatric medicines cannot be interchanged with adult medicines even when providing the same dose through the same route of administration.
- In addition, they should realize that the different trademarks of a paediatric medicine may have different design characteristics and that such differences may result in a different acceptability by the child. Consequently, it is recommended that health care professionals and patients compare the different trademarks of a paediatric formulation in order to select the one that will best meet the child needs.
- Moreover, they should realize that administration errors, lack of adherence, suboptimal clinical outcomes and unexpected side effects may be due to formulations that fail to meet the needs of a specific child. Thus, it is of the utmost concern that parents, nurses and patients will inform the relevant health care professional of any problems experienced with actual medication use.

Recommendations to multiple stakeholders in the medicines' supply chain

- All stakeholders should realize that the historic approach that medicines are best given to infants and preschool children as an oral liquid formulation is not supported by evidence. Thus, the suitability of other types of oral dosage forms should be carefully considered. In any case, there is no reason to question further the acceptability of 4 mm tablets in children from the age of 1 year old.
- We feel that there is a need for a different (holistic) approach to the pharmaceutical development of paediatric medicines within the pharmaceutical industry, health technology assessment bodies, insurance companies, and regulatory authorities as the commercial availability of authorised, but age-inappropriate formulations require special attention.
- Novel approaches to the pharmaceutical development of paediatric medicines should be given a fair chance, especially when aimed at overcoming unlicensed or off-label drug use. All this necessitates bringing together the worlds of drug research (industry and academia), food industry, regulatory affairs, clinical and domiciliary practice, marketing, health technology assessment and, where applicable, politics.
- Regulatory science may be applied as a one of the useful tools to bridge gaps.

Samenvatting

Inleiding

Kindersterfte en het belang van geneesmiddelen

De gemiddelde levensverwachting van een bevolkingsgroep wordt in belangrijke mate bepaald door de sterfte onder moeders en jonge kinderen. Uiteraard is die sterfte sterk afhankelijk van de welvaart van een land en daarmee van de beschikbaarheid van algemene voorzieningen. Zo sterft in Sierra Leone één op de zes kinderen jonger dan vijf jaar door een gebrek aan medische zorg, hygiëne of schoon water of aan een relatief onschuldige aandoening zoals diarree. In Nederland is dit aantal veel lager, ongeveer één op de 250 kinderen.

Zowel in landen met een hoge als lage kindersterfte geldt dat geneesmiddelen een belangrijke rol hebben bij het voorkomen en behandelen van ziektes en overige aandoeningen. Voor een succesvolle behandeling van kinderen is daarbij de beschikbaarheid van op kinderen toegesneden geneesmiddelen (ook wel leeftijdsgeschikte of kindvriendelijke geneesmiddelen genoemd) van invloed. In dit proefschrift worden daarom de diverse aspecten van kindvriendelijke geneesmiddelen onderzocht.

Geneesmiddelen blijken soms schadelijk

Geneesmiddelen blijken soms niet alleen heilzaam, maar ook schadelijk te zijn. Zo zijn rond 1960 veel kinderen met een aangeboren afwijking aan hun ledematen geboren omdat, naar later bleek, hun moeder tijdens de zwangerschap het geneesmiddel Softenon had gebruikt. Bij Softenon wordt het schadelijke effect van het geneesmiddel veroorzaakt door de werkzame stof, thalidomide. Het schadelijke effect van een geneesmiddel kan echter ook worden veroorzaakt door de hulpstoffen die zijn gebruikt om van de werkzame stof een geneesmiddel te maken. Een bekend voorbeeld betreft het overlijden van mensen, en vooral kinderen, aan acuut nierfalen in de jaren 30 in de Verenigde Staten. Dat nierfalen bleek uiteindelijk het gevolg te zijn van de inname van een sulfanilamide antibioticum drankje. Dat drankje bevatte het oplosmiddel diethyleenglycol omdat sulfanilamide niet (voldoende) oplost in water. De firma had er echter niet op gelet of diethyleenglycol wel veilig was voor mensen.

Ook nu nog sterven er mensen, en vooral kinderen, aan het gebruik van drankjes die met (het relatief goedkope) diethyleenglycol zijn vervuild. Zoals in Haïti waar in 1996 85 kinderen stierven door het gebruik van een met diethyleenglycol

vervuilde paracetamoldrank. Of in Panama, waar in 2006 115 mensen stierven aan een hoestdrank die in plaats van het veilige oplosmiddel glycerol, het onveilige diethyleenglycol bevatte.

Softenon aanleiding voor registratie van medicijnen

Veel landen hebben naar aanleiding van de Softenon-affaire besloten dat het noodzakelijk was om toezicht te gaan houden op de bereiding en handel van fabrieksmatig bereide geneesmiddelen. Voordat een firma een geneesmiddel in de handel mocht brengen, moest er voortaan eerst een vergunning (registratie) worden aangevraagd bij de overheid. Die vergunning werd afgegeven als de firma aannemelijk had gemaakt dat het geneesmiddel werkzaam en (relatief) veilig was, en van afdoende kwaliteit. In Nederland werd het toezicht op de toelating van geneesmiddelen tot de markt neergelegd bij het "College ter Beoordeling van Geneesmiddelen" (CBG), dat inmiddels meer dan 50 jaar bestaat.

Sinds de jaren '60 is er veel veranderd. De Europese lidstaten hebben de nationale wetgevingen op het gebied van geneesmiddelen geharmoniseerd in een Europese Richtlijn (Directive 2001/83). En er zijn vele Europese en zelfs internationale richtsnoeren (guidelines) opgesteld waarin op gedetailleerd niveau wordt vastgelegd welke onderzoeken firma's moeten uitvoeren om aan te tonen dat een geneesmiddel voldoende veilig, werkzaam en van afdoende kwaliteit is. Sinds 1995 moeten of kunnen firma's ook in één keer een vergunning aanvragen voor het verhandelen van een geneesmiddel in de hele Europese Unie. Die vergunning wordt afgegeven door de Europese Commissie op voordracht van het Europese Geneesmiddelen Agentschap (European Medicines Agency, afgekort EMA). De EMA wordt daarbij op wetenschappelijk gebied ondersteund door een aantal comités, die op bepaalde kennisgebieden weer worden ondersteund door werkgroepen. Zo wordt het Comité voor Geneesmiddelen voor menselijk gebruik (Committee for Medicinal Products for Human Use, afgekort CHMP) onder andere ondersteund door de Werkgroep Kwaliteit (Quality Working Party, afgekort QWP) en de Werkgroep Veiligheid (Safety Working Party, SWP). De comités en werkgroepen bestaan voornamelijk uit experts die afkomstig zijn uit de landen van de Europese Unie. Het CBG bepaalt wie er vanuit Nederland in de CHMP (en een groot aantal andere comités en werkgroepen) plaatsneemt.

Kinderen zijn anders

Kinderen verschillen van volwassenen. Niet alleen wat betreft hun lengte en gewicht, maar ook wat betreft de mate waarin hun orgaanfuncties, hun motorische vaardigheden en hun sociaal-emotionele ontwikkeling zijn gerijpt. De snelheid waarmee al deze functies zich vanaf de geboorte tot aan het

bereiken van de volwassen leeftijd (18 jaar) ontwikkelen, verschilt aanzienlijk. Om die reden is het noodzakelijk dat de werkzaamheid en veiligheid (risico's) van een geneesmiddel wordt onderzocht bij kinderen in alle leeftijden waarvoor dat geneesmiddel is bedoeld. Bij dat onderzoek moet ook rekening worden gehouden met andere factoren dan de leeftijd van het kind. Bijvoorbeeld met de mate waarin een kind ziek is (een beetje of zwaar benauwd), de omgeving waar het geneesmiddel zal worden gebruikt (thuis of in het ziekenhuis) of met de ernst van de ziekte. Zo kan het bij een geneesmiddel voor een levensbedreigende ziekte nodig zijn om een bijwerking te accepteren die voor een relatief onschuldige aandoening absoluut niet acceptabel zou zijn, bijvoorbeeld haaruitval.

Lange tijd werd het onderzoek van geneesmiddelen bij kinderen als te moeilijk, te duur en/of onethisch beschouwd. Dat heeft er toe geleid dat het aantal geneesmiddelen dat is toegelaten (geregistreerd) voor gebruik bij kinderen veel kleiner is dan het aantal voor volwassenen. Voor kinderen is er bovendien een gebrek aan geneesmiddelen in de juiste sterkte, in een toedieningsvorm die het kind kan en wil innemen en/of in een toedieningsvorm die ouders/verzorgers ook op de juiste wijze kunnen en willen toedienen.

'Off-label use', 'eigen bereiding' en risico's

Een geneesmiddel kan in verschillende sterktes en formuleringen in de handel zijn. Met een formulering wordt een bepaalde toedieningsvorm van het geneesmiddel bedoeld (bijvoorbeeld een capsule of tablet), met een bepaalde samenstelling (bijvoorbeeld met of zonder suiker) en verdere eigenschappen (bijvoorbeeld de vorm en afmetingen van een tablet).

Wanneer er geen geschikte sterkte en/of formulering van een geneesmiddel in de handel is, hebben artsen vaak geen andere keuze dan het voorschrijven van een geneesmiddel buiten het officiële toepassingsgebied. Dus buiten de voorwaarden waaronder dat geneesmiddel door de overheid is toegelaten tot de markt. We noemen dat 'off-label use'. Het kan ook nodig zijn dat artsen een geneesmiddel voorschrijven dat door de apotheek zelf moet worden bereid. We noemen een dergelijk geneesmiddel een 'eigen bereiding'. Eigen bereidingen zijn niet geregistreerde geneesmiddelen omdat ze buiten het (directe) toezicht van de overheid (het CBG of de EMA) worden gemaakt.

De toepassing van een off-label geneesmiddel betekent dat de veiligheid (risico's), werkzaamheid en/of kwaliteit van dat geneesmiddel niet zijn onderzocht, of in mindere mate als gebruikelijk zou zijn bij een aanvraag voor een handelsvergunning. Het kan ook zijn dat de firma, of een andere belanghebbende, de toepassing van het geneesmiddel wel degelijk heeft onderzocht volgens de

eisen die gebruikelijk zijn bij een aanvraag voor een handelsvergunning, maar dat men die informatie niet ter goedkeuring aan de overheid heeft willen of kunnen voorleggen. De toepassing van een off-label geneesmiddel houdt een mogelijk risico in voor de patiënt, omdat de overheid geen toezicht heeft gehouden op de afweging tussen de voordelen en de mogelijke risico's van dat geneesmiddel. Een vergelijkbare situatie geldt voor de toepassing van een eigen bereiding, hoewel daarbij ook nog andere onzekerheden een rol kunnen spelen. Het gaat dan bijvoorbeeld om de houdbaarheid van de eigen bereiding, of de mate waarin de werkzame stof na inname vrijkomt uit de eigen bereiding.

Wetgeving over kindergeneesmiddelen

Aan het einde van de vorige eeuw kwamen experts uit de Verenigde Staten en Europa tot de conclusie dat niet het onderzoek van geneesmiddelen bij kinderen zelf als onethisch moet worden beschouwd, maar juist het gebrek aan goed onderzochte geneesmiddelen in de juiste sterkte en in een leeftijdsgeschikte (kindvriendelijke) formulering. Zij concludeerden bovendien dat het kennelijk niet aan de geneesmiddelenindustrie zelf kon worden overgelaten om dit probleem op te lossen, en dat overheidsingrijpen noodzakelijk was. Mede op basis van eerdere ervaringen in de Verenigde Staten, werd in 2007 in Europa de Verordening betreffende geneesmiddelen voor pediatrisch gebruik (Regulation 1901/2006) van kracht. Eén van de doelstellingen van deze Verordening is de ontwikkeling en registratie van veilige en effectieve geneesmiddelen waarvan het ontwerp is toegesneden op het gebruik bij kinderen.

De genoemde Verordening bevat verschillende wettelijke stimuleringsmaatregelen. Deze richten zich op het verbeteren van de bestaande situatie door de invoering van verplichtingen en beloningen voor de geneesmiddelenindustrie. De belangrijkste verplichting is dat een firma de ontwikkeling van een geneesmiddel niet kan beperken tot volwassenen, maar ook kinderen bij die ontwikkeling moet betrekken. Dat geldt zowel voor de ontwikkeling van een geneesmiddel met een nieuw werkzaam bestanddeel, als voor de ontwikkeling van een nieuwe toedieningsvorm of een nieuw toepassingsgebied (indicatie) van een bestaand geneesmiddel. De Verordening vereist dat firma's een zogenaamd Pediatrisch Onderzoeksplan (Paediatric Investigation Plan, kortweg PIP) opstellen dat ter goedkeuring moet worden voorgelegd aan het Pediatrisch Comité (PDCO) van de EMA (het Europese Geneesmiddelen Agentschap ofwel de European Medicines Agency). Vanzelfsprekend geldt deze verplichting alleen in die gevallen waarbij dat onderzoek bij kinderen ook zin heeft (sommige ziekten komen niet voor bij kinderen) of waarbij niet eerst de resultaten van het onderzoek bij volwassenen moeten worden afgewacht (omdat er nog te veel onduidelijkheid is over de veiligheid en risico's van dat geneesmiddel bij de mens).

Onderzoek naar kindergeneesmiddelen gestimuleerd

De kennis over de ontwerpaspecten van een geneesmiddel die bijdragen aan het goede gebruik van dat geneesmiddel is beperkt. Omdat die kennis wel nodig is voor de ontwikkeling van een kindvriendelijk geneesmiddel, hebben meerdere subsidieverleners besloten onderzoeken op dit gebied te financieren. Voorbeelden zijn het MAGIC project binnen het Meerjaren Activiteiten Programma Strategisch Onderzoek RIVM 2007-2010 (RIVM MAP SOR), het Europese KP7-project en het WHO-programma "Make medicines child size". Dit proefschrift is een van de producten van deze strategische programma's. Het doel van dit proefschrift is om de relatie tussen de beschikbaarheid, het farmaceutische ontwerp, de bruikbaarheid en de effecten bij patiënten (kinderen) te onderzoeken. De kennis die met, of als afgeleide van dit onderzoek is verworven, was mede gericht op het opstellen van goede regelgeving (regulatory science; EMA CHMP/QWP guideline on the pharmaceutical development of medicines for paediatric use).

Beschikbaarheid kindergeneesmiddelen in Nederland

In **hoofdstuk 2** van dit proefschrift wordt ingegaan op de beschikbaarheid van geneesmiddelen voor kinderen.

Knelpuntinventarisatie en nulmeting voor Europese Verordening

In **hoofdstuk 2.1** worden de resultaten gepresenteerd van een onderzoek dat in 2009 werd uitgevoerd naar de mate waarin leeftijdsgeschikte geneesmiddelen verkrijgbaar waren op de Nederlandse markt. Het doel van dat onderzoek was tweeledig. Ten eerste een inventarisatie van de uitdagingen waar de beroepsbeoefenaren in de gezondheidszorg, ouders en verzorgers voor staan bij het voorschrijven en gebruik van geneesmiddelen bij kinderen. En ten tweede een nulmeting van de effectiviteit van de Europese pediatrische Verordening ten aanzien van de beschikbaarheid van geregistreerde en ook leeftijdsgeschikte geneesmiddelen.

Zoals verwacht, bleken er op de Nederlandse markt minder geneesmiddelen voor kinderen in de handel dan voor volwassenen. Ook bleek dat er meer geneesmiddelen in handel waren voor oudere dan voor jongere kinderen. En dat er daarbij verschillen waren tussen de diverse toedieningsroutes (bijvoorbeeld inname via de mond of toediening via injectie).

De registratie van een geneesmiddel bleek bovendien niet altijd te waarborgen dat er van dat geneesmiddel ook een formulering in de handel was die geschikt was voor alle leeftijden waarvoor dat geneesmiddel was geregistreerd. Een voorbeeld hiervan was een geneesmiddel dat geregistreerd was voor kinderen vanaf 1 jaar, terwijl er alleen grote tabletten in de handel waren. Een ander

voorbeeld betrof een geneesmiddel waarbij de jongste kinderen slechts 1 mg per keer zouden moeten innemen, terwijl er alleen een 5 mg tablet in de handel was.

Effect van een verplicht Pediatrisch Onderzoeksplan (PIP)

Hoofdstuk 2.2 beschrijft een onderzoek naar de mate waarin de beschikbaarheid van leeftijdsgeschikte geneesmiddelen wordt gestimuleerd door de Europese pediatrische Verordening. Uit dat onderzoek bleek dat de beoordeling van het Pediatrisch Onderzoeksplan (PIP) door het Pediatrisch Comité (PDCO) van de EMA (het Europese Geneesmiddelen Agentschap) er toe heeft geleid dat veel geneesmiddelen voor een bredere leeftijdsgroep worden onderzocht dan de firma eigenlijk van plan was. Ook bleek dat de beoordeling leidde tot een groot aantal vragen van de EMA over de voorgestelde formuleringen voor kinderen. Die vragen leidden echter maar in beperkte mate tot een wijziging van de essentiële ontwerpaspecten van het geneesmiddel. Dat komt omdat veel van deze vragen betrekking hadden op het ontbreken van een adequate argumentatie voor het gekozen ontwerpaspect, bijvoorbeeld de reden waarom een firma voor een tablet had gekozen en niet voor een drankje. Kennelijk bleek de firma wel over die argumentatie te beschikken toen daarnaar door de EMA werd gevraagd.

Farmaceutisch ontwerp van geneesmiddelen voor kinderen

In **hoofdstuk 3** wordt ingegaan op de keuze van de aspecten die gezamenlijk bepalen of een geneesmiddel al dan niet geschikt is voor een bepaald kind, anders dan de juiste dosis. Het gaat daarbij dan om zaken als de keuze van de toedieningsvorm, de keuze van de hulpstoffen, de smaak van een drank etc. We noemen dit de farmaceutische ontwerpaspecten.

Farmaceutisch ontwerp in relatie tot werkzaamheid en veiligheid

Hoofdstuk 3.1 gaat over de kennis in de wetenschappelijke literatuur over de relatie tussen het farmaceutisch ontwerp van een geneesmiddel en de diverse effecten bij patiënten. Tot 2009 waren er slechts 94 publicaties waarin op deze relatie werd ingegaan. Over dit onderwerp is dus nog maar weinig bekend. Meestal had de informatie in de wetenschappelijke literatuur betrekking op de relatie tussen de aard van de toedieningsvorm of de formulering versus de acceptatie en/of voorkeur van het kind. De indruk bestaat dat de beschreven onderzoeken meer waren ingegeven door marketing overwegingen dan de wens om fundamentele kennis te genereren over de wijze waarop het farmaceutisch ontwerp van een geneesmiddel het beste zou aansluiten bij de specifieke karakteristieken van kinderen met een bepaalde leeftijd.

Aanvaardbaarheid en voorkeur van poeder, suspensie of stroop bij kinderen

De onderzoeksresultaten beschreven in hoofdstuk 3.1 waren aanleiding voor het onderzoek beschreven in **hoofdstuk 3.2**. In dit hoofdstuk worden de aanvaardbaarheid en voorkeur onderzocht van drie verschillende typen toedieningsvormen die veel bij kinderen worden toegepast, namelijk: een poeder, een troebel drankje (suspensie) en een helder drankje (stroop). De resultaten werden met elkaar vergeleken en ook met die van een kleine tablet van 4 mm doorsnede. Zulke kleine tabletten, ook wel mini-tabletten genoemd, zijn in Nederland nog nauwelijks geregistreerd als geneesmiddel, maar wel ruim verkrijgbaar als vitaminepreparaat. Het onderzoek werd uitgevoerd met nepgeneesmiddelen (placebo formuleringen) waarvan de smaak zo veel mogelijk neutraal was gehouden. Het onderzoek vond plaats in Beesd, Beusichem, Culemborg, Zaltbommel en Maurik.

Ouders van kinderen van 1 tot 4 jaar oud uit de genoemde kernen werden tijdens hun bezoek aan het consultatiebureau benaderd door een onderzoeker met de vraag of ze mee wilden doen aan het onderzoek. Meedoen betekende dat de ouders de vier formuleringen ieder twee keer op dezelfde dag thuis aan hun kind moesten aanbieden zonder het kind daarbij onder druk te zetten. Vervolgens moesten de ouders daarover dan een aantal gegevens in een dagboekje noteren. Het ging daarbij om de volgende gegevens: hoe vervelend het kind het vond om de formulering in te nemen; of het kind de formulering helemaal, gedeeltelijk of niet had ingenomen, aan welke formulering het kind de voorkeur gaf en welke formulering de ouder zelf het liefste voor het kind zou gebruiken. De ouders werd ook gevraagd informatie te verstrekken over het kind (onder andere leeftijd en geslacht) en over de wijze waarop iedere formulering was toegediend. Uit de resultaten van dit onderzoek bleek dat de kleine tablet over het algemeen het beste werd aanvaard en ook de voorkeur had van de kinderen en hun ouders.

Bruikbaarheid bij kinderen

In **hoofdstuk 4** is nader ingegaan op de praktische aspecten van het gebruik van geneesmiddelen in de thuissituatie.

Aanvaardbaarheid en voorkeur van poeder, suspensie of stroop bij kinderen

In aanvulling op het onderzoek beschreven in hoofdstuk 3.2 is in **hoofdstuk 4.1** onderzocht hoe de ouders de vier in hoofdstuk 3.2 genoemde formuleringen (tablet, poeder, suspensie, stroop) aan hun kind hadden toegediend. Formeel

gezien zouden de ouders de formuleringen zonder enige verdere handeling moeten hebben gegeven. Dat wil zeggen, zonder bijvoorbeeld de tablet te breken of te verkruimelen, en ook zonder de formuleringen te mengen met wat voedsel of drinken. Dat komt omdat de registratieautoriteiten vinden dat zulke handelingen alleen mogen worden uitgevoerd als op het etiket of in de bijsluiter staat vermeld dat dit mag. En dat was hier niet het geval.

Zoals verwacht, bleek uit het onderzoek dat de tablet soms toch was verkruimeld, dat de formuleringen soms toch met een klein beetje voedsel of drinken op een lepel waren toegediend of zelfs door het eten of drinken heen gemengd. Ook bleek dat ouders eerder geneigd waren om de formuleringen met wat voedsel of drinken te geven als het kind de formulering niet goed accepteerde. En dat de acceptatie van de formuleringen over het algemeen beter werd als de formulering met (meer) voedsel of drinken werd gegeven. Om deze laatste redenen is het belangrijk dat het toedienen van geneesmiddelen met een klein beetje voedsel niet wordt verboden in de bijsluiter zolang er geen directe aanwijzingen zijn dat die handeling van invloed zal zijn op de werkzaamheid van het geneesmiddel.

De bruikbaarheid van een tabletsplitter

In de praktijk van alledag slikken kinderen regelmatig halve tabletten. Bijvoorbeeld omdat er geen kinderformulering in de gewenste sterkte in de handel is, omdat kinderen de speciale kinderdrankjes niet lusten, of omdat het kind moeite heeft met het doorslikken van de hele tablet en daarom liever twee halve inneemt. Het is bekend dat ouders en kinderen het soms lastig vinden om tabletten met de hand te breken. En dat ze dan soms uitwijken naar een tabletsplitter of een keukenmesje. Ook is bekend dat tabletsplitters worden gebruikt door instellingen waar grote hoeveelheden tabletten moeten worden gebroken. In de internationale literatuur waren er steeds meer aanwijzingen dat tabletsplitters niet betrouwbaar waren, dat wil zeggen dat de tablet niet in twee gelijke helften werd verdeeld. Dat betekent dat een kind op die manier een te hoge of te lage dosis kan binnenkrijgen.

Hoofdstuk 4.2 beschrijft een onderzoek naar de betrouwbaarheid van tabletsplitters die verkrijgbaar zijn op de Nederlandse markt. Eerst is na gegaan welke tabletsplitters er in Utrecht te koop waren. Vervolgens is een onderzoeker met goede handfunctie (een 24-jarige farmacie studente) gevraagd om 100 paracetamol tabletten met die splitters en een keukenmesje te halveren en de resultaten te vergelijken met die van breken met de hand. Vanwege mogelijke verschillen, werden steeds drie stuks van hetzelfde merk onderzocht. De doseernauwkeurigheid en precisie van de tabletten die met de hand waren gebroken was beter dan die van de zes onderzochte tabletsplitters

en het keukenmesje. Dat wil zeggen dat breken met de hand betrouwbaarder was dan halveren met de splitters of het mesje. Verder bleek ook dat de nauwkeurigheid en de precisie van de tabletsplitters onderling sterk verschilde en dat de tabletsplitters en het keukenmesje niet voldeden aan de eisen die bij registratie van toepassing zijn voor wat betreft het gemiddeld gewicht/dosis, de gewichtsspreiding en het massaverlies na breken (hoeveelheid gruis).

Conclusie

Het bovenstaande maakt duidelijk dat artsen voor de behandeling van kinderen minder verschillende geneesmiddelen tot hun beschikking hebben dan voor de behandeling van volwassenen. Bovendien blijkt het farmaceutisch ontwerp van de beschikbare kindergeneesmiddelen niet altijd in voldoende mate te zijn toegesneden op de leeftijd en eigenschappen van het kind waarvoor dat geneesmiddel is bedoeld. In zulke gevallen is het waarschijnlijk dat het kind het geneesmiddel (als zodanig) niet kan of niet wil innemen. Artsen, verzorgers en ouders rest dan vaak weinig anders dan het toedienen van het geneesmiddel op een andere manier dan eigenlijk de bedoeling is. Bijvoorbeeld het breken of verkruimelen van tabletten, of het mengen van vieze drankjes met eten of drinken. Er moet dus nog veel werk worden verzet voordat er voldoende kindvriendelijke geneesmiddelen beschikbaar zullen zijn op de Nederlandse en Europese markt. Dit proefschrift levert daar een bijdrage aan.

Dankwoord

To err is human is (het eerste deel) van de titel van een rapport dat in 1999 is uitgebracht door het U.S. Institute of Medicine. Het rapport beschrijft dat in de VS jaarlijks 44.000 tot 98.000 personen overlijden ten gevolge van medische fouten die hadden kunnen worden voorkomen door een andere benadering van zaken en door een goede samenwerking tussen de diverse ketenpartners in de gezondheidszorg. Ik heb geprobeerd om deze observaties in mijn achterhoofd te houden bij dit promotieonderzoek. Om bruggen te slaan tussen de praktijk van alledag, het ziekenhuis, registratie en de academie. Ik heb daarbij veel mensen leren kennen die ieder op hun eigen manier hebben bijgedragen aan de totstandkoming van dit proefschrift. Ik wil hen niet alleen persoonlijk bedanken, maar u daar als lezer ook (enigszins) deelgenoot van maken.

Promotieteam

Allereerst wil ik mijn promotieteam bestaande uit Prof. dr. A.F.A.M. (Fred) Schobben, Prof. dr. A.C.G. (Toine) Egberts en Dr. C.M.A. (Karin) Rademaker bedanken voor de jarenlange samenwerking en dit mooie resultaat waar ik ongelofelijk blij mee ben. Jullie vormden een ijzersterk begeleidingsteam, zowel op inhoudelijk als persoonlijk vlak. Zonder jullie bijzondere steun had ik dit promotieonderzoek niet kunnen afronden. Bedankt.

Beste Fred, we kennen elkaar al bijna twintig jaar via het College ter Beoordeling van Geneesmiddelen waar ik me blijf verbazen over je enorme kennis van de farmacotherapie. Vlak na je aanstelling als hoogleraar heb ik je samen met het toenmalige hoofd van mijn afdeling aangesproken over de mogelijkheid om bij je te promoveren. Dat wilde ik graag en het sloot aan bij de wens van het RIVM dat beoordelaars zich ook op onderzoek zouden gaan toeleggen. Ik wilde iets op het grensvlak van registratie en praktijk en dacht aan onderzoek op het gebied van het toedienen van geneesmiddelen. Je reageerde enthousiast, gaf me de vrijheid om zaken te overdenken en ook te regelen. Er kwam een waarneming, een tweelingzwangerschap en het verwerven van onderzoeksbudget tussendoor. Maar zes jaar later ging mijn promotieonderzoek dan toch echt van start. Het is teveel om te benoemen, en daarom laat ik het bij het feit dat ik gewoon enorm dankbaar ben voor alles wat je in die lange periode voor mij hebt gedaan.

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werkzaamheden. Qua strategische, leidinggevende en sociale competenties. Een groep die snel en kritisch kan analyseren, slagvaardig opereren en die over de nodige creativiteit beschikt. Die weet wanneer aanhaken verstandig is, of ergens ver weg van blijven misschien wel zo handig. Die als geen ander aanvoelt wanneer het tijd is voor overleg of een telefoontje. Die altijd snel hun mail beantwoordt en dankzij wie je altijd morgen weer verder kunt. Beste Toine, ik denk dat jij bij deze kleine groep mensen hoort. Eten, bloemen en een goed gesprek. Bedankt. Geniet van je kinderen. Het is zo cliché en ook zo waar, ze zijn heel snel groot.

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Dear Jose Ferreira, I have always been of the opinion that you should not try to do things yourself what others can do much better i.e. working in a multidisciplinary team is the best way to obtain top results. You were the top statistical expert that our team was missing. I am happy that you have joined. Dear Agnes Saint Raymond, when Toine suggested evaluating the Paediatric Investigation Plans, I realized that it meant working in the same domain as both a regulator and a scientist. I am greatful that you have given me the opportunity to do so and I very much appreciate your valuable support in the data collection and the drafting of the manuscript. Dear Piotr Kozarewicz, for two years we frequently met on the phone to discuss the paediatric guideline. Friday end of day was often the only possibility; meaning dinner would be late for you. Nevertheless,

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List of co-authors of manuscripts presented in this thesis

Affiliations at the time the research was conducted
Presented in alphabetical order

Dr. B. (Bart) J.F. van den Bemt

Department of Clinical Pharmacy, Radboud University Medical Center Nijmegen (UMCN), Nijmegen, The Netherlands &

Department of Pharmacy, Sint Maartenskliniek, Nijmegen, The Netherlands

M. (Myrthe) E. Doeve, BSc

Department of Chemical Pharmaceutical Assessments (CFB), Medicines Evaluation Board (MEB), Utrecht, The Netherlands (internship) &

Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, The Netherlands (internship)

Prof. dr. A. (Antoine/Toine) C.G. Egberts

Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, The Netherlands &

Department of Clinical Pharmacy, University Medical Center Utrecht (UMCU), Utrecht, The Netherlands

Dr. J. (José) A. Ferreira

Department of Statistics, Modelling and Data Management (SMG), National Institute for Public Health and the Environment, Bilthoven, The Netherlands

Prof. dr. Y. (Yechiel/Chiel) A. Hekster

Department of Clinical Pharmacy, Radboud University Medical Center Nijmegen (UMCN), Nijmegen, The Netherlands &

Medicines Evaluation Board, Utrecht, The Netherlands

K. (Karin) E. de Jager, BSc

Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, The Netherlands

P. (Piotr) Kozarewicz, MSc

Unit Quality of Medicines, European Medicines Agency (EMA), London, United Kingdom

B. (Barbara/Koosje) J. de Neef, MSc
Sector Child care, Stichting Thuiszorg en Maatschappelijk Werk Rivierenland, Tiel, The Netherlands

A. (Agnes) E. Nicia, MSc
Department of Chemical Pharmaceutical Assessments (CFB), Medicines Evaluation Board (MEB), Utrecht, The Netherlands

K. (Kim) Notenboom, MSc
Department of Public Health Effects, Center for Health Protection (GZB), National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

Dr. C. (Carin/Karin) M.A. Rademaker
Department of Clinical Pharmacy, University Medical Center Utrecht (UMCU), Utrecht, The Netherlands

E. (Erwin) G.A.W. Römkens, BSc
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, The Netherlands (internship) &
Department of Chemical Pharmaceutical Assessments (CFB), Medicines Evaluation Board (MEB), Utrecht, The Netherlands (internship)

Dr. A. (Agnes) Saint-Raymond
Unit Medicines Special Areas, European Medicines Agency (EMA) London, United Kingdom

Prof. dr. A. (Alfred/Fred) F.A.M. Schobben
Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, The Netherlands &
Department of Clinical Pharmacy, University Medical Center Utrecht (UMCN), Utrecht, The Netherlands,
Medicines Evaluation Board (MEB), Utrecht, The Netherlands

Dr. S. (Steven) Teerenstra
Department of Health Evidence, Radboud University Medical Center Nijmegen (UMCN), The Netherlands

List of collaborating organisations

The studies presented in this thesis were all conducted in close cooperation with

- Utrecht University, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht, The Netherlands.
- University Medical Center Utrecht (UMCU), Department of Clinical Pharmacy, Utrecht, The Netherlands.
- National Institute for Public Health and the Environment (RIVM), Department of Chemical Pharmaceutical Assessment (CFB), Bilthoven, the Netherlands. In 2011, this department was relocated at a different agency under the same ministry (Public Health, Welfare and Sports) where the studies were continued; namely the
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- Radboud University Medical Center, Departments of Health Evidence and Clinical Pharmacy, Nijmegen, The Netherlands
- Sint Maartenskliniek, Department of Pharmacy, Nijmegen, The Netherlands

List of Publications from this author

Publications in bold are published in this thesis

Methods of administering oral formulations and child acceptability
van Riet–Nales DA, Ferreira JA, Schobben AFAM, de Neef BJ, Egberts TCG, Rademaker CMA
Submitted

Practical problems with medication use experienced by older people: a qualitative study
Notenboom K, Beers E, van Riet-Nales DA, Egberts ACG, Leufkens HGM, Jansen PAF, Bouvy ML
JAGS (in press)

Oral medicines for children in the European Paediatric Investigation Plans
van Riet-Nales DA, Römkens EAW, Saint-Raymond A, Kozarewicz P, Schobben AFAM, Egberts TCG, Rademaker CMA
Plos One 2014;9(6):e98348

The accuracy, precision and sustainability of different techniques for tablet subdivision: breaking by hand and the use of tablet splitters or a kitchen knife
van Riet-Nales DA, Doeve ME, Nicia AE, Teerenstra S, Notenboom K, Hekster YA, van den Bemt BJF
Int J Pharm 2014;466:44-51

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A dream (thesis) doesn't become reality through magic (inspiration); its takes sweat (transpiration), determination (frustration) and hard work.

Colin Powell & Toine Egberts

About the author

Diana Alexandra van Riet- Nales was born in The Hague, The Netherlands on 1 March 1966. She grew up in 's-Gravenzande, where she completed secondary school (Atheneum) at the Zandevelt College. Subsequently, she started studying pharmacy at Utrecht University. In 1990, Diana obtained her master degree in pharmaceutical sciences and in 1992 her PharmD. In 1993, she obtained a diploma in marketing from the Nederlands Instituut voor Marketing (NIMA-A) and in 2011 a Master in Epidemiology from the VU University of Amsterdam.

Diana started her professional career as a community pharmacist. After almost two years, she changed direction and started working in regulatory affairs. Diana is now a senior pharmaceutical assessor at the Medicines Evaluation Board (MEB) in The Netherlands and, among other things, the Dutch expert for human medicines in the European Medicines Agency (EMA) Quality Working Party (QWP). Further details of Diana's activities can be found in her Europass curriculum vitae on the EMA internet.

Diana is married to Hans van Riet and the mother of Bauke, Nicky, Ewout, Levine and Wilbert van Riet.