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MANIPULATION OF MEDICINES, NECESSARY IN EVERYDAY PRACTICE FOR INDIVIDUALISED DOSES IN PAEDIATRIC CARE

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Manipulation of medicines, necessary in everyday practice for individualised doses in paediatric care

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“First do what is necessary. Then do what is possible. And before you know it you are doing the impossible.”

- Saint Francis Assisi

POPULAR SCIENCE SUMMARY OF THE THESIS

Imagine sharing a cake with six of your friends. Dividing the cake into seven equal parts is not an easy task, but the biggest problem is that somebody becomes a bit disgruntled. But if a sick child is prescribed a medicine that is only available as a tablet designed for adults and the child's dose corresponds to a one-seventh of the tablet, then it is more important that the dosing is correct.
Administering medicines is the most common health care measure, both for adults and children. When sick children are treated with medicines mainly developed for adults, there is often a need to manipulate the medicine. Examples of manipulations are to split a tablet, crush a tablet and dissolve it in liquid, opening a capsule and empty the content, or even splitting a suppository. Sometimes this is done to help the child take the medicine, but very often it is necessary to take a part of the original dose, i.e., only a part of the dissolved tablet or the content from the capsule is going to be administered. These manipulations are often not authorised from the drug company so healthcare staff or caregivers are forced to do this without guidance and without knowing how exact the dose is going to be. An alternative to manipulation of medicines is pharmacy prepared medicines, also known as extemporaneous preparations, that can be ordered in adjusted strengths.

First of January 2007 the European Paediatric Regulation took effect. The purpose was to increase knowledge around medicines for children, both doses and dosage forms, by making it mandatory for drug companies to include children in their clinical studies.

In this thesis we investigated different aspects of manipulated medicines to children; frequencies of manipulated medicines (study I), pharmacists' and registered nurses' thoughts around manipulation (study II), dosing accuracy with split tablets (study III) and frequencies of extemporaneous preparations (study IV). The assumption was that due to the Paediatric Regulation, more child friendly medicines would be present in 2019, compared to 2009.

From a large registry based on all medicine administrations, all doses administered orally or rectally 2009 and 2019 were included. All doses where part of a tablet, capsule, or suppository was administered, were classified as manipulation. Interviews with open questions were performed with registered nurses and pharmacists. In an experimental study five different brands of tablets were split into halves and quarters, and the parts weighed. Frequencies of patients with at least one extemporaneous preparation was counted and compared between the study years.

The results showed that there was a decrease in manipulations between 2009 and 2019 for patients with rectal administrations, both in the inpatient and the emergency setting and for patients with oral administrations in the emergency setting. Inpatients receiving oral medicines had the same frequency of manipulated medicines both study years. The interviews showed that pharmacists have a comprehensive knowledge of medicines and access to more information sources than registered nurses, who felt that manipulating medicines was difficult and felt unsafe. Only some of the tablet halves fulfilled the

requirements for dosing accuracy and none of the tablet quarters. Between the study years there was an increase in inpatients with oral extemporaneous preparations.

The need to manipulate medicines or use extemporaneous preparations was still high in 2019 due to lack of medicines suitable for sick children. In the future more dosage forms and strengths enabling individual doses to children in different ages and with different capabilities of taking medicines is desirable. Pharmacists are valued members in the ward team, contributing with specific knowledge around medicines.

POPULÄRVETENSKAPLIG SAMMANFATTNING (SVENSKA)

Tänk dig att ni är sju personer som ska dela på en tårta. Det är ganska svårt att skära sju lika stora bitar, men den största risken är att någon blir lite missnöjd. Men om ett sjukt barn har fått en ordination på ett läkemedel som bara finns tillgängligt i en tablett avsedd för vuxna och barnets läkemedelsdos motsvarar en sjundedel av tabletten, då känns det genast viktigare att det blir exakt rätt.
Läkemedel är den vanligaste vårdåtgärden för både vuxna och barn. När sjuka barn behöver behandlas med läkemedel som huvudsakligen tagits fram för att passa vuxna patienter, kan läkemedlet behöva anpassas. Andra ord för anpassning av läkemedelsformen är manipulering eller omformulering. Exempel på detta kan vara att dela en tablett, krossa en tablett och lösa upp i vätska, öppna en kapsel och tömma ut innehållet. Ibland görs detta bara för att barnet ska kunna få i sig läkemedlet, men väldigt ofta behöver man också ge en mindre dos av läkemedlet. Då tar man en liten del av den upplösta tabletten eller det uttömda kapselinnehållet. Ofta är inte läkemedlet godkänt för att göra sådana anpassningar utan vårdpersonal eller föräldrar behöver göra det utan att egentligen veta hur korrekt dosen blir. Förutom att anpassa vuxenläkemedel kan också apotekstillverkade läkemedel, s.k. extemporepreparat, beställas i anpassade styrkor.

2007 kom en europeisk föreskrift med syfte att öka informationen kring läkemedelsdoser till barn och också stimulera utvecklingen av nya läkemedelsformer. Detta sker genom att det är obligatoriskt för läkemedelsföretagen att inkludera barn i sina läkemedelsstudier.

I denna avhandling har vi studerat olika aspekter av anpassade läkemedel till barn; frekvenser av anpassade läkemedel (studie I), farmaceuters och sjuksköterskors tankar kring manipulering (studie II), dosnoggrannheten för delade tabletter (studie III) och frekvens av extemporepreparat (studie IV). Antagandet var att det tack vare den europeiska föreskriften skulle finnas fler barnvänliga mediciner 2019 jämfört med 2009.

Ur ett register baserat på alla läkemedelsadministreringar, togs alla doser som administrerats via munnen (oralt) eller via ändtarmen (rektalt) 2009 och 2019 fram. Alla doser som innebar att en del av en tablett, kapsel eller suppositorium behövde administreras räknades som manipulering. Intervjuer med öppna frågor genomfördes med sjuksköterskor och farmaceuter. I en experimentell studie delades fem olika sorters tabletter, i halvor och i fjärdedelar och därefter vägdes delarna. Andelen barn som fått minst ett extemporepreparat sammanställdes och jämfördes mellan de inkluderade åren.

Resultaten visar att för barn som fått rektala läkemedel, både på vårdavdelning och på akuten, hade andelen som fick manipulerade läkemedel minskat mellan studieåren. Samma resultat gäller för barn med orala läkemedel på akuten. För barn på vårdavdelning som fått orala läkemedel var det lika hög andel som fått manipulerade läkemedel båda studieåren.

Intervjuer visade att farmaceuterna har god läkemedelskunskap och tillgång till fler informationskällor jämfört med sjuksköterskorna som ofta tycker att det känns osäkert och svårt att manipulera läkemedel. I tablettdelningsstudien var flera av tabletthalvorna ok, men inte någon av fjärdedelarna. Andelen barn på vårdavdelning som fått minst ett oralt extemporepreparat hade ökat.

Behovet att manipulera läkemedel eller använda extemporepreparat var fortsatt stort 2019, då det saknades läkemedel lämpliga för barn. Det vore önskvärt med beredningsformer och styrkor som gör det möjligt att administrera individuella doser till barn i olika åldrar och med olika förmåga att ta läkemedel. Farmaceuter är en viktig del av vårdteamet och bidrar med specifik kunskap om läkemedel.

ABSTRACT

Introduction: Manipulation of medicines is often necessary in the paediatric setting due to lack of medicines suitable for paediatric patients. There are previous short-term frequency studies in different paediatric settings, but no long-term studies and no comparison between two different years in the same setting. In 2007 the Paediatric Regulation was implemented in Europe to stimulate drug companies to develop more information around medicines for children and new dosage forms suitable for paediatric patients. An alternative to manipulation of medicines is to use extemporaneous preparations in correct strengths.

Aim: The overall research aim of this thesis was to study how and to what extent manipulation of medicines is being done and its effect on dosing accuracy in paediatric care. A specific aim was to compare the use of extemporaneous preparations in two different years.

Methods: The setting for three of the four studies was a large paediatric university hospital in Sweden, and the fourth study was performed at a hospital pharmacy. Data for paper I and IV were extracted from a large registry containing material regarding patient data, care, and medicines from the hospital electronic health record, TakeCare. In Paper I data regarding all solid oral and rectal administrations where a part of a solid dosage form needed to be administered were counted. Comparisons were then made between the included study years 2009 and 2019 and between inpatients and patients at the emergency department. Semi-structured interviews with registered nurses and pharmacists were performed in Paper II. All interviews were audio recorded, transcribed verbatim, and analysed qualitatively using content analysis. In Paper III five different brands of tablets were split into halves and quarters. The resulting parts were then weighed and compared with expected weight, according to criteria in the European Pharmacopoeia and the United States Pharmacopoeia. The frequency of patients with at least one oral extemporaneous preparation was counted from the registry data and compared for inpatients in 2009 and 2019 in Paper IV.

Results: There was no difference in the frequency of inpatients with manipulated oral medicines, when comparing data from 2009 and 2019. For manipulations of rectal medicines there was a statistically significant decrease for both inpatients and patients at the emergency department, as well as for manipulations of oral medicines to patients at the emergency department. Registered nurses and pharmacists state that manipulation of medicines to paediatric patients is frequent, and forces both professions to work outside the box. Splitting of tablets into halves results in more correct parts than splitting further into quarters. The frequency of patients with extemporaneous preparations increased between the study years.

Conclusion: There is still a lack of suitable dosage forms and strengths of medicines to paediatric patients in 2019 which leads to manipulation of medicines, or the use of extemporaneous preparations. For individual substances the introduction of a dosage form suitable for paediatric use, decreases, or even erases the need to manipulate or use extemporaneous preparations. Pharmacists are valued members in the ward team, contributing with specific knowledge around medicines.

LIST OF SCIENTIFIC PAPERS

This doctoral thesis is based on the following original papers, which are referred to in the text with Roman numerals (I – IV).

I. **Andersson ÅC**, Eksborg S, Förberg U, Nydert P and Lindemalm S
Manipulated Oral and Rectal Drugs in a Paediatric Swedish University Hospital, a Registry-Based Study Comparing Two Study-Years, Ten Years Apart
Pharmaceuticals 2022 Dec 21;16(1):8.

II. **Andersson ÅC**, Lindemalm S, Eksborg S, Onatli D, Chowdhury S, Förberg U
"Working outside the box" – an interview study regarding manipulation of medicines with registered nurses and pharmacists at a Swedish paediatric hospital
Submitted

III. **Andersson ÅC**, Lindemalm S, Eksborg S
Dividing the Tablets for Children – Good or Bad?
Pharm Methods, 2016;7(1):23-7.

IV. **Andersson ÅC**, Eksborg S, Förberg U, Nydert P and Lindemalm S
Use of extemporaneous preparations at a paediatric university hospital: a register-based study comparing two study-years, ten years apart
Submitted

CONTENTS

LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Chemical (classification system)
EMA/EMEA	European Medicines Agency (EMEA former abbreviation, in use until 2009)
ePed	Experience and Evidence-based database for Paediatric Drugs, Sweden
FDA	Food and Drug Administration, the United States
GMP	Good Manufacturing Practice
KarDa	Karolinska Hospital's internal data warehouse
MA	Marketing Authorisation
MODRIC	Manipulation of Drugs in Children
NPPG	Neonatal and Paediatric Pharmacist Group, the United Kingdom
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PUMAs	Paediatric Use Marketing Authorisations
RN	Registered Nurse
RSD	Relative Standard Deviation
SmPC	Summary of Product Characteristics
USP	United States Pharmacopoeia
WHO	World Health Organisation

DEFINITIONS

2 – 5 years	From the day someone turns 2 to the day before their 6th birthday (2 - <6 years).
Caregivers	In this text the word is used as a generic term that includes legal guardians or other caregivers responsible for the raising of the child.
Liquid dosage form	Oral or rectal medication that is intended to be administered in the liquid form such as drops, mixtures or suspensions and that can be administered in individual doses without manipulation.
Solid dosage form	Oral or rectal medication that is intended to be administered as a whole dosage form such as tablets, capsules, and suppositories. In this study dispersible tablets are included in this definition.

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1 PREFACE

When I worked as a hospital pharmacist in the early 2000s, one of my job assignments was to answer questions at our Medicines Information Centre, from registered nurses (RNs) and physicians at our hospital. One day I remember getting a phone call from a RN at our Paediatric Intensive Care Unit, asking about the 25 mg Viagra® tablet she had just suspended in 5 mL of water. She wanted to know if the blue "flakes" present in the suspension contained any active pharmaceutical ingredient and for how long she could keep the suspension. By that and similar questions I realised that administering children e.g., 2 mg sildenafil from a 25 mg tablet forces the RN, pharmacist, or caregiver to be creative. Unfortunately, sometimes more creative than correct, and my interest in dosing accuracy to paediatric patients started growing. As a pharmacist, being trained in the importance of accuracy and knowing how drug companies put a lot of effort into the formulation of drugs, it felt precarious that we handled drugs in this way for our youngest patients.

During the years from my newly awakened interest and the finish of this thesis, a lot has happened in the field of paediatric drug formulation and regulation. Following numerous studies about the off-label use of medicines to children a growing interest around new formulations, strengths, and indications for children started.

In the United States the Best Medicines for Children Act was implemented 2002 and in 2007 the European Union followed with the Paediatric Regulation. The demand for pharmaceutical industry to present a Paediatric Investigation Plan (PIP) with their applications for new drugs, new indications or dosage forms has led to interest groups focusing on paediatric drug formulation, e.g., European Paediatric Formulation Initiative (EuPFI) and many scientific studies regarding suitable dosage forms for different age groups, swallowability, taste, and taste masking, etc.

In 2013 a research group from Alder Hey Children's Hospital in Liverpool published a guideline for different types of manipulation of medicines in children, MODRIC (Manipulations Of Drugs Required In Children), based on systematic reviews of available information. This document has been a great inspiration for this thesis.

2 INTRODUCTION

The paediatric patient group is heterogeneous, ranging from premature newborns to 18-year-old patients. There is a wide difference in what medicines children can take, depending on age, ability, and diagnosis. To be able to treat children of all ages with different abilities and preferences, a dream scenario would be a whole set of dosage forms or a dosage form that easily and safely can be transformed into individual doses. This is unfortunately not the reality and there is still a lack of child-appropriate dosage forms and dosing information worldwide. The consequence of this is that many paediatric patients are treated off-label or with unlicensed products, despite regulatory initiatives in both the United States and Europe. Another consequence is that caregivers or healthcare personnel are forced to manipulate medicines to obtain the required dose, which may lead to dosing inaccuracy and other problems.

The United Nations Convention on the Rights of the Child consists of several articles concerning the need and rights of all children, and article 24.1 is about health:
"States Parties recognize the right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health. States Parties shall strive to ensure that no child is deprived of his or her right of access to such health care services." (1).

Article 24 could be interpreted as giving all paediatric patients the right to age-appropriate medicine formulations that enable safe and accurate drug treatment regardless of age and physical capabilities. Sweden ratified the convention 1990, and 1st of January 2020 the Convention on the Rights of the Child became part of the Swedish law.

Paediatric patients include patients of a wide variety of age, weight and organ maturity, and many physiological changes take place during the childhood years, which may influence the pharmacokinetics and pharmacodynamics of drugs (2, 3). Often medicines to children are prescribed based on a dose per kilogram (dosing according to body weight) or per square metre (dosing according to body surface area) (4, 5).

Dosing in children is often not optimal, due to lack of pharmacokinetic data. If then another set of uncertainty is introduced regarding what dose is really administered to the patient, the evaluation of the treatment of that diagnosis, with that drug, in that dose, is very hard to perform. Sometimes a treatment is rejected and regarded as a treatment failure, though it might be that the dose has not been accomplished or a sophisticated drug formulation has been ruined because of manipulation in a manner not suitable.

3 LITERATURE REVIEW

This background, or literature overview, is written as an introduction to the field of manipulated medicines in the paediatric setting.

3.1 DEFINITION AND CLASSIFICATION OF PAEDIATRIC PATIENTS

Medicines in different dosage forms are a major part of treating sick children of all ages. According to the definition of the United Nations in the Convention on the Rights of Children "a child means every human being below the age of eighteen years." (1).

Different age-groups have their special needs, challenges and capabilities and the childhood period (newborn – 18 years) is often subdivided further into subgroups to better reflect developmental, both physiological and psychological, stages.

One widely used way of defining age-groups during the childhood period is the one proposed by the European Medicines Agency (EMA) (6):

- preterm newborn infants
- term newborn infants (0 to 27 days)
- infants and toddlers (28 days to 23 months)
- children (2 to 11 years)
- adolescents (12 to 18 years)

In the current projects the age-groups above one month were applied with the addition that the age-groups infants and toddlers (28 days to 23 months) and children (2 to 11 years) were split into two groups, respectively. The groups for infants and toddlers used in our studies were 1 month -< 1 year and 1 -< 2 years. The groups for children used in our studies were 2 -< 6 years and 6 -< 12 years. The reasons for doing this was that the development is rapid in these age groups and further division enabled comparisons to be made between age groups.

3.2 DEFINITION OF MANIPULATION OF MEDICINES, UNLICENSED, OFF-LABEL, AND EXTEMPORANEOUS PREPARATIONS

Due to lack of medicines suitable for paediatric patients, the use of manipulated medicines, unlicensed medicines and extemporaneous preparations is high in the paediatric setting. The use of all the above-mentioned categories of medicines can either be on-label or off-label.

3.2.1 Manipulation of medicines

Dose or dosage form modification (7-10), altering dosage forms (11) and manipulation of drugs (12-15) are all different expressions for the same phenomena, that the dosage form of a medicine is changed in some way from its original (most often intended) formulation. This is almost always done due to patient characteristics. Sometimes this practice is also included in the term extemporaneous compounding, depending on in which setting the manipulation

takes place (16, 17). Fractional dosing is another expression, which clearly indicates the need to take part of a dose, mainly in the paediatric setting (18, 19). In this thesis the expression manipulation will be used, with the definition:
The physical alteration of a medicine, with the intention to give the required dose (20).

Sometimes the whole dose is given but the medicine needs to be manipulated because of patient characteristics e.g., has swallowing difficulties or has a feeding tube, but this is not the main purpose in this thesis.

Examples of manipulations are shown in Table 1, inspired mainly by the MODRIC-project by Richey et al. (20-22). Administration of small volumes of injections or oral solutions (<0.2 or even <0.1 mL) is sometimes also regarded as manipulation, since this practice often requires the volume to be further diluted before administration, but this is not included in Table 1 (23). Mixing medicines with food or beverages outside information given in SmPC is sometimes also considered manipulation and included in frequency numbers (24).

Table 1. Manipulation of dosage forms to obtain the prescribed dose, examples.

Drug dosage form	**Manipulation**
Tablet	• Split and a part given • Crushed and a proportion of the powder given • Dispersed in liquid and a proportion given
Capsule/sachet (powder)	• Opened and dispersed in liquid and a proportion given • Opened and a proportion of the powder/granules given
Suppository	• Cut/split and a part given • Suppository melted and part of the solution given
Rectal solution	• Proportion of unit dose given and the rest discarded • Proportion of contents discarded and the remainder given
Nebuliser solution	• Proportion given
Transdermal patch	• Patch cut and a part applied • Proportion of patch uncovered and applied

Manipulation of medicines can be regarded as being on-label or off-label depending on whether the information is included in the SmPC or not (16). Examples of on-label manipulations would be the splitting of tablets containing carglumic acid into quarters and

then dispersing them in water before administration (25) or the mixing of montelukast oral granules in some cold food as applesauce or ice cream before administration (26) because both these procedures are described in the SmPCs. The most common is however that the SmPC lacks information on manipulation and different ways can then be applied to seek information. Healthcare professionals have different sources where they can look for information, including the Pharmaceutical Specialties in Sweden (FASS) (27). There are also different handbooks describing which medicines can be crushed and/or dissolved to administer in enteral feeding tubes (28, 29). Caregivers may want to seek advice from other caregivers, e.g., on the internet in discussion groups (30). Inappropriate advice might be given there, and as a result unauthorised manipulation can be performed in a way that risks the patient's safety. Even in the scientific literature one might find examples of less suitable advice, such as the article that describes a coffee grinder as being useful when manipulating all sorts of medicines for children (31).

3.2.2 Off-label and unlicensed medicines

The definition of off-label use is normally the use of a medicine with a Marketing Authorisation (MA) outside what is approved and/or licensed, e.g.in relation to age, dose, indication or route of administration (32). The definition of unlicensed medicines is the use of drugs without a MA in the specific country. In Sweden the prescribing of unlicensed drugs is possible only after a special permission has been granted from the Swedish Medical Products Agency.

There has been a lack of a unified definition of whether manipulation of medicines should be regarded as an off-label practice or unlicensed, which makes comparison of different studies complicated. One reason for including manipulation of medicines in unlicensed medicines is the legal aspect of responsibility after altering a dosage form outside the information in the SmPC (33, 34). The drug company will not take responsibility for use outside their information and that is valid also for use of medicines outside indication, age, and route of administration. One of the earliest studies on unlicensed medicines to children in the United Kingdom included manipulated medicines (35) and following studies used their definition (36, 37). Other studies regard manipulation of medicines as one of many possible ways of using a medicine off-label (38-40). Some studies regard it as both (41) and in some studies it depends on whether the manipulation is made on the ward/by the caregiver or in a more controlled environment at the pharmacy (16).

To harmonise the definitions of off-label and unlicensed use of medicines in paediatric medicine in Europe and make comparisons between research possible, a Delphi questionnaire was sent to different experts to agree on given statements (42). The question regarding which category manipulated medicines should be included in, was one of the two most difficult statements to agree on, but finally the panel agreed on the following definitions (stated on page 320 in the cited article):

Off-label use:

"all uses of a marketed drug not detailed in the SPC including therapeutic indication, use in age-subsets, appropriate strength (dosage), pharmaceutical form and route of administration".

Unlicensed use:

"all uses of a drug which has never received a European Marketing Authorisation as a medicinal for human use in either adults or children." (42).

With this new definition the manipulation of a drug with a MA should be regarded as off-label use, if it is done without supporting information from the drug company.

3.2.3 Extemporaneous preparations

The definition of extemporaneous preparations, sometimes also called magistral preparations, is: "the preparation of a therapeutic product for an individual patient in response to an identified need" (43).

Paediatric patients are one of the main groups of patients receiving extemporaneous preparations, due to the lack of registered medicines to fulfil their identified needs. In a Swedish study from 1995, the ratio of extemporaneous prescriptions to registered medicines was over 4% in the age group 0 – 14 years, but only 2% in all patients older than 14 years (44). Many of these prescriptions were for active pharmaceutical ingredients (APIs) deemed controversial, like dicyclomine hydrochloride for infant colic and cough mixtures, where recommendations now have been changed (45). Extemporaneous preparations is another category of medicines often included in the terms off-label or unlicensed use of medicines (46), but despite the numerous studies on off-label use, there are few studies on frequency of extemporaneous preparations alone. A Swedish study found that extemporaneous preparations on average represented 10% of all inpatient drug orders to paediatric patients, ranging from 22% for neonates to 4.5% for adolescents (38).

There are concerns about the quality of extemporaneous preparations in some countries, including stability, microbiology and whether the stated content is concordant with the actual content (47-49). Bioavailability data is most often missing for the extemporaneous preparations even though they are available for original products of the same API (50). In the Swedish context, and in this thesis, the term extemporaneous preparations denote medicines prepared for the individual patient or in batches by a few extemporaneous pharmacies according to Good Manufacturing Practice (GMP). These are a better alternative to off-label manipulation, but they are not available for all APIs and usually they are produced to order, leading to a delivery time of some days.

3.3 SCORE LINES (BREAK MARKS) IN TABLETS

Even though many tablets are designed with a score line (break mark) the score line is not always intended for splitting the tablet into two equal parts (18). The European Pharmacopoeia (Ph. Eur.) was the first to implement criteria for the subdivision of scored tablets in 2002 (51). The United States Pharmacopeia (USP) published an article in 2009 proposing criteria for loss of mass and accuracy of subdivision for split tablets (52) and in 2013 the Food and Drug Administration (FDA) issued a Guideline for Industry on the scoring of tablets (53). But to my knowledge there is still no guideline in the USP for split tablets and therefore an adopted version of the relative standard deviation (RSD) for intact tablets has been used in several articles examining the dosing accuracy of split tablets (54-56).

The European Commission has since 2010 stated in their Guideline on Summary of Product Characteristics (SmPC) that for tablets designed with a score line, information on whether or not reproducible dividing of the tablets has been shown according to the rules in Ph. Eur., one of the following phrases should be used in the SmPC (57):

"The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses" or
"The tablet can be divided into equal halves".
There are also tablets with a score line that should not be split.

In the FDA guideline the phrase "functional scoring" is suggested to be included in the prescribing information for tablets that meet the criteria, to communicate to healthcare staff that this is a tablet suitable for fractional dosing (53).

It is of great importance that information is included in the SmPC if a tablet with a score line must not be divided (18). The World Health Organization (WHO) has stated that tablets containing active ingredients with a narrow therapeutic window should generally not be presented with break-marks for subdivision, and that non-functional break-marks should be avoided (58).

3.4 FREQUENCY OF MANIPULATION OF MEDICINES TO PAEDIATRIC PATIENTS

Manipulation of adult dosage forms for paediatric use should be the last resort, as stated by the EMEA in the Reflection paper "Formulations of choice for the paediatric population", but the paper also states that this is unavoidable in many cases (4).

Since earlier studies on the frequency of manipulation of medicines to children vary in their inclusion criteria, the results are difficult to compare. The results were ten percent in a study including manipulated medicines and administrations of small volumes of both oral and intravenous medicines (23). A Norwegian study included manipulated medicines both where a proportion was given and when the whole dose was given and the result was that 17% of the administrations were manipulated (59). A Dutch study also included coadministrations with food or liquid other than that stated in the SmPC in the frequency of manipulated

medicines. The strength of this study is that it was done in both the outpatient and the inpatient setting, with similar results (52% of the patients in the outpatient setting and 60% in the inpatient setting) (24). In a German study more than half of all paediatric patients in a paediatric hospital were affected by at least one manipulated medicine. These manipulations were also valued as to whether they were authorised or unauthorised, according to information in the SmPC (60).

Most of these studies are observational studies performed during a shorter period. In one study from France the researchers have analysed all oral drug administrations in a paediatric hospital for one year, a total of more than 117,000 administrations. They have made a thorough compilation of what dosage forms children in different age-groups receive, what medicines are administered (categorised according to their Anatomical Therapeutic Chemical [ATC] classification system) and in what dosage form, but unfortunately, they have not studied how often part of a solid oral dosage form was administered which they also stated was a weakness in their study (61).

3.5 RISKS WITH MANIPULATION OF MEDICINES

Unauthorised manipulation can result in dose inaccuracy and sometimes changed effect. Whether this is clinically relevant or not is depending on the formulation, type of manipulation, if the drug has a narrow or broad therapeutic range, the disease, and the patient. When a dosage form is altered in a way not recommended by the drug company it usually means that there are no official studies of the outcome of this behaviour.

Several studies report the dosing accuracy of split tablets, both from a paediatric perspective and for older patients, but only few present data on the clinical relevance (62-65). Anti-epileptic treatment is usually monitored by plasma concentrations and a study examining both weight variation in tablets and plasma concentrations in children receiving anti-epileptic drugs showed that neither the drug content nor the plasma concentrations reached optimal levels with split tablets (66). In some settings tablet splitting is considered a suitable way of saving money (especially in the United States, where tablets often cost the same regardless of strength) or a convenient way of achieving a smaller dose (64, 67-70) whereas others emphasize the risk of inaccurate dosing (55, 71-73). Crushing of tablets might alter the exposure of the drug, compared to when the tablet is swallowed intact (74), and might in worse case lead to a toxic dose being released. There are case reports describing deaths in adult patients after having been administered crushed sustained-release cardiovascular drugs (75).

There are some studies describing the dosing accuracy after dispersing tablets in liquid and taking a proportion of the dispersion. These studies show that the way manipulation and dose extraction is performed has a great impact on the resulting dose (76). Doses varied from 23% to 188% of expected dose in a study with conventional aspirin tablets (77). In another study comparing four different tablet formulations of aspirin only fractions taken from the dispersible tablet were within 20% of the intended dose (78).

Mixing crushed tablets with food is common in both the paediatric and geriatric setting, but it may alter the pharmacokinetics and effect and impact the treatment efficacy (79). A case-report describes a young child treated for tuberculosis who failed treatment with crushed isoniazid tablets mixed with apple sauce, but improved when given the parenteral form of isoniazid mixed with apple juice orally (80). Phenytoin, known to interact with certain brands of enteral nutrition, has been shown to interact also with vanilla pudding (81).

Several studies have compared different methods of splitting tablets or letting different persons (e.g., trained or not trained, young or old) do the splitting but there are only minor differences in the results (82). The formulation characteristics of the medicine seem to be the major contributor to weight uniformity or not (83-87). Formulation characteristics could e.g., be hardness, depth of score line, shape, and size of tablet (88, 89).

There are also risks and consequences of manipulating other dosage forms than tablets, but not many studies. To my knowledge there is only one study of the splitting of torpedo-shaped suppositories with the conclusion that only intact suppositories should be administered due to difficulties in achieving the accurate target dose after splitting (90).

Transdermal medical patches have fixed dosing in the same way as tablets and capsules. Cutting transdermal patches to receive part of the dose is presented in Table 1 as a form of manipulation but there are only few articles presenting dosing accuracy after this procedure. The plasma concentrations seemed to be less predictable when using cut patches of transdermal clonidine compared to patients with intact patches (91). A case report showed a clear link between a cut fentanyl patch and an opioid-intoxication (92). On the other hand, a European guideline for inducing puberty in girls with Turner syndrome, suggests using estrogen patches cut down to 1/16 (93). Earlier studies have shown reliable results with this practice as well as stability for the remainders of the patch, so they can be kept and used for the next dose (94, 95). Depending on the formulation of the transdermal patch manipulation might be ok but leakage of the API can lead to overdosing (96, 97). Patches with a matrix design have a dose correlated to the surface of the patch and might be cut into smaller pieces, while patches with a reservoir system must not be cut.

To be exposed to the drug substance is another risk for the person performing the manipulation (98-100). Caregivers to paediatric oncology patients are forced to manipulate oral anticancer drugs in the home setting and will need proper training and guidance to minimise the risks (101, 102).

There is a higher risk for adverse events when paediatric patients have used medicines off-label (103-105). Due to the different inclusions in the concept “off-label” this could be due to changed effects from manipulating medicines.

Often a bitter tasting tablet is coated to minimise the exposure of the taste for the patient. Splitting or crushing such a tablet will expose the bitter taste, and sometimes a split tablet has rough edges causing discomfort for the patient swallowing it.

Manipulating medicines is also more time-consuming than just administering an intact tablet to a patient (106, 107).

3.6 DRUG FORMULATION FOR PAEDIATRIC PATIENTS

One important part of drug development is the formulation of the drug. A proper pharmaceutical dosage form must be easy and safe for the patient/caregiver or healthcare staff to handle and administer a correct dose from. Without a suitable formulation, the drug will not be as beneficial as intended. Clinical studies including paediatric patients should have a formulation suitable for administering doses in the included age range (4, 108).

A perfect paediatric product should provide suitable dose flexibility to enable accurate dosing across the defined age range, and ideally this should be accomplished without the need to manipulate the product (109). There are many different aspects that influence the choice of pharmaceutical dosage forms to paediatric patients; age, disease, physical abilities to take and swallow the drug (108, 110).

Dosage forms already on the market will be more or less suitable for paediatric patients, since they are a heterogeneous group of patients. Children of different ages have different capabilities and different needs. Guidelines have been constructed to guide drug companies developing new formulations (4, 6, 111). A suitable age-appropriate drug formulation can most likely enhance compliance (112).

Oral administration is the most common administration route (38) and there are many different oral dosage forms available. Normally the oral dosage forms are categorised as either solid or liquid dosage forms.

A common (mis)belief is that oral liquids are the preferred dosage form for children, but there are advantages and disadvantages with both liquid and solid dosage forms. An advantage with liquids is the convenient individual dosing, but there are also disadvantages such as issues concerning the stability and shelf-life of the drug, the need for unsuitable excipients like preservatives or ethanol and sometimes the volume for older/bigger children gets very large (113, 114). The cost to produce oral liquids is usually higher than conventional tablets (69). Several studies have also shown a high risk of measuring errors when administering liquid medicine (115, 116). Many drug substances are bitter and taste masking is more difficult in liquids than in solid formulations (117). Excipients may give rise to concern; sugar is often used to mask bitter taste and ethanol is sometimes used as a solvent.

The advantages with solid dosage forms are easier to transport and store, stability (longer shelf life) and they are often cheaper to produce. The major disadvantages are the non-flexible dosing and that patients experience problems with swallowing.

Many attempts have been made to determine from what age children can swallow tablets and what sizes of tablets are appropriate in different age-groups (118). One common statement is that children under the age of 6 years have difficulties swallowing solid oral dosage forms.

This statement is emanating at least partly from a Dutch study where prescriptions were analysed regarding at what age as many children got a solid dosage form prescribed as a liquid oral dosage form (the age of conversion) (119). In the first draft of the EMA Guideline on Pharmaceutical Development of Medicines for Paediatric Use suitable dimensions for tablets to be used in different age groups were proposed (120). Due to lack of scientific evidence this table was removed in the final version of the guideline (121-123).

A Norwegian study has compared the age of conversion between liquid and oral dosage forms, i.e., the age where 50% of prescriptions are for liquid dosage forms and 50% of prescriptions are for solid dosage forms. The result was that the age when as many children got tablets or capsules as liquids has increased from 5.7 years to 7.9 years of age in 2004 and 2016, respectively (124). Since the capability of Norwegian children to swallow solid dosage forms has not changed during these years, there are probably other factors influencing the choice of dosage form. In a French study from 2016, RNs stated from which age they believed children could swallow tablets and capsules and their estimations were between 7 and 8 years of age (125). One important factor influencing a child´s ability to swallow a solid oral dosage form is the size and shape of the tablet or capsule (118, 126, 127). The ability to swallow tablets can be enhanced through training, both for children and adults (128-130). Another factor that influences the ability to take medicine is the capability to feel bitter taste, which can vary between people depending on taste sensors. Children more genetically disposed to feeling bitter taste preferred solid oral dosage forms compared to children without these taste sensors (131). Different medical aids can help children swallow solid dosage forms, i.e., Pill Glide which is a flavoured spray that the patient sprays in the mouth before and after taking the medicine, or a coating that is wrapped around the tablet before administration. Children as young as 2 years old could swallow tablets when using a tablet coating (132, 133).

A WHO expert forum proposed a shift of paradigm toward solid dosage forms already in 2008, based on a solid platform technology, i.e., multiparticulate solids (granules, mini-tablets) that can be made into tailored strengths and dosage forms at the time of administration (134, 135). Mini-tablets have the advantage of a very small size and can either be administered as single doses or be combined in different amounts for children in different ages. Studies comparing mini-tablets with oral liquids have shown that mini-tablets can be successfully administered to patients as young as six months and that both caregivers and patients preferred them over liquids (114, 136, 137).

Many studies have focused on children’s acceptability of medicines and one focus in many of the studies is the flavour of the drug, i.e., the palatability (131, 138, 139). This is an extensive area of research and flavour can be considered a combination of taste, smell, and chemical irritation (140). Since there is a large interindividual and even cultural difference in the preference of flavour, attempts have been made at introducing an electronic tongue for taste tests during the product development (141).

3.6.1 New innovative oral dosage forms

As a response to the new paediatric regulations and the increasing awareness of challenges in drug formulation for the paediatric population, some new intriguing oral dosage forms suitable for children have been and are being developed. Examples available on the Swedish market as registered products are orodispersible tablets containing e.g., paracetamol and desloratadine. Other examples, not yet available for Swedish patients are mini-tablets, orodispersible films and even 3D-printed tablets (136, 142-148). In 2015 FDA approved the first 3D-printed tablet, containing levetiracetam (Spritam®), designed to be rapid melting, needing only a sip of water (149). These tablets come in predefined strengths but there are ongoing studies to make more individual doses closer to the patient, at the ward or even at home (150). 3D-printing allows for different approaches, either to make very small tablets that are easy to swallow or to make chewable or soluble tablets in all different shapes to make them more appealing to the paediatric population, e.g., stars or animal shapes (151). There are still regulatory and production aspects of this new manufacturing method to be solved before this can become a reality. 3D-printing is also a technique suitable for producing orodispersible tablets, mini-tablets, or even suppositories (152, 153). Medicine looking like breakfast cereal has also been produced using 3D-printing technology (154).

Conventional tablets can be made into novel dosage forms by adding functional score lines to enable interval dosing. An example of this is a large, rectangular, soluble tablet with several score lines combining two antiretrovirals for treatment of HIV, developed to enable dosing per 5 kg interval. It showed good breakability and the dosage content both in the whole tablet, and in the smallest part (1/8) was in accordance with requirements in the Ph. Eur, Figure 1. (155).

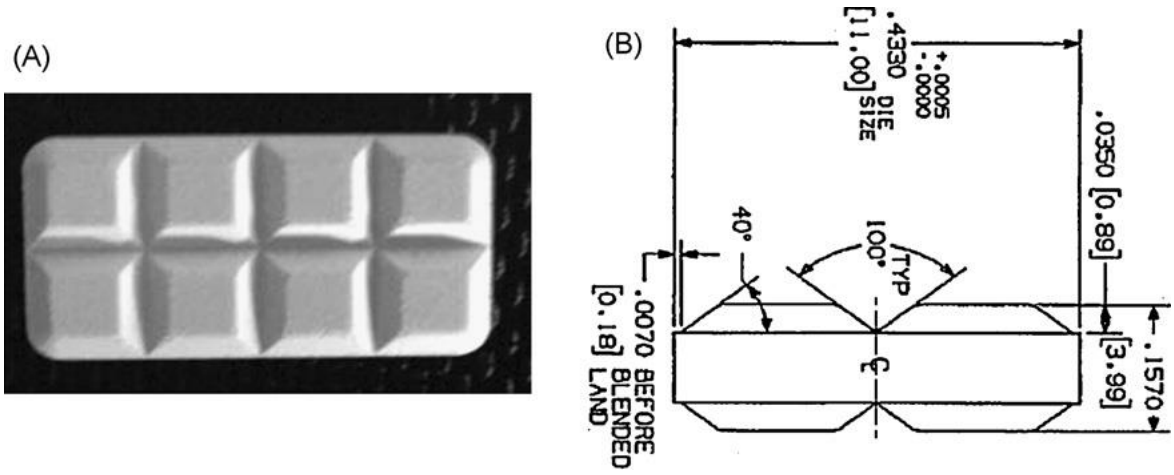

Figure 1. Design of rectangular tablets: topview (A) and side view along shortest axis (B). Reprinted from, Int J Pharm Vol 370, E. Kayitare et al., Development of fixed dose combination tablets containing zidovudine and lamivudine for paediatric applications, 41-6., Copyright (2009), with permission from Elsevier.

The dose sipping technology is another interesting preparation which combines the advantages of solid dosage forms such as stability and shelf life with the convenience of a liquid for the child. Granules of the medicine are inserted in a prefilled drinking straw in predefined doses and when it is time to administer the medicine the child chooses a liquid to drink through the straw (156, 157).

Product development to make more acceptable dosage forms for children carry a risk-benefit balance between making medicines look and taste nice so that the children will take them and the risk of children mistaking them for candy or cereal or regard them as innocuous (158-160).

3.7 PAEDIATRIC REGULATION

"it is expected that the number of authorised paediatric medicinal products and the knowledge on the quality aspects critical to these products will rapidly increase" (123)

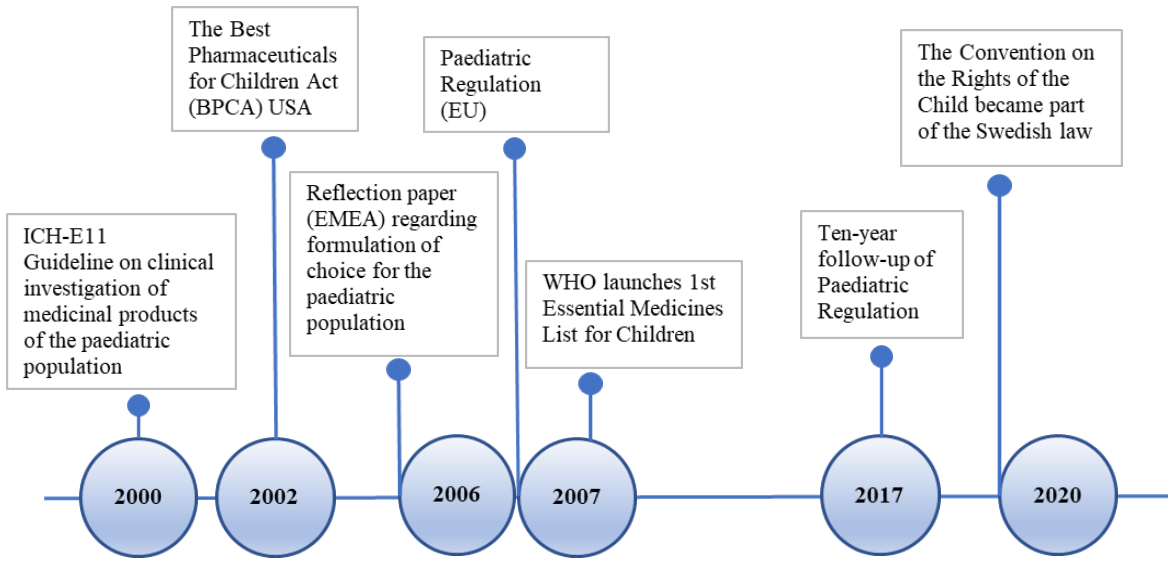

Figure 2. Timeline indicating important events, documents, and regulations promoting research and development of medicines suitable for paediatric use.

To speed up the development of medicines suitable to paediatric patients, regulatory incentives have been introduced, both in the United States and in Europe, Figure 2. The European Union Paediatric Regulation came into force in January 2007 and has thus been in practice for more than ten years. The aims of the regulation are to achieve more data regarding the use of medicines in children to improve the information available to prescribers and families and to encourage drug companies to develop more child-friendly dosage forms and strengths of medicines (161).

Has this regulation made any difference? The ten-year report from the European Commission is a summary of all clinical trials with paediatric patients involved, new drugs with paediatric information on the market and new paediatric information for old drugs, already on the

market. The results are positive and promising when it comes to the development of new drugs (267 new drugs on the market) and pharmaceutical forms (43 new pharmaceutical forms) and there has also been an increase in the number of clinical trials involving children. The incentive for drug companies to perform studies on children for older off-patent drugs, seems to be low since only 3 so-called PUMAs (Paediatric Use Marketing Authorisations) have been authorised through the centralised procedure at EMA during these ten years (162, 163). Since the 10-year report at least three other PUMAs have been authorised.

Lack of paediatric data on off-patent drugs means that a lot of drugs are still used without supporting data. Often this is combined with a lack of suitable dosage forms, which leads to a further need to manipulate medicines to achieve the prescribed dose.

A review from 2015 investigating whether the paediatric regulations in the United States and Europe had had any impact on the level of unlicensed and off-label use of medicines in paediatrics could not see any pronounced difference, probably due to the short time interval since implementation. Other problems identified in the study were that there were few studies in the field, no separate study included in their review had a ‘before and after study’, and the definitions of unlicensed and off-label vary between included studies, as well as the study setting (164). A Finnish study investigated the use of off-label and unlicensed use of medicines in a paediatric setting before (year 2001) and after (year 2011) the implementation of the Paediatric Regulation, but in contrary to their hypothesis that the regulation had diminished the need to use off-label and/or unlicensed medicines, they saw a higher frequency of patients receiving at least one off-label drug in 2011 compared to 2001 (79% vs 58%) (165). This is probably due to the short period of time that the regulation had been operative and the fact that many of the drugs used in paediatrics are old, off-patent drugs for which no paediatric data has been accomplished. The development of child-friendly medicines and dosage forms is a long process, and we will hopefully see more development in the years to come.

3.8 COMPARISON WITH THE GERIATRIC SETTING

Herregud & Co

The paediatric and the geriatric patient population share some similar features when it comes to using medicines (166). Manipulation of medicines is a common practice in the geriatric setting as well, mainly due to elderly people having difficulties swallowing medicines, but sometimes also to administer a fraction of a dose. Older patients are in general more frequently prescribed medicines so this is a substantial problem. In Sweden in 2021 older adults (> 70 years of age) contribute to 15% of the population and are prescribed 52% of all medicines (167)

A Norwegian study focused on medicines where there is information in the SmPC stating that the tablets/capsules should not be crushed or split, and in this study ten percent of the patients received at least one “Inappropriately Altered Medication”. In addition, 23% received at least one drug mixed with food or beverages, which can also influence the effect of the medicine (168).

In an Irish study 35% of the patients in an aged care facility received a manipulated medicine and in 80% of the manipulations the purpose was to administer part of the dose (19). Since frequencies are expressed either from medications (21-26% manipulated) (169, 170), doses (25% manipulated) (7), or patients/residents (44% received a manipulated medicine) (170) comparisons between different studies is difficult also in the geriatric setting.

The same problems described for manipulations in the paediatric setting are also seen in the geriatric setting, i.e., risk of over- or underdosing, lack of information, and environmental risks for the person manipulating are described in this setting (171).

An interesting similarity between the geriatric and the paediatric setting is that the term age-appropriate medicines is used in both patient groups as a term for medicines suitable for their age group (161, 171).

4 RESEARCH AIMS

The overall aim of this project was to study how and to what extent manipulation of medicines is being done and its effect on dosing accuracy in paediatric care. This has been studied using both qualitative and quantitative methods; interviews, weighing of split tablets and analysis of large data sets.

4.1 HYPOTHESIS

Manipulation of medicines to paediatric patients is common practice for healthcare professionals and caregivers and can influence the dosing accuracy.

Due to the European Paediatric Regulation, there are more child friendly dosage forms available on the market and the need to manipulate medicines has declined between the years 2009 and 2019.

The use of extemporaneous preparations is one alternative to manipulation of medicines and an indicator of the lack of child appropriate dosage forms and strengths.

4.2 SPECIFIC AIMS

The specific aims were:

I. To compare the frequency of manipulated solid oral and rectal medicines at a Swedish paediatric hospital analysing the emergency setting separately from the ward setting and comparing two separate study years, ten years apart
II. To explore how registered nurses and pharmacists reason about manipulation of medicines to paediatric inpatients
III. To explore how exact the weights of halved and quartered tablets will be using a tablet splitter and splitting manually
IV. To compare the frequency of patients receiving an extemporaneously prepared medicine at a Swedish paediatric hospital, comparing two separate study years, ten years apart

4.3 OUTCOME MEASURES

I. Frequencies of patients with manipulated solid oral or rectal medicine, related to age, ATC-group of medicine and study year
II. Categories and subcategories around manipulation of medicines to children, derived through inductive content analysis of interviews with RNs and pharmacists
III. Split tablets, halves and quarters, correspondence with criteria in the European Pharmacopoeia and the United States Pharmacopoeia
IV. Frequencies of patients with extemporaneous oral preparations, related to age, ATC-group of medicine and study year

5 MATERIALS AND METHODS

The methods section will contain information about study design, settings, data sources, data collection and analyses. Detailed description of methods can be found in the individual papers.

5.1 STUDY DESIGN

This thesis includes four studies presented in four papers. Both quantitative and qualitative methods have been used to explore different aspects of manipulated medicines to children. Table 2 presents an overview of the papers included in this thesis.

Table 2. Overview of papers and study design.

Paper	Design	Aim	Sample	Data collection
I	Registry-based retrospective study	To compare the frequency of manipulated solid oral and rectal medicines analysing the emergency setting separately from the ward setting and comparing two separate study years, ten years apart	All patients 1 month - 18 years with oral or rectal administrations	KarDa (registry)
II	Qualitative study	To explore qualitatively how registered nurses (RNs) and pharmacists reason on manipulation of medicines to paediatric patients	Purposive sampling of RNs and pharmacists	Semi-structured interviews
III	Experimental study	To quantitatively explore how exact halved and quartered tablets will be using a tablet splitter and splitting manually. The results will be compared to criteria according to Ph. Eur. and USP	Five selected brands of tablets	Experiment, split tablets
IV	Registry-based retrospective study	To compare the frequency of patients receiving extemporaneously prepared medicines, comparing two separate study years, ten years apart	All patients 1 month - 18 years with oral administrations	KarDa (registry)

5.2 SETTING

Papers I, II, and IV were performed at a paediatric hospital, Astrid Lindgren Children's Hospital, within a large university hospital, Karolinska Hospital, in Stockholm. The paediatric hospital has different specialties such as neonatology, paediatric surgery, intensive care, oncology, paediatric medicine, orthopaedics, operating theatre and anaesthetics and paediatric emergency care. The paediatric hospital generally admits patients from 0 to 18 years of age, and had a capacity of 250 beds, around 2,000 employees, and provided care for approximately 25% of all children in Sweden.

The electronic health record used at most of the wards at the hospital, TakeCare (TakeCare, CompuGroup Medical, Solna, Sweden) was implemented late 2004 and the medication record part of it was implemented late 2008 at the paediatric hospital. Data regarding patient data, care and medicines documented in TakeCare can be retrieved from Karolinska Hospital's internal database (KarDa).

Paper III was performed at the Karolinska University Hospital Pharmacy, Apoteket AB.

5.2.1 Swedish health care

In Sweden health care services are primarily government funded, though private health care exists. Health care is organised on three levels: national, regional, and local (municipality), where the national level sets the principles and political agenda for health and medical care. The regional level is responsible for acute and primary care including general hospital care. General and university hospitals provide care for the regional catchment area with some specialties being provided only by a few national centres. The municipalities are responsible for social care and care for the elderly.

5.2.2 Registered nurses

Registered nurses (RNs) are the most common healthcare profession at the current hospital, constituting approximately one third of all employees. They have a three-year academic training, leading to a bachelor's degree in Nursing Science. After completion of basic education, clinical specialisation can be done, e.g., in paediatric care, leading to a 1-year master's in nursing. Besides being responsible for nursing care, planning of care interaction with other healthcare professions, RNs have the main responsibility for medicines including preparing them for administration and administering them to the patient. In Sweden most hospital wards order medicines from a hospital pharmacy in whole drug packages to a ward floor stock where either RNs or ward pharmacists reconstitute and prepare the medicines for administration (172).

5.2.3 Clinical pharmacists / ward pharmacists

Pharmacists employed by the ward, is a relatively new profession in paediatric wards in Sweden. At the current paediatric hospital, it started out as a project in 2014 and since 2017 there have been pharmacists employed on a more regular basis. Most of the pharmacists in

the paediatric hospital are rather ward pharmacists than clinical pharmacists. Their tasks include reconstitution of drugs, drug ordering, developing routines and guidelines and training RNs in drug handling and reconstitution.

5.2.4 The Paediatric Drug Therapy Group / the ePed central editorial office

Since 2008 there has been a Paediatric Drug Therapy Group at the Astrid Lindgren Children's hospital. What started out as a small group of two paediatric pharmacists, one paediatrician and a registered nurse has now grown to seven pharmacists, two paediatricians and a registered nurse, specialised in paediatrics. The main local responsibilities are writing drug order sets in the different electronic health records used at the hospital, managing drug shortages, and teaching newly employed physicians and RNs the drug chart in the most frequently used electronic health record, TakeCare. The group is also responsible for writing paediatric drug information sheets, published weekly as pdf-documents on a website, under the name ePed (evidence- and experience-based database for paediatric drug information). This work is since 2014 financed nationally on a joint basis by all the Swedish regions. The group at Astrid Lindgren Children's hospital is the central editorial office, collecting information and questions from all over Sweden and producing the documents. The regional offices (one in almost all regions in Sweden) decides on which ones of the documents that are concordant with their local guidelines and traditions and approve them for use on the regional list.

5.3 DATA SOURCES AND DATA COLLECTION

5.3.1 Registry data (Papers I and IV)

Data was extracted from the hospital based electronic data register from the main electronic health record, TakeCare (KarDa). Data regarding all oral (including via enteral feeding tube), and rectal administrations of medicines were collected for all patients, 1 month - <18 years during the years 2009 and 2019, respectively. Since the medicine chart was implemented late 2008, the first full year with data is 2009, enabling us to study two separate years, ten years apart. The number of administrations and patients included in **Papers I and IV** respectively are presented in Table 3.

Table 3. Number of included patients and administrations in Paper I and IV.

Paper	**Setting**	**Patients**		**Administrations**	
		2009	2019	2009	2019
I, IV	Oral inpatient	4,905	4,718	117,023	128,638
I	Oral emergency	5,260	15,038	6,680	24,013
I	Rectal inpatient	2,355	1,240	12,449	5,315
I	Rectal emergency	3,883	5,902	4,639	9,979

5.3.2 Qualitative data (Paper II)

Semi-structured interviews were performed with 12 purposely selected RNs at four different wards at the children's hospital, using a semi-structured interview guide. A pilot interview was performed ahead of the study. The interviews were performed by the first author (ÅCA). The following semester a pharmacy student performed semi-structured interviews with seven ward pharmacists, also following a pilot interview leading to minor changes in the interview guide. All interviews were performed at a location in or nearby the ward and during working hours. All interviews were audio recorded and transcribed verbatim.

5.3.3 Tablet splitting (Paper III)

Five brands of tablets were chosen after asking RNs at the children's hospital what tablets they usually manipulated. These tablets were Alvedon® (paracetamol), Prednisolon® (prednisolone), Hydrocortone® (hydrocortisone), Tavegyl® (clemastine), and Catapresan® (clonidine). Three tablets were registered in Sweden at the time of the study (Alvedon®, Prednisolon®, and Tavegyl®) and two brands were unlicensed requiring a license from the Medical Products Agency to prescribe and use the medicine (Catapresan® and Hydrocortone®). According to the test for split tablets in the European Pharmacopoeia, (Ph. Eur.) thirty tablets of each brand were first split into halves and then further to quarters. Half of the tablets were split by hand and half of them with a tablet splitter, sold by the pharmacy, besides from Tavegyl® which was only split with the tablet splitter due to size and hardness. All tablet halves were then split once more into quarters, using the tablet splitter. All tablets were weighed intact and from that weight the predicted weight of halves and quarters were calculated. Subsequently all parts were lifted on the scale with a tweezer and weighed on a Mettler HK 160 scale.

5.4 ANALYSES

5.4.1 Registry data (Papers I and IV)

The registry data were thoroughly checked for omissions and some ATC-groups were reclassified to the one that it is used for in our paediatric setting, e.g., sildenafil was classified as ATC-group C (cardiovascular system) and naloxone orally against constipation as A (alimentary tract). Solid and liquid dosage forms were classified from the dosage form stated by the drug company according to a list defined by the research team. Tablets, capsules, and dose sachets as well as suppositories and enemas, are all examples of solid dosage forms. Manipulations were defined as drug orders for parts of solid dosage forms, e.g., 0.5 tablets or mL of a tablet implying that the tablet had been dissolved or suspended in some liquid. Parts of solid dosage forms as well as extemporaneous preparations were manually classified. In **Paper IV** only data regarding oral administrations of medicines in the inpatient setting were included in the results, since analysis of the data showed that there were almost no rectal extemporaneous preparations and the use of extemporaneous preparations in the emergency department was insignificant.

Patients with no documentation of sex were excluded. Patients with no documentation of age but a given body weight were assumed to have an age corresponding to the weight according to the growth chart in the electronic health record. Frequencies of patients with manipulated medicines or extemporaneous preparations were counted and comparisons were made between the study years, and between the inpatient setting and the emergency department. Correlations were also made with patient age and ATC-group and active pharmaceutical ingredient (API). Extemporaneous preparations were classified based on their name, the strength of the preparation compared to registered products and extensive clinical experience of the drugs used locally at the children's hospital.

5.4.2 Text analyses (Paper II)

The interviews were transcribed verbatim by two pharmacy students and the transcripts were then double checked by the first author against the audio file. The transcripts were then read through several times to get a sense of the whole. The content analysis was made using manifest qualitative content analysis with an inductive approach (173). The condensation of the text into meaning units and codes were performed separately by two of the authors and for the interviews with RNs and pharmacists separately. The condensing of codes from both professions into subcategories and main categories were made together by two of the authors, and all authors discussed the emerging findings until agreement was reached.

5.4.3 Split tablets (Paper III)

The Ph. Eur. test for subdivided tablets was applied, signifying that out of 30 tablet halves only one individual half is allowed outside the 85 – 115% range of predicted average mass and no individual tablet half outside the 75 – 125% range of predicted average mass, for the tablet to fulfil the criteria. In addition, and as a comparison, the relative standard deviation (RSD) test from the United States Pharmacopoeia (USP) was applied, stating that the product passed the test if the RSD is less than 6%.

5.5 STATISTICS

Data from the registry KarDa was extracted by QlikView 11 (Qlik Technologies, Inc. PA, US). Initial descriptive statistics for **Papers I and IV** were evaluated by MS Excel (Microsoft, Redmond, WA). GraphPad Prism version 5.04 (Graph Pad Software, San Diego, CA) was used for further statistical analysis in **Papers I, III and IV**. Differences in proportions were compared by the chi-squared test. Significance was defined as $p < 0.05$. Reported p-values are from two-sided tests.

In **Paper III** the variance ratio test was used for the comparison of the variability of data in the two populations. The Fischer's exact test for comparison of data from two independent populations was used. The two populations were tablets split by hand and tablets split using a tablet splitter. Significance was defined as $p < 0.05$. Reported p-values are from two-sided tests.

5.6 ETHICAL CONSIDERATIONS

The semi-structured interviews in **Paper II** were conducted with a permit from the head of the paediatric hospital.

Papers I, II, and IV were conducted with an ethical permit from the Swedish Ethical Review Authority (Dnr 2019-02811, 1 July 2019). For **Paper III** no ethical permit was needed, since there was no ethical dilemma, the split tablets were never given to any patients.

All data in **Papers I, and IV** were pseudonymised i.e., each patient has a unique identification number making it possible to link all administrations to a single patient, knowing the sex and the age, but at the same time keeping the identity of the patient unknown.

In **Paper II**, the RNs and pharmacists chosen for interviews were informed verbally and in writing, and if willing to participate in the study signed a written consent form. All participants had the option to withdraw from the study for any reason. All transcribed interviews received a number instead of name or initials to protect confidentiality, and all citations are chosen to protect the identity of the individual participant.

6 RESULTS

In this section the main results from the presented papers in this thesis are presented;
Lack of child friendly medicines (Papers I, II and IV)
Thoughts around manipulation (Paper II)
Impact of manipulation (Papers II and III)
Alternatives to manipulation (Papers II and IV).

For further details, please see the full-text manuscripts included at the end of the thesis.

6.1 LACK OF CHILD FRIENDLY MEDICINES

Manipulations of medicines (**Paper I**) as well as the use of extemporaneous preparations (**Paper IV**) are indicators of a lack of child friendly medicines.

In **Paper I** the frequencies of patients receiving at least one manipulated oral or rectal medicine, was compared between the study years, 2009 and 2019, respectively. During the work with this thesis more oral manipulations for ATC-group A was discovered in the registry data for inpatients, year 2019. When these are included in the material the result is that for patients with oral administrations in the inpatient wards there was no difference between the years (19% and 19%, p =0.62), Table 4. An erratum has been sent to the journal and we are waiting for their decision. In contrast, for patients with oral administrations in the emergency department there was a significant decrease (11% to 5%, p <0.0001). The frequencies of patients receiving a manipulated rectal medicine also decreased, in the inpatient wards from 22% to 10%, (p <0.0001), and in the emergency department from 35% to 7%, (p <0.0001) (174).

Table 4. Revised Table 1 from Paper I, indicating the higher number of patients with manipulated solid oral medicines 2019.

	ORAL ADMINISTRATIONS			
	Inpatient units		Emergency department	
	2009	2019	2009	2019
Number of patients	4,905	4,718	5,260	15,038
Male patients (%)	56	56	58	55
Number of administrations	117,023	128,638	6,680	24,013
Number of administrations/patients	24	27	1.3	1.6
Number of patients with solid manipulated medicines (%)	953 (19)	**897 (19)**	581 (11)	767 (5)

The decrease in manipulated medicines could be due to the introduction of new medicines, with more appropriate strengths and dosage forms or a shift to dose banding. It could also be

due to the use of extemporaneous preparations, which was further investigated in **Paper IV**. Patients receiving at least one extemporaneous oral preparation increased in the inpatient setting between 2009 and 2019 from 1,072 (22%) to 1,878 (40%), ($p < 0.0001$). The frequency of extemporaneous administrations of all oral administrations were 22,405 (19%) and 26,124 (20%), in 2009 and 2019 respectively ($p < 0.0001$). The number of rectal extemporaneous preparations was very low both study years and the usage of extemporaneous preparations in the emergency setting was also very low and no comparisons were made for these groups. An overview of the results from Paper I and Paper IV are presented in Table 5.

Table 5. Overview of results from Paper I and IV.

Paper	**Setting**	**Patients with manipulated medicine (%)**		**Patients with extemporaneous prep. (%)**	
		2009	2019	2009	2019
I, IV	Oral inpatient	19	19	22	40
I	Oral emergency	11	5	NA	NA
I	Rectal inpatient	22	10	NA	NA
I	Rectal emergency	35	7	NA	NA

NA = not applicable

Since there were no major differences between female and male patients, the results were presented for the whole material, divided in age-groups. Administration of a manipulated oral medicine was more common to older children, the age-groups 6 -<12 years and 12 -<18 years had the highest frequency in both the inpatient setting and the emergency department, both study years. In the emergency department almost no patients younger than 2 years received a manipulated solid oral medicine. For manipulated rectal solid medicines on the contrary, it was more common for the youngest age-groups (younger than 2 years) to receive a manipulated dosage form, both in the inpatient setting and the emergency department, both study years.

That manipulation of medicines to children is a very common part of the daily practice was confirmed by the interviews with both RNs and pharmacists in **Paper II**.

> "*A necessary evil"* (Nurse 1)
>
> *"The most common [situation] is that we need to manipulate. Yes, almost always!"* (Pharmacist 7)

The different ATC-groups differ in availability of medicines suitable for paediatric use and consequently also in how much manipulations were performed or how much extemporaneous preparations were used. To see trends over time it is most interesting to analyse APIs separately. In Table 6 the top ten APIs for 2009 are listed, which represented over 43% of all administrations. In 2019 the top ten most prescribed APIs represented over 45% of all administrations. These are presented in Table 7.

Table 6. Top ten oral APIs 2009 for inpatients.

2009	Active Pharmaceutical Ingredient (API)	n	%	ATC	Manip.	Extemp.
1	Paracetamol	14,751	12.6	N	1,025	0
2	Clonidine	9,848	8.4	N	568	8,241
3	Naloxone	4,852	4.1	A	0	4,852
4	Furosemide	4,138	3.5	C	122	0
5	Sodium chloride	3,481	3.0	A	0	0
6	Prednisolone	2,963	2.5	H	697	2
7	Ibuprofen	2,959	2.5	M	20	0
8	Potassium chloride	2,663	2.3	A	13	0
9	Nystatin	2,625	2.2	A	0	0
10	Amoxicillin (incl comb with enzyme inhibitor)	2,299	2.0	J	6	0

n = Total number of administrations = all oral administrations of this API, including manipulated and extemporaneous.
Manip. = manipulated administrations. Extemp. = extemporaneous preparations

Table 7. Top ten oral APIs 2019 for inpatients.

2019	Active Pharmaceutical Ingredient (API)	n	%	ATC	Manip.	Extemp.
1	Paracetamol	18,794	14.6	N	951	0
2	Clonidine	12,287	9.6	N	323	11,027
3	Macrogol (single and combinations)	5,148	4.0	A	436	0
4	Naloxone	5,102	4.0	A	0	5,102
5	Ibuprofen	4,061	3.2	M	14	0
6	Vitamin D	3,032	2.4	A	0	0
7	Sodium chloride	2,672	2.1	A	0	249
8	Amoxicillin (incl comb. with enzyme inhibitor)	2,601	2.0	J	7	0
9	Esomeprazol	2,530	2.0	A	655	0
10	Levetiracetam	2,355	1.8	N	59	0

n = Total number of administrations = all oral administrations of this API, including manipulated and extemporaneous.
Manip. = manipulated administrations. Extemp. = extemporaneous preparations

The two tables 6 and 7 clearly show that the two most frequently used APIs are the same both years. Other APIs like naloxone, sodium chloride, ibuprofen, and amoxicillin are also among the top-ten both years. Furosemide, prednisolone, nystatin, and potassium chloride are no longer among the ten most prescribed APIs 2019. Instead macrogol, vitamin D, esomeprazole, and levetiracetam have entered the list.

A new marketed product can make a large impact in how an individual API is handled. A clear example from **Papers I** and **IV** is sildenafil, which was the most frequently (ten percent) manipulated API in 2009. The same year it was also highly prescribed as an extemporaneous preparation (80% of all sildenafil-administrations). During the ten-year period before the next study year, sildenafil was registered in Sweden as a powder for oral suspension (Revatio®) with the paediatric label pulmonary hypertension leading to no manipulations or extemporaneous prescriptions in 2019, Table 8.

Table 8. Administrations of sildenafil in 2009 and 2019.

	n	Manipulated	Extemp.	Man. + Extemp.
2009	1,645	1,175	1,309	918
2019	483	0	0	0

n = Total number of administrations = all oral administrations of this API, including manipulated and extemporaneous.
Manipulated = manipulated administrations. Extemp. = extemporaneous preparations. Man + Extemp. = manipulated extemporaneous preparation

The manipulation of rectal solid dosage forms decreased significantly between 2009 and 2019, **Paper I.** At the emergency department 35% of all rectal solid administrations were parts of a suppository in 2009, but in 2019 only 7% of the administrations were for parts of solid rectal dosage form. The corresponding figures for inpatients were 22 and 10%, respectively. The frequency did not only decrease but there was also a shift from parts of suppositories to parts of enemas, with almost no suppositories split in 2019. In 2009 the majority of manipulated rectal solid medicines were from the ATC-groups M (musculo-skeletal) and N (nervous system), mainly suppositories. In 2019 almost no manipulations were from ATC-group M, but more from ATC-groups A (alimentary tract), mainly enemas. This was also confirmed by the RNs interviewed in **Paper II**. None of the RNs said that they manipulated suppositories, and almost all of them said that if they got a drug order including part of a suppository, they would find an alternative way of administering the medicine, as in rounding off the dose, combining two different strengths or even to complement it with some oral medicine. A few of the RNs that had worked several years remembered that splitting of suppositories was done in the past.

6.2 THOUGHTS AROUND MANIPULATION

In the qualitative analyses in **Paper II** important aspects of manipulation of medicine in a paediatric setting were identified. In total four categories with three subcategories each emerged during the analysis, Table 9.

Table 9. Categories and subcategories from analyses of interviews with RNs and pharmacists.

CATEGORIES	SUBCATEGORIES
Medicines management in paediatric care	Working outside the box
	Strategies to avoid manipulations
	It all comes down to the child
Sources of knowledge	Knowledge base
	Written information
	Networking
Human interactions	Registered nurses and pharmacists
	With physicians
	With caregivers
Organisational factors	Time
	Documentation
	Working environment

Medicines management in paediatric care

Every step in the drug handling process is more complicated in the paediatric setting, due to lack of information and suitable products. Both professions expressed a feeling of working outside the box and developing strategies for how to manipulate or find alternatives to manipulation. Often the choice of how to manipulate or what alternative to choose is made based on the child's preferences.

> *"I wonder how this turns out really, or I mean, it is not completely by the book, you can understand that, but you think I hope it did not cause too much harm."* (Nurse 3)

Sources of knowledge

Both the knowledge base, i.e., what each profession was taught during their training, and sources to seek new knowledge, were included in this category. There was a difference in what sources and networks each profession had access to, with pharmacists having knowledge of more sources to look in and the knowledge base to interpret the information.

> *"… You look at what kind of substance it is, what is the molecule size, does it look like anything else that I recognise? Hmmm, and I mean, you can always read about the substance and pH-value and stuff. There is lots and lots of information around, so I still need to use my pharmaceutical knowledge and think logically."*
> (Pharmacist 3)

Human interactions

The most frequent interaction was the one between RNs and pharmacists since they work in the same setting and share the same medicine room. Both professions expressed that having a pharmacist at the ward made the RNs feel safe and the pharmacists were appreciated members of the teams. Both professions stated that they did not have as much interaction with physicians, and they were not perceived to have special knowledge of manipulation of medicines. Interactions with caregivers is an important part of medicine handling, both asking how they normally handle medicines at home, or teaching them before discharge.

> *"… the parents have handled the medicines at home, so you need to ask the parents how they have done. Because even if it says that you shouldn't do things a certain way, if the parents have done it that way and the child is set on that way, I am thinking of antiepileptics, hmmm, if they have found the plasma level that works for that child, then it is important to do the same way as at home."*
> (Pharmacist 3)

Organisational factors

Registered nurses often talked about lack of time as a reason for not documenting the manipulation, or not having time to go to another ward to collect an alternative medicine. Having a pharmacist at the ward meant that they could do these tasks. If RNs did not document how or even if they manipulated a medicine due to lack of time, it meant that colleagues administering this medicine the next time did not know how it was done previously.

Working environment was a subcategory most often mentioned by pharmacists, although the RNs at the oncology ward were aware of the improper handling of medicines they had to do.

> *"… in certain circumstances we even split cytotoxic tablets which is a bit of a big No no, but … we try to at least have a separate tablet splitter for those tablets."*
> (Nurse 1)

6.3 IMPACT OF MANIPULATION

In **Paper III** five different brands of tablets were split into halves and further into quarters and the resulting parts were compared to criteria in Ph. Eur. and USP. According to Ph. Eur. no more than one individual mass is allowed outside the range of 85 – 115% of the expected weight, and no individual mass is allowed outside the 75 - 125% limits. The test criteria is set up for halves, but we used the same criteria for quarters. The USP had no criteria for split tablets, so an adopted version of the criteria for intact tablets was applied. In addition to the ranges from Ph. Eur. the RSD limit from USP was applied, stating that products with an RSD less than 6% fulfilled the criteria.

In our study only ¼ Tavegyl tablets, ½ Prednisolon tablets, ½ Hydrocortone tablets and ½ Alvedon tablets fulfilled the criteria in Ph. Eur. According to the RSD limit of 6% only ½ Hydrocortone tablets fulfilled the criteria (RSD = 4.7%), even though ½ Prednisolon tablets and ½ Alvedon tablets were just outside the limit (RSD = 6.1% and 6.5% respectively). The loss of tablet weight due to the splitting procedure was less than 1.2% for all parts. Figure 3 shows the results from the split tablets, in alphabetic order.

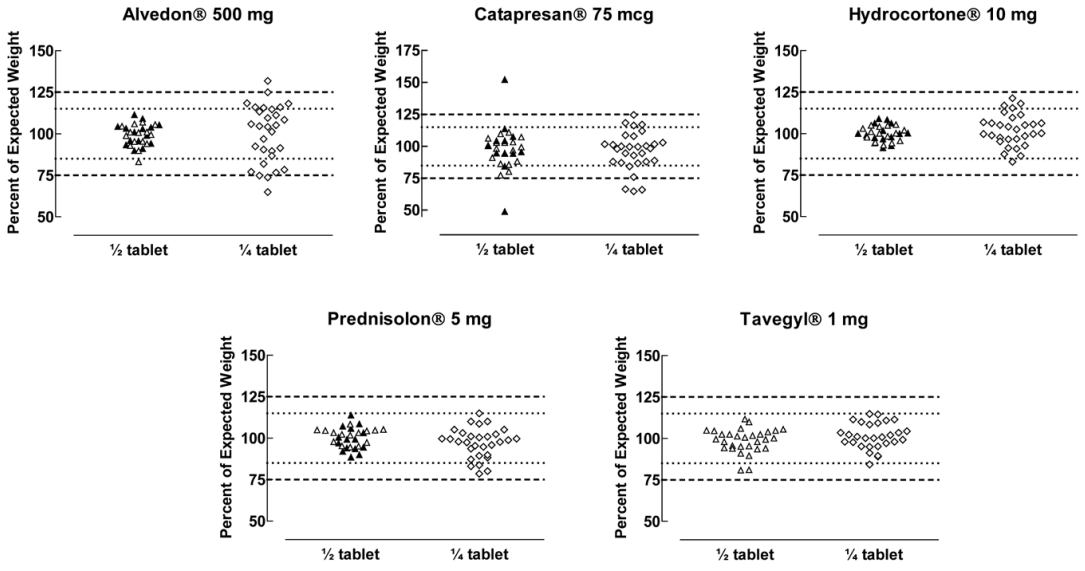

Figure 3. Results from tablets split into halves and quarters.

Filled figures=split manually
Non-filled figures=split by the use of a tablet splitter
The Ph. Eur. limits for uniformity of mass of subdivided scored tablets are presented with dotted lines:
..... =85 and 115%
---- =75 and 125%.

Results from the interviews in **Paper II** showed that especially RNs felt insecure about how correct the dose will be when manipulating medicines, e.g., dissolving a tablet in water and taking a fraction of the suspension:

> *"If I dissolve a tablet and then I am supposed to extract the dose from the "sludge…"*
> (Nurse 10)

6.4 ALTERNATIVES TO MANIPULATION

Extemporaneous preparations can be used instead of manipulated medicines. The results in **Paper IV** showed an increase in the number of patients with at least one extemporaneous preparation between the study years. In the first study year, 2009, 1,072 out of 4,905 patients (corresponding to 22%) received at least one extemporaneous preparation and in 2019, the number of patients had increased to 1,878 of 4,718 patients (corresponding to 40%) ($p<0.0001$). The increase was seen in all age-groups, Figure 4. For extemporaneous preparations to be a better alternative they need to be available with the right strength. In 2009 almost six percent of the extemporaneous preparations needed to be manipulated before administration, in 2019 the corresponding figure was less than half a percent.

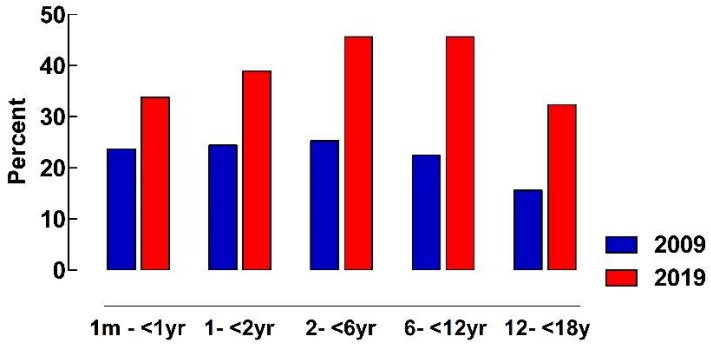

Figure 4. Frequency of patients with at least one oral extemporaneous preparation in different age-groups.

Sometimes suitable alternatives to manipulating medicines are available as registered products in other countries, but not in Sweden. These are so-called unlicensed medicines and can be used after a permission from the Swedish Medical Products Agency. Another alternative to manipulating is dose banding i.e., rounding off the dose to the nearest tablet or suppository. Rectal manipulations of suppositories almost vanished between 2009 and 2019 (**Paper I**), probably mainly due to rounded doses in "as needed" drug orders managed by the Paediatric Drug Therapy group.

Switching to another dosage form might be an alternative to manipulating a medicine. The RNs said in the interviews in **Paper II** that depending on their working experience, situation, and API, they could do this without contacting the prescriber. The physicians most often don't know the child's preferences or which medicines are available at the ward.

> *"If I would switch from half a tablet to a whole tablet... with the correct strength, then I would decide it myself. ... And the same if I would switch from half a tablet to oral solution, I would do that also without asking."*
> (Nurse 10)

7 DISCUSSION

Based on the overall findings in this thesis, five main factors related to manipulate medicines in paediatric care will be discussed:

1) Child friendly or age-appropriate?
2) Dosing accuracy of manipulated medicines, clinical impact?
3) Knowledge of drug manipulation by different healthcare professionals
4) Drug formulations suitable for paediatric use; attributes and availability
5) Similarities with the geriatric setting

7.1 CHILD FRIENDLY OR AGE-APPROPRIATE?

Both the expressions child friendly and age-appropriate are used to describe medicines to the paediatric population. In my opinion neither of them fully describes the complexity of the situation.

Child friendly is an expression used not only in relation to medicines, but also e.g., child friendly cities (175). The definition of child friendly in this setting is that children should have access to a safe environment where they can live, play, grow and make their voice heard. Based on this definition child friendly medicines are safe medicines, made accessible to children in different ages. It should be kept in mind that there is always a balance of making medicines friendly enough without being too tempting causing a risk for intoxication.

Age-appropriate is another expression used among others by the EMA, referring to people in young ages and their different capabilities to take medicines in different dosage forms (123). The same expression is used also by researchers in the geriatric setting. While paediatric patients normally gain capabilities and grow physically to adult levels in body size and organ maturation, elderly people slowly lose capabilities and their organ function declines. The disadvantage with the expression age-appropriate is that capabilities to e.g., swallow tablets are more linked to other things, rather than just age. Young children can be taught to swallow tablets through pill schools and on the other hand there are lots of adults that find it very difficult to swallow tablets or capsules (128, 129).

Individualised or personalised medicine is becoming more common since it has become possible to detect a patient's genetic code and base the diagnosis and treatment on that, but this refers to individual dosing and does not include the needs for individual dosage forms.

It would be desirable to find an expression that includes both the individual need for different dosage forms and individual dosing. The individual dose must be possible to achieve in a safe and easy way with as little manipulation as possible. The resulting dose and dosage form must then be accepted, including palatability, by children in different ages and with different capabilities. Beside all this, medicines should also be easy to produce, preferably cheap and stable for a long period of time.

"Medicines suitable for paediatric use" is an expression that combines both individualised dosing and dosage forms that are easy to administer to children in different ages and with different abilities. Such dosage forms will also be useful in the adult and geriatric setting where swallowing difficulties are common, but in this discussion, I will use the term medicines suitable for paediatric use.

7.2 DOSING ACCURACY OF MANIPULATED MEDICINES, CLINICAL IMPACT

The dosing accuracy of a manipulated medicine can be analysed using chemical investigations, e.g., HPLC (high performance liquid chromatography) (76, 176-178). If the manipulation is a split tablet, where the API is uniformly distributed in the tablet, the weight uniformity test can be applied (85, 179, 180).

7.2.1 Tablets with a score line

A common, and sensible, misbelief among patients and healthcare staff is that tablets with a score line are suitable to split in two equal parts. In fact, some tablets with a score line are suitable to split and the parts will contain half the dose, but for others the score line is just for splitting the tablet in smaller parts, and the parts need to be administered at the same time. Some tablets with a score line are not intended to be split at all and some may even contain hazardous substances. The WHO has stated that they disagree with tablets with non-functional score lines (58).

In **Paper III** four of the tablets had a score and one had a cross score. The results showed that splitting a tablet once, i.e., into halves was more often acceptable, than splitting it further into quarters. Three of the tablet halves and one of the quarters fulfilled the criteria from Ph. Eur. and only one of these fulfilled the RSD test from the USP. The conclusion in **Paper III** was that the dosing accuracy after splitting tablets was generally low, but in this thesis, I would like to question myself a bit. When looking at the figures in Figure 2, the visual impression of ½ Alvedon, ½ and ¼ Hydrocortone, ½ and ¼ Prednisolon and ½ and ¼ Tavegyl is that they are nicely clustered within the 75-125% range. In Table 10 only the tablet parts fulfilling any of the tests are included, with an added column for visually ok (or rather all tablet parts within 75-125%). Depending on which API, which dose and which patient, a ± 25% deviation might be acceptable. When splitting tablets in the home environment quite often the other part of the tablet is kept for the next dosing occasion and that partly compensates for the splitting inaccuracy. In the stressful environment in the hospital wards, RNs in **Paper II** were aware that saving the other part for the next dosing occasion would lead to a better overall dose but did not feel that it was feasible to do so. To mark the cup with the patient's name, the name and strength of the medicine and to inform the colleague responsible for administering the next dose, all of this would require extra time and therefore this was not prioritised.

Table 10. Tablets fulfilling any of the tests in **Paper III.**

Trade name	API	Original size(mm) ¤	Half or quarter	Ph. Eur.	RSD %	USP	Visual	SmPC
Tavegyl	clemastine	7.0*2.4	½	Failed	7.3	Failed	Yes	Yes
Tavegyl	clemastine	7.0*2.4	¼	Passed	8.2	Failed	Yes	NS
Prednisolon	prednisolone	8.0*2.7	½	Passed	6.1	Failed	Yes	Yes/No
Prednisolon	prednisolone	8.0*2.7	¼	Failed	9.3	Failed	Yes	NS
Hydrocortone	hydrocortisone	10.8*2.7	½	Passed	4.7	Passed	Yes	Yes#
Hydrocortone	hydrocortisone	10.8*2.7	¼	Failed	9.4	Failed	Yes	NS
Alvedon	paracetamol	16.2*7.7*5.8	½	Passed	6.5	Failed	Yes	Yes

¤ size = diameter * height,
for Alvedon length * width * height
# information from products available 2023
NS = not specified

In our study we could see that the smallest, round tablet (Catapresan, ø 6 mm) split most unevenly and therefore no parts of this tablet are included in Table CC. Other studies have also shown that larger (>8 mm) and oblong tablets split more accurately (88, 181).

When our tablet splitting experiments were performed there was no divisibility information included in the Swedish Handbook of Pharmaceutical Specialities. When looking now at the tablets that were included in the study Alvedon, Tavegyl, may according to their SmPCs be split in two equal parts. For Prednisolon it is stated for one brand that the score line is not intended to split the tablet but the two generic products may be split in two equal parts.

Catapresan and Hydrocortone are unlicensed products making it more difficult to find information regarding divisibility. In 2023 there are two different brands of hydrocortisone tablets registered in Sweden, both with a score line and text in the SmPC supporting that they can be split in two equal parts.

In our study more tablet parts fulfilled the criteria according to Ph. Eur. than the USP. In another study comparing the guidelines in Ph. Eur. and USP for two brands of tablets, indicated by the SmPC that splitting was allowed, all tablet parts fulfilled the criteria in Ph. Eur. but one brand failed the criteria of RSD in the USP (182). Since the USP has more rigid criteria, an earlier study suggested that the Ph. Eur. should apply the more rigid RSD value from the USP (54). To my knowledge this has not been done. If the RSD criteria is applied in Ph. Eur. as well, fewer products will fulfil the criteria and the question is how rigorous the test needs to be, to be clinically relevant. The clinical experience from manipulating medicines is that most often it works "bloody well" (Quote from Pharmacist 1 in **Paper II**), despite that the dose is most likely not exact. The important information for healthcare professionals and caregivers are the medicines that must not be manipulated, e.g., slow-release products that will lose the slow-release properties if manipulated, or medicines with a

narrow therapeutic interval, where the consequences of manipulation can impact the outcome negatively.

In **Paper I** the frequency of manipulated solid oral dosage forms where the drug order included half a tablet went from 64% in 2009 to 72% in 2019 for inpatients. In the emergency setting the number was 97% both study years. This implies that there are fewer drug orders for "odd" parts of a tablet, such as 0.33 or 1.7 tablets, in 2019.

An exact dose of 1.7 tablets is most likely calculated from the patient's body weight and then transferred to the electronic health record without further thinking on how this dose should be prepared and administered. Between the study years a dose range check was implemented for high-risk medications (183) and at the same time a system enabling physicians to prescribe according to patient weight. The system will then convert the dose to the corresponding number of tablets or millilitres of a liquid. In 2009 the drug chart in the electronic health record was recently implemented, implying that there were more beginner's mistakes. In 2019 most physicians were more familiar with the system. The Paediatric Drug Therapy Group continuously teaches prescribers to fill in correct and feasible drug orders.

Not all drug orders for half tablets will be split, sometimes the RN or caregiver might decide to dissolve the tablet in some water and then withdraw half the amount. Studies on how to dissolve a tablet and withdraw a part of the solution show a wide variation in the amount of drug substance recovered (77, 184). In our studies the RNs explained that they rarely had time to document how (or even if) they did a manipulation, and from the registry data there is only few manipulated doses that have a commentary from the RN or pharmacist explaining how the manipulation was performed, or an instruction from the prescriber how to reconstitute the dose.

Over the years more information has been presented concerning whether tablets with a score line may be split to give two equal parts or just to produce smaller parts to enhance swallowing. But even when information is available it is most often only stated if the tablet may be split once, into halves, and rarely into quarters, not even for tablets with cross scores.

Captopril is one of the APIs for cardiovascular diseases not available in a strength suitable for young children in Sweden. The 25 mg tablet Captopril Viatris has a score-mark dividing the tablet in four parts but this score line is only intended for splitting the tablet to facilitate intake, Figure 5. This might be especially misleading since many of the starting doses, even for adults, in the SmPC correspond to half or a quarter of a tablet. When contacting the drug company, they confirm that the tablet is not intended for fractional dosing and there are unfortunately no plans for studies to include this information in the SmPC. Most doses of captopril were from extemporaneous preparations both study years, 80% and 98% in 2009 and 2019 respectively, **Paper IV**.

Figure 5. Captopril Viatris 25 mg (from www.fass.se, March 2023)

Phenobarbital is an API also commonly used as a liquid extemporaneous preparation, **Paper IV**. For a couple of years there are no longer any solid dosage forms registered on the Swedish market. One of the alternatives is a German product, Phenobarbital Neuraxpharm, which can be imported and used as an unlicensed product in Sweden. The 100 mg tablet from this drug company has a cross score and a clear instruction in the SmPC stating that the tablet may be split into quarters, Figure 6.

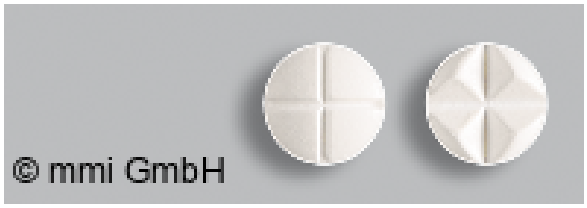

Figure 6. Phenobarbital Neuraxpharm 100 mg (from www.gelbe-liste.de, March 2023).

Hydrocortisone was one of the tablets split in **Paper III** and was also one of the APIs ordered/administered as an extemporaneous preparation. It is also one of the relatively few granted PUMAs (Paediatric Use Marketing Authorisation) by the EMA during the study years (Dec. 2017, marketed in Sweden 2019) with a new dosage form; granules in capsules intended to be opened. It has been registered and marketed in four different strengths with the brand name Alkindi®. The alternative to prescribing Alkindi or extemporaneous hydrocortisone capsules is crushing conventional tablets (185). In 2021 EMA launched a safety signal that patients are at risk for acute adrenal insufficiency when switching from crushed normal tablets to Alkindi granules. "Due to the insolubility of hydrocortisone, not preparing hydrocortisone soluble tablets in accordance with manufacturer's instructions may risk variable dosing and make conversion to other forms of hydrocortisone in the youngest children difficult" (186).

The problem described in the safety signal mentioned above is that the patient most likely was stabilised on a dose, slightly higher than the prescribed dose, when using crushed tablets. When switching to the prescribed dose, using Alkindi, that might be lower than what the child was administered before and there is a risk for adrenal insufficiency. In the interviews in **Paper II** both RNs and pharmacists expressed that sometimes slightly incorrect handling at home was allowed to carry on since it seemed to work for the individual patient.

7.2.2 Example from the registry data (Paper I)

Despite the increased knowledge of how to prescribe in the electronic health record, problematic drug orders can still be found in the registry data from 2019. This is an example from the inpatient setting:

Gabapentin 100 mg capsule to a 4-year-old child with an enteral feeding tube:
"dissolve 2 tablets in 2 mL sterile water, administer 1.7 mL in the enteral feeding tube"
This drug order was prescribed as 1.7 pieces of the capsule and the instruction to dissolve it and give 1.7 millilitre was written in a free text field. Had this not been a part of a capsule this manipulation might not have been included in the study. Drug orders in millilitres for solid dosage forms such as capsules were manually searched for and classified as manipulations. But since manipulations due to administration in enteral feeding tubes were most likely not included in the drug orders, these manipulations will not be included in our frequencies.

My personal thoughts around this short instruction:
The physician is very accurate in writing that the solid dosage form must be dissolved before administration, what liquid to dissolve it in and that the medicine is to be administered in an enteral feeding tube.

Gabapentin is a 100 mg capsule (not a tablet) which according to different sources can be handled in the following way:
SmPC: The capsule should be swallowed intact together with a glass of water (27).
ePed: For administration via enteral feeding tube the oral solution (unlicensed product) is recommended. The capsule may be opened and the content dissolved in approximately 10 mL of water (187).
Handbook of drug administration via enteral feeding tubes: "Capsules can be opened and the contents mixed with 10 mL of water; the 100 mg capsule is quite fiddly owing to its small size. The powder mixes easily with water and flushes down an 8Fr NG tube without blockage" (28).

The conclusion from the above information is that the capsules might be opened and the content dissolved in approximately 10 mL of water per capsule. It will then be feasible to administer via a nasogastric tube of a size appropriate for a 4-year-old. But in our example the physician had written that it was a tablet and the tablets should be dissolved in 2 mL of water. When making an experiment reproducing this drug order, it turned out surprisingly well. The content from two 100 mg capsules dissolved in 2 mL water after some stirring with the oral syringe is shown in Figure 7.

Figure 7. The content from two 100 mg gabapentin capsules dissolved in 2 mL water.

There is no comment from the person reconstituting (pharmacist or RN) and administering (RN) this dose in the registry data, though it might have been written somewhere else in the electronic health record, as was stated in the interviews (**Paper II**). According to the experiment they might have dissolved the content from 2 capsules in 2 mL of water and withdrawn the prescribed dose. Hopefully the person responsible for preparing the medicine opened the capsules first. This experiment also shows us that when there is either official or non-official information available giving advice on how to administer this capsule in an enteral feeding tube, it might not be appropriate for younger children. The amount of water recommended for dissolving the medicine and flushing the enteral feeding tube, can often result in volumes too large for a child and making the administration of other fluid and nutrition precarious (28).

7.2.3 Dosing accuracy of rectal solid dosage forms

The dosing accuracy after taking split torpedo shaped suppositories was low and this behaviour was not recommended (90). In the registry data in **Paper I**, a significant decrease in manipulated rectal dosage forms was shown, both in the inpatient setting and in the emergency setting. The manipulations still made in 2019 were mainly for parts of enemas. These findings were confirmed in **Paper II**, where RNs stated that they did not and would not manipulate suppositories. The reasons for this can be several, but there was clearly a feeling of going too much outside the box and not feeling comfortable with the dosing accuracy when splitting a torpedo-shaped suppository. Changes in available products might also have influenced the need for manipulation. For ibuprofen suppositories there has been a change in available strengths between 2009 (only 125 mg available) and 2019 (only 60 mg available). The Paediatric Drug Therapy Group had taken over the responsibility to prefill the "as needed" drug orders between the study years and there are no longer any split suppositories included in them. In general, the RNs seemed to have gained an increased awareness around the dosing inaccuracy of split suppositories.

Suppositories can be prescribed as extemporaneous preparations, but in **Paper IV,** the use of extemporaneous rectal preparations was low both in the inpatient setting and the emergency department, both study years. Patients younger than 1 month were excluded in this study and there might be a more frequent use of extemporaneous suppositories or rectal solutions in this patient group.

In a review from 2014 regarding rectal administration of drugs to children, a novel, stick-shaped suppository is mentioned. This stick-shaped suppository has a break-mark which enables it to be split in two equal parts (188), but to my knowledge it is not an authorised product.

7.2.4 Dosing accuracy experienced by healthcare professions

In the interviews in **Paper II** both RNs and pharmacists were asked a direct question if they knew of a situation where a patient had experienced a side effect or loss of effect due to manipulated medicines. None of the respondents could think of any situation and neither did the patients receive any extra checkups after receiving manipulated medicines. Since neither physicians nor RNs document the manipulation, it is not likely that any side effects would be attributed to the manipulated drug. To study side effects, linking them to manipulated medicines and not receiving the exact dose, would need a very stringent prospective study. This is not possible to detect in our registry data.

7.3 KNOWLEDGE OF DRUG MANIPULATION BY DIFFERENT HEALTHCARE PROFESSIONALS

Medicines management, i.e., prescribing, reconstituting, and administering medicines, is more complex in the paediatric setting compared with the adult setting, due to individual dosing and lack of suitable dosage forms and strengths. The need to manipulate medicines is one of the areas where there is often a lack of information. There are few other studies comparing different healthcare professions knowledge and views on manipulated medicines in the paediatric setting. A Finnish study held focus groups with RNs, physicians, and pharmacists, one profession in each focus group. All professions agreed that cooperation between the different professions around medicines management is important (189).

7.3.1 Registered nurses

Besides caregivers, RNs are most likely the healthcare professionals that best know what the child prefers (190) and, in the interviews, RNs said that they sometimes switched to another dosage form, either to avoid manipulation or due to the child's preferences. This was often done without giving feedback to the physician.

The two most frequent answers were related to manipulation of medicines; poor solubility of tablets and problems with splitting tablets into appropriate doses, when Turkish nurses were asked what activities they experienced as most difficult with preparation and administration of drugs (191). In our interviews with RNs, they also expressed concerns around taking a

proportion of a dissolved tablet and whether it was allowed to dissolve a tablet in liquid. The concern regarding dosing accuracy of manipulated medicines was particularly present when administering medicines to the youngest children.

An earlier Swedish study with RNs at paediatric wards without ward pharmacists, gathered RNs in focus groups to discuss medication safety in a broader context than manipulation of medicines (192). In the results manipulation of medicines is mentioned in one sentence showing that RNs felt uncertain about the dosing accuracy when administering medicines via an enteral feeding tube or when crushing tablets and dispersing them in water. The RNs in that study also expressed that they thought a ward pharmacist would help improve safe medication practice.

A study from Strathclyde University examined how much paediatric nurses know about medicines through interviews and questionnaires. The results showed that the RNs were unaware of stability problems that may arise when mixing crushed medicines with different food (106). In this study RNs also expressed that if a physician had prescribed something they did not question it. The same feelings of not having to search for information was expressed in our interviews:

> *"I usually do not search for information but follow the prescription. If the doctor has prescribed half a tablet I give half a tablet."*
> Nurse 1

In an earlier study focusing on RNs thoughts around medication administration errors and influence of policies, younger RNs stated that there were situations where they choose to not follow policy strictly, but rather act in the best interest of the child (193). This corresponds with our subcategory "It all comes down to the child", where sometimes the medicine needs to be prepared in a way or mixed with something that the child will accept to take.

Minor errors were expressed as being almost a part of the daily practice by some respondents and they almost excused themselves with quotes like "we're only human" (194). This was interpreted by the authors as a feeling of being powerless in preventing the errors, and similar feelings of not being able to prevent error or have an impact on the result of manipulated medicines were expressed in the interviews in **Paper II**:

> *"I wonder how this will turn out, it is not completely by the book, I understand that, but I hope it won't cause too much harm" (Nurse 3)*

Even though several studies have concluded that RNs and other healthcare staff, not always follow guidelines (195, 196) it was expressed from the RNs in **Paper II** that many of them wanted to have easily accessible information on which medicines could be manipulated and how.

7.3.2 Pharmacists

Pharmacists are the profession with most knowledge of medicines and medicine formulation. In the interviews in **Paper II** the pharmacists stated that they felt confident with the recommendations they gave to RNs and physicians, because they interpreted the current situation based on their previous knowledge. If they were not confident about a manipulation, they would recommend against performing it.

> *"… if I wasn't comfortable manipulating something…then I don't do it. No. I mean clichés are clichés for a reason, but I always think to myself: Would I be fine if this was to be administered to my own child. If I'm not, then I don't want to manipulate it."*
> Pharmacist 4

In our interviews both RNs and pharmacists expressed that the RNs felt secure when the pharmacist was present at the ward, even when they did not have anything specific that they needed help with at the time. Pharmacists are appreciated members of multidisciplinary teams, reduce medication errors, and improve drug administration in different paediatric hospital settings (197-201). Pharmacists are perceived as medication experts and their knowledge about medicines is particularly appreciated when medicines are used off-label (202).

Administration of drugs in enteral feeding tubes almost always involves manipulation. Pharmacists often have more knowledge about manipulation of medicines and drug administration in enteral feeding tubes and can educate RNs, physicians, and caregivers on this subject (203-205).

7.3.3 Physicians

Unfortunately, we do not have any first-hand information from physicians concerning their knowledge and thoughts around manipulation of medicines to paediatric patients. Pharmacists and RNs in the interviews talked about physicians, stating that there was a wide variation in knowledge around manipulation of medicines and how precisely the drug orders were written.

In some other countries physicians may only prescribe API, dose, and route of administration, and the RN will decide upon the dosage form (189). In the Swedish setting dosage form is a part of the drug order made by the physician, but they do not have access to the medicine rooms. They might therefore not know the availability of different medicines and dosage forms unless they ask an RN or pharmacist. They might also not know the patient from the aspect of which dosage form the patient prefers.

There are some studies regarding physicians' views on off-label prescribing of medicines, which is like manipulation of medicines in terms of lack of information. In one study physicians expressed fear of legal implications when prescribing off-label medicines but they

also confessed that they were probably unaware of some off-label use, because they had been using it for a long time (206). The same perfunctory behaviour might be seen with manipulated medicines, if it has been used for a long time it might be thought of as a safe practice.

7.4 MEDICINES SUITABLE FOR PAEDIATRIC USE; ATTRIBUTES AND AVAILABILITY

Medicines suitable for paediatric use should be dosage forms ready-to-administer and the medicines should be approved and available in different strengths, in all countries. Since the paediatric population is heterogeneous and requires many different strengths and dosage forms to cover all situations for children 0 – 18 years, having appropriate dosage forms for all ages might not be realistic. Second best would be to have "intermediate" dosage forms that can be manipulated to appropriate strengths and forms after a minor process, stated in the SmPC and with supporting data from drug companies (16).

If medicines are not made available in all countries, the import of unlicensed medicines from other countries should be made easier. If none of the above-mentioned alternatives are available, extemporaneous preparations compounded according to GMP, preferably from a standardised formula can be used. Unauthorised manipulations made by healthcare staff or caregivers should only be used as a last resort.

The combined overall results from **Papers I and IV** show that the frequency of patients with manipulated oral medicines in the inpatient setting was the same between the study years, and the frequency of patients with oral extemporaneous preparations had increased. This might be interpreted as less available oral medicines suitable for paediatric use in 2019 compared to 2009, but it needs to be analysed for each separate API since there are large differences between individual APIs. Some products have been registered during the years (e.g., Revatio and Alkindi) and some might have been withdrawn from the Swedish market (e.g., Kåvepenin (phenoxymethylpenicillin) tablets with the lowest strength and Dexametasone oral solution). Shortages of different medicines is an increasing problem all over the world, and this situation might also lead to an increased need for manipulation of medicines or use of extemporaneous preparations in the paediatric setting. During this winter there has been a widespread shortage in dosage forms and strengths suitable for paediatric patients for medicines with paracetamol, a commonly used medicine in children. There is a need for a simplified regulation around labelling and packaging of licensed medicines to enhance the incentive for drug companies to market medicines also in smaller countries, such as Sweden.

The use of unlicensed medicines and extemporaneous preparations bring some problems other than lack of availability. Information is often hard to find and when present often inadequate. Available information is not always written in a consistent way between different countries and systems. When electronic health record systems are used, the information needs to be separated into different positions, in Sweden rarely done for the unlicensed products.

Differences in how the strength is expressed is also a problem, with content stated per millilitre in Scandinavia or per 5 millilitres in e.g., Great Britain.

Two of the APIs prescribed as extemporaneous preparations to 100% in **Paper IV** were Calcium and Minerals e.g., phosphate, indicating that there are no products available on the Swedish market suitable for use in the paediatric patient group. This is not only a problem in Sweden, which is a small and sometimes not prioritised country for the drug companies, but the same situation is true also in other countries, e.g., in Great Britain. Since there are no oral liquid calcium or phosphate products licensed in Great Britain and the extemporaneous situation is a bit different from the one in Sweden, a position paper has recently been published informing caregivers and healthcare professionals how to use effervescent tablets for fractional dosing (207). This is error prone, especially since effervescent tablets displace a substantial volume of the water it is dispersed in. To be able to calculate an approximate strength of the solution to withdraw a dose from one need to know the displacement volume of the tablet.

When there is a lack of registered medicines suitable for use in the paediatric setting, or a lack of on-label manipulating instructions or when there is a discontinuation of a formerly used product, different interest groups might publish instructions on how to manipulate available products in the best way to administer recommended doses. One recent example is a Position Statement from the Neonatal and Paediatric Pharmacist Group (NPPG) concerning dosing of rectal diazepam after the discontinuation of Stesolid Prefill in low doses, which has been a problem in Sweden as well (208). Although the main goal would be to have licensed products available in the right doses, instructions like this can be very helpful for both caregivers and healthcare personnel.

The so-called PUMAs (paediatric usage marketing authorisation) is an incentive for drug companies to generate information and develop dosage forms suitable for paediatric use for off-patent drugs. It was implemented at the same time as the Paediatric Regulation, in 2007. In 2013 a priority list for off-patent medicinal products needing paediatric studies was compiled by the EMA (209). Only a few PUMAs have been authorised by the EMA since 2007, and not all of these are available in all European Union countries, Table 11.

Table 11. Availability in Sweden of PUMAs authorised by EMA.

Brand name (API)	Dosage form	Availability
Buccolam (midazolam)	oromucosal solution	Available
Hemangiol (propranolol)	oral solution	Available
Sialanar (glycopyrronium bromide)	oral solution	Available
Alkindi (hydrocortisone)	granules in capsules*	Available
Kigabeq (vigabatrin)	soluble tablets	Not available
Slenyto (melatonin) small (3 mm ø)	prolonged release tablet	Not available

* intended to be opened

From the registry used in **Papers I and IV**, information around Alkindi can be found in the data from 2019, contributing to 16.5% of all hydrocortisone administrations. The relatively low frequency is probably because the introduction of a new product on the market takes time, despite that the drug company makes a lot of effort in promoting their product. In this case it was a new dosage form of an old drug, which also had a higher cost for the healthcare than the old, extemporaneous preparation. It was also a so-called child friendly dosage form, labelled from newborns to 18-year-old teenagers, but not licensed for administration via an enteral feeding tube, thus excluding all these patients.

Sometimes new medicines are developed and marketed in a dosage form suitable for paediatric use, but with a narrow label, not covering all use in the paediatric setting. An example of this is Hemangiol®, an oral solution containing propranolol, but only labelled for treatment of hemangioma (210).

As I mentioned in the preface, one of my first memories of odd questions from the Children's hospital was the question about a suspended Viagra-tablet and whether the flakes of coating contained any drug substance. Sildenafil (the active pharmaceutical ingredient in Viagra) is a good example of an API where the introduction of a dosage form suitable for paediatric patients totally has wiped out the need for manipulation of adult dosage forms or the use of extemporaneous preparations.

The Paediatric Regulation will help in bringing more medicines and dosage forms suitable for the paediatric age-groups on the market, but there will probably always be a need to manipulate medicines to paediatric and other patients. Information regarding manipulation of medicines must be readily available, reliable, and easy to understand and must contain information not only about manipulation for administration in enteral feeding tubes, but also whether taking a proportion of the dose is suitable or not, and what the best way of doing that would be.

Mini-tablets is one of the newer dosage forms that have been included in several studies showing good acceptability, but unfortunately there are still no registered drugs in Sweden in this dosage form. Orodispersible films is another innovative dosage form, suitable both for paediatric and geriatric use. Setofilm (Ondansetron Rapidfilm) is a registered product in several major European countries, but not in Sweden (211, 212).

A novel product available on the Swedish market is Flexilev®, where the dispenser, MyFID, is part of the medicine. The drug is a mix of carbidopa and levodopa, and it is designed as spherical mini-tablets, 3 mm in diameter. The mini-tablets are dispensed from the device at a dose programmed by the physician or RN, and are dissolved in some water before intake. The dosing dispenser also has a function that reminds the patient to take the medicine, Figure 8. (27, 213)

Figure 8. Flexilev, mini-tablets with electronic dispenser MyFID for treatment of Parkinson's Disease.

The same company that produces MyFID also has a manual dispenser for mini-tablets, 3 mm in diameter, OraFID. It can dispense from one to twenty mini-tablets at a time, by rotating the dispenser to the desired number. The mini-tablets are then collected in a small tray at the bottom of the dispenser and when a button is pressed, it will release all tablets at a time. This device is currently not for sale with any specific API, Figure 9.

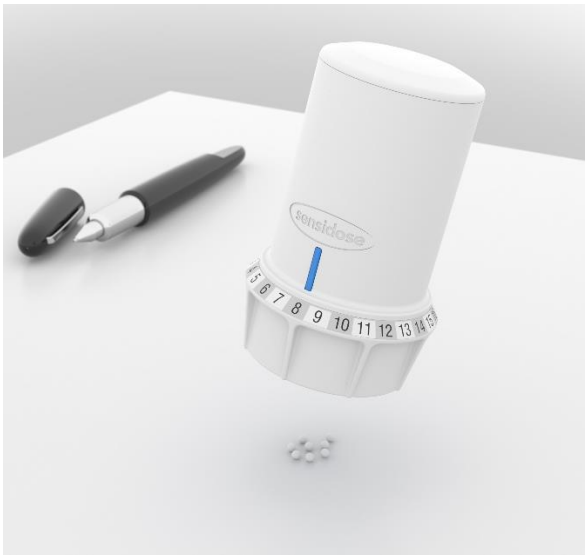

Figure 9. OraFID, dispenser for mini-tablets.

When asking children in different ages in a European study about their preferred dosage form, the answers differed depending on age and previous experience of taking drugs (214). Children younger than 12 years mainly preferred liquids wheras older children preferred solid dosage forms, such as tablets and capsules. Children with a chronic disease, who were regularly taking medicines, also preferred solid dosage forms, whereas healthy children preferred dosage forms easy to swallow, e.g., liquids and orodispersible tablets. Most children seemed to be unfamiliar with newer, flexible dosage forms like orodispersible films and

tablets, probably because they are only available in a few countries. A similar, smaller questionnaire study in the UK, Jordan and Saudi Arabia showed that children in general preferred pink, orally disintegrating tablets with strawberry flavour, but there are differences both between gender and regions (215). There are several studies investigating acceptability of dosage forms in both the paediatric and geriatric setting, but many of them lack specific data on how the tests were performed (216).

WHO has since 2007 published a list of Essential Medicines for Children (217). The medicines included are based on world-wide disease prevalence and public health relevance for children up to 12 years of age. Medicines put on the list should be available everywhere, all the time, in appropriate dosage forms, be of good quality, and be affordable. Whether the APIs included in the list are available in different settings, and if so, in a dosage form suitable for paediatric use has been studied with the results that there are still need for improvements (218-221) A lot of effort has been put in making child-friendly oral dosage forms suitable for use in resource-limited settings. Good examples can be found for treating tuberculosis and HIV (155, 222). In 2020, the Global Accelerator for Paediatric Formulations Network (GAP-f) was launched by WHO to build on the good initiatives started by the HIV community (223). Unfortunately, it is sometimes problematic to import and use these medicines in non-resource-limited settings such as Sweden.

Veterinary medicine show the same need as paediatric medicine for dosage forms that can be altered and allow fractional dosing, since pets come in very different sizes. A recent study compared human and veterinary tablets containing furosemide split into halves and quarters. Compliance of parts after splitting was compared to criteria in both Ph. Eur. and USP. The conclusion was that the veterinary product split most correctly, probably due to its characteristic four-leaf clover shape (224). A Swedish example is prednisolone for cats and dogs which comes in a tablet, suitable for splitting in quarters, Figure 10.

Figure 10. Splitting of Prednicortone® vet. tablets in ¼. (Photo: Synnöve Lindemalm)

It will be interesting to see whether the EMA presents a 20-year report from the Paediatric Regulation in 2027, and if so, what the results will be. When reading scientific papers and

attending conferences in this research area, there is a lot of ongoing interesting development with different novel dosage forms, suitable for paediatric patients. Cardiovascular drugs is an ATC-group that has been lacking medicines suitable for paediatric patients for a long time and that was also shown in our **Papers I and IV** (36, 225, 226). Promisingly there has been several Paediatric Investigation Plans approved for cardiovascular drugs during the first ten years of the Paediatric Regulation, but few of them are available on the market (210). One example is enalapril which is being studied and developed in several dosage forms suitable for neonates to adolescents, orodispersible mini-tablets, oral solution, and orodispersible films (146, 227).

7.5 SIMILARITIES WITH THE GERIATRIC SETTING

The lack of appropriate medicines, both strengths and dosage forms, is not a unique problem in the paediatric setting. The similarities between the paediatric and the geriatric setting are many, with patients that are either gaining the ability to swallow solid dosage forms or losing the ability. The need for fractional dosing, common in the paediatric setting, is sometimes also necessary to older patients. Both these patient groups would benefit from novel dosage forms that are easier to swallow and enable individual dosing (157, 166).

In **Paper II**, several of the RNs, and to some extent the pharmacists, expressed a feeling of unsafety around dosing accuracy after manipulation of medicines. This quotation from an RN working in a geriatric setting, could equally well have been from our study (228):
" You're never too sure what and how much they're getting, or whether you're actually interfering with the strength of drugs by crushing and mixing them into the medium before you give it, and you're not too sure just … how it is being received in the stomach"

7.6 METHODOLOGICAL CONSIDERATIONS

7.6.1 Background to the thesis

As probably all PhD-students and researchers can relate to; there was a long and winding road leading to this little book, and the work with this thesis was not performed in the order the papers are presented. After having started a PhD-project straight after pharmacy school, which due to several reasons as not finished, I told myself I would never start another PhD-project. I started working as a clinical pharmacist at the Karolinska Hospital Pharmacy and eventually it was decided that my clinical focus should be paediatrics. I started working in different projects with physicians from the Children's Hospital and after a couple of years, Staffan encouraged me to set up the tablet splitting study as a small side project. I still did not have any thoughts of a PhD-thesis.

The years went by, I went on maternity leave and while being home with my oldest son, I was offered a post as a paediatric pharmacist at the Children's Hospital which I accepted. Encouraged by Staffan and Synnöve, I wrote a paper of the tablet splitting data, with them as co-authors. During these years I had gained more knowledge in the field of paediatric

pharmacology and answered more questions about dosing medicines primarily developed for adult patients to paediatric patients. When writing the paper, my curiosity was aroused and suddenly, I could think of several research questions I wanted to explore. I felt ready to apply for a PhD-project and some of these research questions have been answered in this thesis. The first was how frequent this practice was at our paediatric hospital. Since I combined my research with regular work, time passed quickly. In the end that turned out fortunate because then I got the opportunity to compare registry data from the year 2009 (the first available year) with data from 2019. Analysing the results from this study led to a curiosity about what registered nurses think about manipulating medicines. The first part of the qualitative study was set up and was performed as semi-structured interviews with RNs at our hospital. Many of the RNs in the interviews talked very appreciatively of their ward pharmacists and we therefore decided to do a follow-up on the qualitative study, using the same interview guide while interviewing the ward pharmacists.

During my PhD-time my focus has shifted from wanting to look at the dosing accuracy of manipulated medicines to the broader perspective of the availability of medicines suitable for paediatric use. The use of extemporaneous preparations is also a sign that dosage forms and strengths are not available as registered products and so the research question for the fourth study was created.

7.6.2 The overall study design

Two of the papers included in this thesis (**Paper I and IV**) are based on retrospective analysis of registry data from the medical record in the electronic health record. **Paper II** is based on a qualitative study design and **Paper III** was based on my own experiments. All papers explore the subject of manipulating medicines to children and availability of medicines suitable for paediatric use from different perspectives. This variation of techniques is one of the strengths of this thesis. The limitations are described in detail under each heading.

7.6.3 Registry data

Data from a registry will never be better than what is put into the registry first hand. In **Paper I and IV** we used large material with more than 100,000 oral administrations each study year and rectal administrations in addition. Data was thoroughly scrutinized for omissions and corrections were made for e.g., APIs where another ATC-classification better correlates with the paediatric use at the local hospital. Children with no documentation of sex were excluded since we wanted to analyse if there was a difference between female and male patients. As there were no major differences between female and male patients, the results were presented for the whole material. Since the excluded patients were less than one percent (0.7% and 0.4% in 2009 and 2019 respectively) no effort was made to analyse these patients separately.

When combining the results from **Papers I** and **IV**, it was not possible to determine if the patients receiving manipulated medicines were the same patients that also received

extemporaneous preparations. For some patients this was most likely the case and for some patients the use of extemporaneous preparations made it possible to avoid manipulation. The same patient might also have been prescribed both oral and rectal manipulated medicine, both at an inpatient ward and at the emergency department. But as the results are presented for each separate group it therefore felt like the correct way of analysing the material.

The results in this thesis are presented as frequencies of patients with at least one manipulated medicine (**Paper I**) or extemporaneous preparation (**Paper IV**). The material was not analysed for how many patients received more than one manipulated medicine or extemporaneous preparation. This could have been interesting as more than one manipulated medicine to the same patient implies a higher safety risk and it will be more time-consuming to prepare and administer the medicines to that patient.

To my knowledge there are no other studies comparing two different study years, neither for manipulated medicines nor extemporaneous preparations, so the only other results to compare these results with are from mainly short time studies. Another problem with finding comparable frequency numbers is that the definition of manipulations or extemporaneous preparations vary a lot between different studies. In this thesis the definition of manipulations were only the situations where we from the register could conclude that part of a solid dosage form needed to be administered to achieve the prescribed dose. Manipulations due to swallowing difficulties or administration via a feeding tube, were not included in this study.

Since all manipulations and extemporaneous preparations were manually classified in **Paper I and IV** there is a risk of errors. One example of this is the erratum to **Paper I**, where missing manipulated dosage sachets were found in the data from 2019. Further checks were made on the material for large groups of manipulated medicines and extemporaneous preparations but no other mistakes were found. In the published **Paper I** there was a statistically significant decrease for manipulated oral medicines to inpatients, but the clinical relevance of a decrease from 19% to 17% of all patients is limited.

Manipulations have in some studies been evaluated according to information in the SmPC, i.e., whether the manipulations are on-label or off-label. We chose not to do that in our registry study for three reasons. The first is the huge number of administrations where each brand of tablets would have needed to be evaluated separately, since there can be differences in available information for different brands of the same API. Secondly, since the first study year was 2009 it would have been difficult to collect data from that year (some tablets might have changed the appearance and other tablets are no longer available on the market). Thirdly, since it is a registry study and not an observational study, it might be possible that the brand name prescribed differ from the one administered to the patient. There is a problem that not all brands of a generic product have the same information in the SmPCs, leading to difficulties in assessing off-label use (229). Sometimes original products have a paediatric label, and generic versions might lack this information. The Paediatric Drug Therapy Group is responsible for making pre-filled order sets in the electronic health record, based on procured and available products, but not all physicians use the pre-filled order sets when

prescribing, and sometimes there is a shortage of products forcing the RNs and pharmacists to administer other products.

In other studies, on frequencies of manipulated medicines, figures are stated as frequencies of administrations (59, 230, 231) and in some studies figures for both administrations and patients are given (14, 24, 232). In our **Paper I** the figures are presented as frequencies of patients with at least one manipulated medicine, oral or rectal. In **Paper IV** the results are presented for both patients and administrations and there is a significant increase in both results, but the clinical importance of an increase from 19% to 20% of administrations is not substantial. It turns out statistically significant due to the large number of administrations included. Interestingly the patients receiving at least one extemporaneous preparation has increased from 22% to 40%, implying that more patients receive fewer doses. The average number of extemporaneous preparations per patient was 21 and 14 in 2009 and 2019, respectively. When the results are presented as frequencies of patients receiving a manipulated medicine or an extemporaneous preparation, patients with a long length of hospital stay will not influence the results. Especially in 2009, there were a few patients with a very long hospital stay, that would influence the number of both manipulated administrations and extemporaneous preparations.

7.6.4 Qualitative study

In **Paper II** individual semi-structured interviews were held with first RNs and then pharmacists. Alternative study designs to gather the information could have been questionnaires or focus groups. Questionnaires have the limitations that the response rate may be low due to lack of time by the respondents but mostly it is difficult to gather extensive information and to ask follow-up questions. Focus groups would have been an interesting alternative and could lead to more information being shared because colleagues might inspire one another. On the other hand, all participants might not feel equally comfortable talking freely in a group.

The interview guide was put together by a pharmacist, which might lead to the use of words that RNs were not familiar with. In the interviews this can be sorted out by asking questions to check whether the respondent has understood the question. This would not have been feasible with a questionnaire.

All RNs and all pharmacists were female, only one male RN was approached and he rejected participation. Whether this has any influence on the results is difficult to say, but all pharmacists and most RNs were female at the time of the study. Both experienced and newly graduated RNs were included in the study and they worked at four different paediatric wards, covering different therapies and patient groups, which enhances the *credibility* of the study.

The mean duration of the interviews with RNs was 12.5 minutes and the mean duration of interviews with pharmacists was 43 minutes. The difference in duration could be due to several reasons. One is that the RNs were more stressed and some of them also got

interrupted during the interviews, the other is that the pharmacists were more information rich in this subject. Preparing and administering medicines is an important part of RNs daily tasks, but it is still just a part of all the daily tasks. For pharmacists on the contrary, medicines are their main task. Ordering them, preparing them, instructing RNs, physicians, and caregivers how to handle them, and answering questions about them. Including informants rich in information in a qualitative study means that the number of participants can be lower (233).

My background as a pharmacist might influence how the interview guide was put together, how the interviews with nurses were performed and the coding and categorisation of the transcribed interviews. To avoid this bias, the study was set up in close collaboration with all supervisors which make up a multidisciplinary team with one paediatrician, one registered nurse and one pharmacy professor. A pilot interview was then performed with a RN to test the interview guide. The first author and one of the other authors coded all the interviews separately and then worked together with the categories and subcategories. All findings were then discussed with the rest of the authors until agreement was achieved. All subcategories were exemplified by quotations to increase *trustworthiness*. The use of the same interview guide, with just minor changes between RNs and pharmacists increase the *dependability* of the study.

In qualitative studies the word generalisability is normally not used, but rather the expression *transferability*, which refers to if the findings can be applied to other settings and situations (173). Based on a thorough description of study participants, setting, and analysis the reader self decides upon the transferability of the study.

7.6.5 Tablet splitting

The tablet splitting study was performed with five brands of tablets, chosen after a short survey with RNs at the Children's Hospital. Since this survey and study were performed before the registry study (Paper I) only three out of five tablet brands in Paper III are among the most frequently manipulated in Paper I. Had these studies been made in reverse order, other tablet brands would most likely have been chosen. A strength is that all tablet brands were split into both halves and quarters, as this is done in the paediatric setting, and not just halves. The splitting and weighing were performed by one person only (ÅCA) to avoid interpersonal differences in performance. On the other hand, it could have been interesting to let RNs and caregivers split tablets their normal way, to see how this affected the results.

8 CONCLUSIONS

The results from this thesis show that despite the implementation of the European Paediatric Regulation 2007, there is still a lack of suitable drug dosage forms and strengths in 2019 for children. This absence forces healthcare personnel and caregivers to manipulate medicines to children. One alternative to manipulation is the use of extemporaneous preparations, which has increased in the inpatient setting between 2009 and 2019.

Our results have also shown that registered nurses feel uncomfortable having to manipulate medicines, especially to the youngest children. Pharmacists employed by the wards are important members of the team caring for the patient, with their special knowledge round medicines.

When splitting tablets, it is crucial to know that the tablet is suitable for splitting, and halving a tablet normally results in an acceptable dose. When splitting further into quarters the dose deviation will be larger, and it is thus important to consider whether this is acceptable in the specific situation, with this drug, to the specific patient, and with the prescribed dose.

There is a need for the development of more medicines suitable for paediatric use. Suitable products developed and marketed in one country should be made available worldwide.

Regulatory institutions must set requirements for drug companies to show that tablets with either score lines or cross scores can be split into equal parts, enabling fractional dosing, and this information shall be clearly stated in the SmPC. Non-functional score lines should not be present. Good examples have been shown in this thesis that tablets which are suitable for splitting in halves and quarters can be produced. There is a clear need for more tablets that allow fractional dosing and products containing mini-tablets, with or without a dosing device. Such products will benefit not only paediatric patients, but also adults with need for a lower dose and/or swallowing difficulties.

Therefore, the overall conclusion of this thesis is stated in the picture on the cover page:

If we create a world that is good for children, it will be good for everybody!

9 POINTS OF PERSPECTIVE

9.1 CLINICAL IMPLICATIONS

The results from this thesis have added valuable knowledge on the use of manipulated solid oral and rectal dosage forms, comparing two full years, ten years apart, showing that there is still a lack of child friendly strengths for oral medicines. Extemporaneous preparations is an alternative to manipulation but need to be available in the right strengths. Newly approved drugs have in some cases almost eliminated the need for manipulation.

Following the interviews with registered nurses and pharmacists, the ePed central editorial office has focused on producing and updating drug instructions for oral medicines such as tablets and capsules, to include information about divisibility and administration through enteral feeding tubes.

The tablet splitting study showed that larger tablets split more correctly, and halving tablets often yield an appropriate dose. But when there is a need to split further into quarters or even smaller parts, the dosing accuracy will be affected.

9.2 FUTURE RESEARCH

This thesis is based on data from the hospital setting, in a paediatric hospital with ward pharmacists. In the future it would be interesting to study the following research questions:

- The frequency of prescriptions to paediatric patients in outpatient care that include fractional dosing, comparing different age groups and different ATC-groups.
- The frequency of prescriptions for extemporaneous preparations to paediatric patients in outpatient care, comparing different age groups and different ATC-groups.
- Interviews with registered nurses at a paediatric hospital without ward pharmacists to find out how they reason around manipulation of medicines to children.
- Interviews or focus groups with physicians, both in the inpatient and outpatient setting, to explore how they reason around manipulation of medicines and where they look for information.
- Pharmacokinetic studies comparing administration of split or crushed tablets with administration of an oral liquid containing the same API.
- Comparison with the aged care setting. How often are manipulations made in this setting? Are the manipulations due to swallowing difficulties or due to fractional dosing? Are the medicines that are manipulated to elderly patients the same as to paediatric patients or are they different ones?
- A follow-up of the registry studies for manipulated medicines and extemporaneous preparations in 2029.

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