Access to Pharmacist's Recommended Medicines for Paediatric Patients

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Dedication

To my two other siblings in heaven, Benjamin and Isaac-Emanuel.

Abstract

The rationale of this study was driven by the limitations in the availability of formulations of pharmacist-recommended medications for paediatric use. The objective of this study was to identify products which are available for paediatrics which are pharmacists recommended and to assess scientific evidence on safety and efficacy of these products. Scenario analysis was carried out by reviewing all the Summary of Product Characteristics of non-prescription medications having a marketing authorisation listed on the Malta Medicines Authority website. The age range used for this study was that of neonates up to 12 years of age. The product's safety was assessed by reviewing the pharmacodynamic and pharmacokinetic data. Medicinal products available, their intended use and information on the safety and efficacy data for the products were identified. It was observed that a total of 163 medicinal products, contributing to 196 formulations are available on the Maltese market for paediatric use as non-prescription medicines. Cough and cold preparations (n=21) are the most available non-prescription products for paediatric patients. The most common side-effects listed are those affecting the gastro-intestinal system (n=27). There is a total of 31 products that have no pharmacokinetic data available on the SPC whereas the most pharmacokinetic data available is excretion da ta (n=44). In conclusion, this study identifies pharmacist-recommended available products for paediatric use and the symptomatology they cover. Details on pharmacokinetic and pharmacodynamic data of these products are weak. Guidelines in order to help pharmacists during dispensing of medications are developed.

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List of Abbreviations

AAGP	Alpha-1-acid glycoprotein
ADEs	Adverse Drug Effects
ADME	Absorption, Distribution, Metabolism, Excretion
ADMET	Absorption, Distribution, Metabolism, Excretion, Toxicity
ADRs	Adverse Drug Reactions
API	Active Pharmaceutical Ingredient
BBB	Blood Brain Barrier
BNF	British National Formulary
BPCA	Best Pharmaceuticals for children Act
CNS	Central Nervous System
EC	European Commission
EU	European Union
FDA	US Food and Drug Administration
GFR	Glomerular Filtration Rate

GI	Gastrointestinal
GP	General Practitioner
HHS	Health and Human Services
ICU	Intensive Care Unit
IRB	Institutional Review Board
NSF	National Science Foundation
ODTs	Orally Disintegrating Tablets
OTC	Over the Counter
PIP	Paediatric Investigation Plans
PPAG	Paediatric Pharmacy Advocacy Group
PREA	Paediatric research Equity Act
SPCs	Summary of Product Characteristics
STEP	Safety and Toxicity of excipients for paediatrics
UK	United Kingdom
US	United States
Vd	Volume of Distribution
WHO	World Health Organisation

Chapter 1: Introduction

1.1 Background

Roberts et al (2003) described children as therapeutic orphans. The reason behind this is that there is limited knowledge available on the behaviour of drugs in paediatrics. This knowledge is based mainly on information resulting from studies carried out in healthy volunteers and patients (Vet et al, 2011). Ivanovska et al (2014) stated that "Children differ from adults in many aspects of pharmacotherapy, including capabilities for drug administration, medicine-related toxicity, and taste preferences. It is essential that paediatric medicines are formulated to best suit the child's age, size, physiologic condition, and treatment requirements. Different routes of administration, dosage forms, and strengths may be required to ensure adequate treatment of all children. Many existing formulations are not suitable for children, which often leads to unlicensed use of adult medicines."

1.1.1 Definition of Paediatrics

"Paediatrics is the branch of medicine dealing with the health and medical care of infants, children, and adolescents from birth up to the age of 18."[1] The word paediatrics comes from the "Greek words: *pais* which means child and *iatros* which means the doctor or healer." Paediatrics therefore means healer of children.[1]

The paediatric population differs from adults with regards to medication mainly because an infant's or child's body is smaller than that of an adult. An important statement made by Mandal and Cashin-Garbutt (2014) is that "treating children is not like treating a miniature adult".[1]

The primary target for the study of paediatrics is not only the immediate treatment of their illnesses but to improve their quality of life, disability and survival. The aim is the reduction of death rates

Mandal A, Cashin-Garbutt A. What is Pediatrics. Medical Life Sciences [Internet]. 2014 [cited 2020 Jul 23]; Available from: http://www.news-medical.net/health/What-is-Pediatrics.aspx

in infants and children, the spreading control of infectious diseases, promotion of healthy lifestyles and aid children and adolescents who suffer from chronic diseases.[1]

1.1.2 Classification of the Paediatric Population

Paediatric population is sometimes divided by age. This division is largely arbitrary as there are a lot of different conventions applied in sub-dividing this population. Most of the drugs are preferred to be administered on a weight basis as mg/kg until an adult dose or an arbitrary weight ceiling is reached (Knoppert et al, 2007). Both the British National Formulary (BNF) for Children and the US Food and Drug Classification (FDA) classify paediatrics in a different way. The BNF (2017) classification is as follows: Post-term neonate at 42 weeks, Neonate from 0 up to 28 days of age or for the first 4 weeks of life, infant from 28 days up to 2 years of age and child from 2 years up to 12 years of age and adolescent from 12 years up to 18 years of age. The FDA classification is neonate: birth to 1 month, infant: 1 month to 2 years, child: 2 to 12 years and adolescent: 12 to less than 16 years.

The subsequent age groupings have received widespread acceptance. Unless data is available to support a larger absolute dose in children, weight-based drug dosing is recommended up to the adult dose. One needs to notice the critical importance of both gestational age and corrected gestational age for dosing in premature new-borns and neonates. As defined by Murphy (2007) gestational age is: “the number of weeks from the first day of the last normal menstrual period to birth”. These ages must be taken into consideration in addition to weight in this sub-population (Knoppert et al, 2007).

Knoppert et al (2007) suggested that the paediatric population should be divided as follows: children having less than 38 weeks of gestational age are classified as premature new-borns, while those having more than 38 weeks of gestational age are classified as term new-borns.

1.Mandal A, Cashin-Garbutt A. What is Pediatrics. Medical Life Sciences [Internet]. 2014 [cited 2020 Jul 23]; Available from: http://www.news-medical.net/health/What-is-Pediatrics.aspx

Paediatrics having zero to thirty days of age are classified as neonates and those from one month to two years are classified as infants. For paediatrics to be classified as young children their age should be between two to six years while ages between six to twelve years are classified as children.

The age range for paediatrics to be considered as adolescents is twelve to eighteen years. Keiser et al (2011) and Batchelor and Marriott (2015) suggested a similar classification with a minor change in infants and young children. Paediatrics having more than twenty-eight days up to twelve months were classified as infants and paediatrics between two to five years were classified as young children according to Batchelor and Marriott (2015) while according to Keiser et al (2011) children were as classified as a whole from two to eleven years.

1.1.3 Access to Pharmacists

Primary health care can be defined as the "patient's first point of contact with the healthcare system." (Tsuyuki et al, 2018). Pharmacists play an extensive role as primary health care workers and they are one of the most accessible health professionals. Patients visit their pharmacists more often than they visit any other health care practitioner. This shows the importance of the community pharmacist to be highly accessible and knowledgeable about drug treatment in order to enhance patient outcomes in various ways (Kelling, 2015; Collins, 2016; Tsuyuki et al, 2018). Tsuyuki et al, (2018) also describes that the strength of the primary care system is what essentially drives a country's health care system.

Pharmacists play a vital role in paediatric care since a significant percentage of the population is represented by paediatrics in both hospital and community settings. This further shows the importance of accessibility of pharmacists as health care providers as well as to be knowledgeable about the pharmacokinetics of paediatrics and dosing challenges presented in this population (Mukattash et al, 2019).

1.2 Paediatric Pharmacokinetics

Drug concentrations in the body are continuously changing with time. The pharmacokinetic profile of a drug can be determined by several factors including anatomical and physiological ones. Pharmacokinetics is based upon concepts of drug disposition, the process for the drug absorption, distribution, metabolism and excretion and (ADME) properties (Peck et al, 1997; Dale and Haylett, 2004; Downes et al, 2014; Batchelor and Marriott, 2015).

The paediatric population is constantly growing and developing. It comprises several physiological changes leading to growth and maturations. Paediatric maturation is affected by several factors including organ size, body functions and composition and metabolic activity as seen in Table 1.1 (Allegaert et al, 2014).

It is crucial for healthcare professionals to understand these anatomical and physiological changes affecting pharmacokinetic profiles so they can be fully aware of the consequences of dose adjustment in paediatrics (Batchelor and Marriott, 2015).

1.2.1 Absorption

Allegaert et al (2014) states that: "Absorption relates to physicochemical characteristics and patient factors that influence the translocation of a given compound from its exposure site (for example; enteral, pulmonary, cutaneous) to the bloodstream or another effect compartment". The amount of drug absorbed is evaluated by means of its bioavailability factor, referred to as 'bioavailability' (Rosenbaum, 2011). Bioavailability is the proportion of the administered dose that reaches the systemic circulation. Poor absorption of the drug will result in low bioavailability (Dale and Haylett, 2004).

The prediction of oral bioavailability can be challenging with additional factors such as the drug having low solubility or permeability, metabolism and transportation in the gut wall. Changes in development of both biochemistry and physiology of the GI tract are very fast. These changes augment the challenges of oral bioavailability (Johnson et al, 2018).

The extent of oral drug absorption occurring through the gut wall is influenced by several factors including gastric pH, blood flow, gastrointestinal (GI) motility, metabolism, gastric acid secretion, fluid volume dynamics, surface area of absorption site, fluid composition. All of the mentioned factors can alter with race, gender, diseases and food (Murphy, 2007; Batchelor and Marriott, 2015; Johnson et al, 2018).[2]

Gastric pH at birth is neutral, this is shown by an elevated pH in the neonatal period (Keiser et al, 2011). Reports state that it takes about 24-48 hours for the pH to decrease to 3. The absorption of a drug can be impacted by the discrepancy in gastric pH that occurs between adults, children and neonates (Keiser et al, 2011).

In the case of penicillin, greater peak concentrations are noticed in new-borns having higher gastric pH when compared with infants and children. Gastric pH also affects weakly basic drugs. Taking the example of itraconazole, one can notice the relatively small amount of gastric pH levels and higher serum concentrations. The absorption characteristics and the bioavailability of drugs are determined by the pH and the volume of acidic gastric acid. In neonate's gastric acid secretion is decreased, making the absorption of many drugs variable (Batchelor and Marriott, 2015).

[2]Berlin C, Sharp M, Corp C. Pharmacokinetics in Children. Penn State University College of Medicine [Internet]. [cited 2020 Jul 23]; (2013). Available from: http://www.merckmanuals.com/professional/pediatrics/principles-of-drug-treatment-in-children/pharmacokinetics-in-children

Table 1.1: Overview of Children's Developmental Features That Can Affect Pharmacokinetics

Developmental Feature	Relevant Age Period	Pharmacokinetics
Body Composition: lower lipid content, greater water content.	Birth through 3 months	Less partitioning and retention of lipid-soluble chemicals, larger Volume of distribution (Vd) for water soluble chemicals.
Larger liver weight/body weight	Birth through 6 years but largest ratios in first 2 years.	Greater opportunity for hepatic extraction and metabolic clearance; however, also greater potential for activation to toxic metabolites.
Immature enzyme function: phase I reactions, phase II reactions	Birth through 1 year but largest differences in first 2 months	Slower metabolic clearance of many drugs and environmental chemicals; less metabolic activation but also less removal of activated metabolites.
Larger brain weight/body weight; greater blood flow to Central Nervous System (CNS); higher blood brain barrier (BBB) permeability.	Birth through 6 years but largest differences in first 2 years	Greater CNS exposure, particularly for water soluble chemicals which are normally impeded by BBB.
Immature renal function	Birth through 2 months	Slower elimination of renal cleared chemicals and their metabolites.
Limited serum protein binding	Birth through 3 months	Potential for greater amount of free toxicant and more extensive distribution for chemicals which are normally highly bound.

Reproduced from: Ginsberg G, Hattis D, Miller R, Sonawane B. Pediatric Pharmacokinetic Data: Implications for Environmental Risk Assessment for Children. Pediatrics. 2004;113(4):973-983.

Gastric emptying rate reaches adult capacity by six to eight months and is significantly delayed in infants. Delayed gastric emptying time causes a decline in the drug absorption rate. The increase in bioavailability of drugs may occur due to slower transit times (Batchelor and Marriott, 2015). Murphy (2007) discussed that "in the first 2-3 weeks of life, bile secretion is known to be poor with luminal concentrations lower than adult intestines (2-4mm vs 3-5mm respectively). Bile salt concentration causes an increase in drug solubility and this difference in concentration may affect absorption in younger patients. Poorly soluble drugs such as hydrocortisone are at a particular risk (Batchelor and Marriott, 2015).

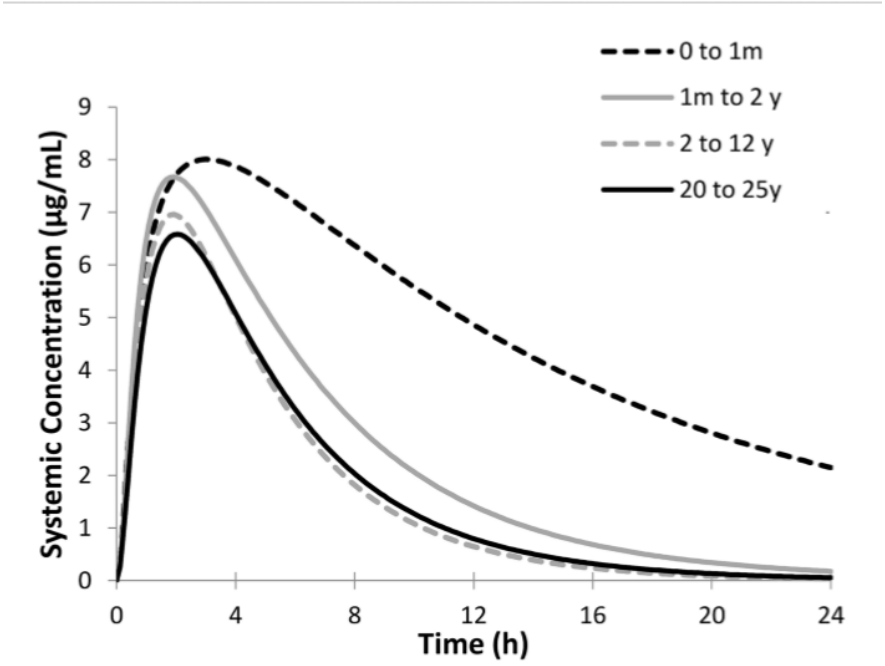

Figure 1.1: Stimulated Mean Plasma Concentration- Time Profiles of Paracetamol Following Administration of an Oral 15mg/kg Suspension Dose to Neonates, Infants, Children and Adults (n=50 per group.) *Reproduced from: Johnson T, Bonner J, Tucker G, Turner D, Jamei M. Development and applications of a physiologically-based model of paediatric oral drug absorption. European Journal of Pharmaceutical Sciences. 2018;115:57-67.*

1.2.1.1 Methods of Administration

A study carried out by Martir et al (2016), revealed a variation of 11% and 93% in which paediatrics adhere to their medication. One way of improving this adherence is through formulation acceptability. Physiological understanding is required in order to provide the best method of administration. There are two factors which affect the ability of a child to swallow a solid dosage form. These are the patient's health status and the interpatient variability (Martir et al, 2016).

Whichever method of administration is used, the overall acceptance of the dosage form is very important. The main features that determine the patients' acceptability of a medicine especially paediatrics is the volume or size of the dosage form, taste, flavour and the texture of the medicine. This leads to administration of food or drinks with the medicine in order to improve patient adherence (Martir et al, 2016).

Children and adults not only have biological and anatomical differences in the GI tract, but they also have differences in both food composition and feeding frequency. The Paediatrics gastric emptying rate is affected by the fact that compared to adults; they have a reduced volume of ingestion. The absorption pattern of a drug can be affected by changes in water content and also degree of vascularisation due to developmental changes happening in the skin, muscle and fat (Murphy, 2007; Martir et al, 2016).

In paediatric patients there is an increase in percutaneous drug absorption as a response to a greater skin hydration, thinner or immature stratum corneum and a greater body surface area to weight ratio in this population. In premature neonate, percutaneous absorption is noticeable due to the thin epidermal barrier which is often poorly developed. Drugs applied topically having limited safety experience in neonate should be used with caution (Murphy, 2007).

Trans-rectal route may be used in paediatrics due to the rich blood supply in the rectum, usually when the oral route is unavailable. In the rectal cavity there is a difference in venous drainage system and absorption which may be influenced by the siting of the drug. Another issue is that before significant absorption is accomplished, young infants may expel the drug.[2]

Absorption of injected drugs after intramuscular administration may be affected by several factors including the surface area, blood flow, diffusion through the endothelial capillary walls and muscle activity. Intramuscular absorption is a variable in premature new-borns as they have skeletal muscle and subcutaneous fat that only form a limited percentage of body weight when comparing them to older infants, children and adults (Murphy, 2007).

There are multiple factors that could decrease the rate or extent of intramuscular absorption in newborns including circulatory insufficiency, hypoxia, and being exposed to a cold environment. Intramuscular injections can be painful and should only be administered when oral administration is not indicated or intravenous access is unavailable (Murphy, 2007).

1.2.2 Distribution

The movement of a specific drug from one site to another through tissues, fluid spaces etc., within the body is described as distribution and is usually measured by the distribution volume using the following equation: (Vd = total amount of a given drug/concentration). The volume of distribution is influenced by various factors including maturational physiological changes such as body composition, regional blood flow, plasma protein concentrations, organ size or barriers (Allegaert et al, 2014).

[2]Berlin C, Sharp M, Corp C. Pharmacokinetics in Children. Penn State University College of Medicine [Internet]. [cited 2020 Jul 23]; (2013). Available from: http://www.merckmanuals.com/professional/pediatrics/principles-of-drug-treatment-in-children/pharmacokinetics-in-children

In one study, pharmacokinetic parameters of 45 different drugs were compared in both children and adults. Ginsberg et al, (2004) stated that in children of all age groups, there is a tendency towards larger volumes of distribution.

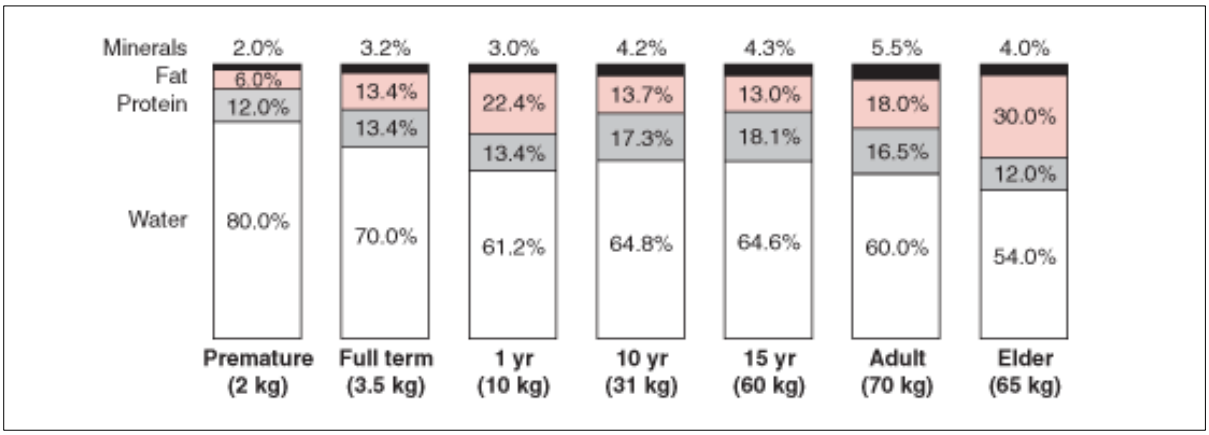

Figure 1.2: Changes in body Composition with Growth and Aging. *Reproduced from: Berlin C, Sharp M, Corp C. Pharmacokinetics in Children. Penn State University College of Medicine [Internet] 2013 [cited 2020 Jul 23]. Available from: http://www.merckmanuals.com/professional/pediatrics/principles-of-drug-treatment-in-children/pharmacokinetics-in-children*

At birth, body water is present at a percentage of 70% whereas body lipid is 13.4% (Figure 1.2). There is an increase in total body fat at one year of age, continuing to increase between five to ten years and decreases in boys around the age of seventeen. At puberty, in females there is a sudden increase in percent body fat reaching twice the value compared to males. The volume of distribution of hydrophilic drugs is greater in neonates than in adults because of a greater water volume. Diazepam, being a lipophilic drug, has a 0.7 ratio of adult volume of distribution to that of a new-born. The volume of distribution of lipophilic drugs is higher in obese patients (Ginsberg et al, 2004; Murphy, 2007; Batchelor and Marriott, 2015).

Another important factor which alters the distribution of a drug is protein binding. Many drugs strongly bind to proteins, including albumin and alpha-1-acid glycoprotein (AAGP) resulting in a small amount of free drug in the circulation. The free drug is important as it is the only part of the drug that can pass through the placenta, can be eliminated via the kidneys, pass through the blood

brain barrier, or metabolised in the liver. In the presence of extensive protein binding, the elimination process is delayed and the amount of free drug to exert its effect is decreased. Protein-binding levels are less in neonates with respect to both albumin and AAGP (Ginsberg et al, 2004). The concentration and affinity for drug binding of these proteins are reduced in neonates approaching adult levels of 10 to 12 months.[2] Drugs with low protein binding in new-born babies include phenytoin, salicylates and ampicillin (Batchelor and Marriott, 2015).

Table 1.2: Comparative Protein Binding in Paediatric Populations Compared with Reference Adult Values

Parameter	Neonate	Infant	Child
Total protein	Decreased	Decreased	Equivalent
Plasma protein	Decreased	Equivalent	Equivalent
Plasma globulin	Decreased	Decreased	Equivalent
AAGP	Decreased	No data available	Equivalent
Free fatty acids	Increased	Equivalent	Equivalent
Unconjugated bilirubin	Increased	Equivalent	Equivalent

Reproduced from Batchelor H, Marriott J. Paediatric pharmacokinetics: key considerations. British Journal of Clinical Pharmacology. 2015;79(3):395-404.

1.2.3 Metabolism

Besides a drug's pharmacological action, the way the body responds to the drug is another important factor. Metabolism is the process within the body which responds to a drug entering the body as being a toxic foreign molecule (Dale and Haylett, 2004). The primary site where drug

[2] Berlin C, Sharp M, Corp C. Pharmacokinetics in Children. Penn State University College of Medicine [Internet]. 2017 [cited 2020 Jul, 23]; (2013). Available from: http://www.merckmanuals.com/professional/pediatrics/principles-of-drug-treatment-in-children/pharmacokinetics-in-children

metabolism takes place is the liver. The skin, intestines, lungs and kidneys may also be involved as secondary sites. Hepatic drug metabolism can be influenced by the binding affinity, extraction efficiency, hepatic blood flow and enzyme activity which depends extensively on patient age (Murphy, 2007). A vital system for drug metabolism present in both the small bowel and liver is controlled by the P-450 (CYP 450), a cytochrome enzyme system. The most valuable metabolic pathways are the CYP3A4 and CYP1A2. In most cases the activity of these metabolic pathways differs in paediatrics when compared to adults (Choonara and Sammons, 2014).[2]

In biotransformation, Phase I and Phase II reactions are found as two primary enzymatic processes. Oxidation, reduction, hydrolysis and hydroxylation are found in Phase I reactions in which a substrate will be introduced with a functional group serving as a location for the Phase II reaction. In children, cardiac output, respiratory rate and liver mass are greater per body weight than adults (Murphy, 2007). At birth, the rate of oxidizing enzymes is significantly lower resulting in prolonged elimination of drugs such as phenytoin and diazepam. In neonates a prolonged half-life and reduced hepatic clearance is observed which is due to the immaturity of hepatic enzymes (Ginsberg et al, 2004).

The most important Phase I enzymes are the cytochrome P450 isoforms having CYP1, CYP2, and CYP3 genes important for drug metabolism. Enzymes CYP 1A2 have different responsibilities and are responsible for the metabolism of caffeine and Theophylline. The activity of CYP 3A4 increases during the first year of life being it's the lowest at birth. P- 450 activity can be induced or inhibited by co-administered drugs. When induction occurs, there is a reduction in drug concentration and effect whereas with inhibition there is an increase in the concentration and effect. Inhibition and induction can both lead to drug toxicity in the paediatrics (Murphy, 2007, Choonara and Sammons, 2014).[2]

[2] Berlin C, Sharp M, Corp C. Pharmacokinetics in Children. Penn State University College of Medicine [Internet]. [cited 2020 Jul 23]; (2013). Available from: http://www.merckmanuals.com/professional/pediatrics/principles-of-drug-treatment-in-children/pharmacokinetics-in-children.

Substrates may be conjugates of endogenous agents such as: sulphate, acetate, glucuronic acid, glutathione, and glycine in Phase II reactions, resulting in a water-soluble compound with an increase in polarity in a more polar, water-soluble compound that can easily be disregarded by the biliary system and/or the renal system. Glucuronosyltransferases, sulfotransferases, arylamine N-acetyltransferases, glutathione S-transferases, and methyltransferases make up the Phase II enzymes in which all play an important role in biotransformation of drugs. Not all Phase II enzymes follow the same growth patterns and conclusive differences can be seen between adults and children. The relevance to increasing knowledge of drug metabolism and pharmacokinetics is to assure appropriate dose intake of various medicines in different paediatric age groups (Murphy, 2007, Choonara and Sammons, 2014).

Metabolism and clearance of numerous environmental toxicants can be modulated by the generalised phenomenon of the pharmacokinetics immaturity in the perinatal period. Both the removal of parent compounds and metabolites can be affected and cause a conversion from chemicals to toxic metabolites.

Childhood metabolism and the elimination of xenobiotics takes place in adulthood when the immaturity of the hepatic system is overcome (Ginsberg et al, 2004).

1.2.4 Excretion

Allegaert et al (2013) stated that: "Metabolism and elimination clearance (excretion) combined, reflect the clearance capacity of volume of blood or plasma from which a drug is completely removed per unit of time."

According to Berlin et al (2013) and Batchelor and Marriott (2015) the kidneys are the main site where elimination of drugs and their metabolites take place. Renal blood flow, Glomerular Filtration Rate (GFR), tubular secretion and urinary pH2 are all factors that affect renal elimination (Batchelor and Marriott, 2015).

These processes develop at different stages in paediatrics and by the first 2 years of life they reach adult levels. The dominant pathway of elimination is renal excretion. The systemic exposure of drugs in different age groups may be influenced by age as it develops throughout a year. Renal plasma flow at birth is 12 ml/min, and by the age of 1 year it reaches adult levels of 140ml/min.[2]

The urinary pH can influence the reabsorption and elimination of weak acids or bases. Infants have a urinary pH that is less than that of an adult and leads to an increase of reabsorption of weakly acidic drugs (Batchelor and Marriott, 2015).

In the first months of life, the cardiac output reaching the kidney is found to be at a low rate and renal clearance is impeded. There are various factors which are important for glomerular filtration such as functional capacity of glomerulus, amount of renal blood flow and degree of protein binding. At birth, both the glomerular filtration rate and transporter systems of the proximal convoluted tubule are insufficient. The glomerular filtration and tubular function are immature due to incomplete glomerular development (Ginsberg et al, 2004, Murphy, 2007).

Drugs that are dependent on glomerular filtration or tubular function are influenced by these variances, resulting in a longer half-life. The adult glomerular filtration rate is met by infants when they reach their first year of life (Murphy, 2007; Batchelor and Marriott, 2015).

[2]Berlin C, Sharp M, Corp C. Pharmacokinetics in Children. Penn State University College of Medicine [Internet]. [cited 2020 July 23];(2013). Available from: http://www.merckmanuals.com/professional/pediatrics/principles-of-drug-treatment-in-children/pharmacokinetics-in-children

1.3 Pharmaceutical Care

In the original definition of pharmaceutical care, Hepler and Strand (1990) stated that "Pharmaceutical care involves not only medication therapy but decisions about medication selection, dosages, routes and methods of administration, medication therapy monitoring and the provision of medication-related information and counselling to individual patients."

The role of pharmacists in the community is to help people maintain and improve their health to ensure the patient's wellbeing. Reliance and assurance are two vital themes in a pharmacy. In the United Kingdom (UK) the General Pharmaceutical Council outlines seven principles that a pharmacist professional must refer to. These are outlined and reproduced hereunder by the General Pharmaceutical council rule of conduct (Sukkar, 2014; Torjesen, 2017).

1. The first concern must be the patient - Values, needs and concerns are subjective. Pharmacy professionals can provide person-centred care by being aware of what is important to the individual and then adjust to meet the patient's needs, prioritising the care of the person. The pharmacist's decisions and behaviour can affect the care or safety of the patient whether there is direct contact or not. It is vital that all information is gathered before any steps are taken. It is in the pharmacist's interest to ensure that the provided services are safe.

2. Pharmacist's professional judgement should be used in the concern of patients and the public - What makes a judgement professional is the balanced consideration of the needs of an individual in the light of current societal needs. Such judgement is essential for professional practices.

3. Show of respect for others - In forming and maintaining skilled relationships, respect is important. Pharmacists should respect cultural variations and recognise diversity as individuals are entitled to convey their personal values and beliefs. People should be treated politely, humanely and with dignity always.

4. Both patients and the public should be encouraged to contribute in decision making about their care. Communication and collaboration are the key to successful involvement of patients and the public when deciding over treatment and care to the individual. In order to be able to make the best decisions, any information given must be updated regularly and the patients and the public should be informed about all available options including the risks and benefits.

5. Professional knowledge and competence should be continuously developed - It is crucial that the pharmacist's knowledge and skills are kept up to date throughout their career using evidence.

6. Pharmacists should be honest and trustworthy - The pharmacist's role is to ensure trust which in turn preserves the reputation of their profession.

7. Pharmacists should be responsible for their working practices. An important part of professional practice is teamwork. This relies on respect, co-operation and communication between pharmacists or any other professions that are involved.

The American Society of Hospital Pharmacists (1994) stated that paediatric patients have been referred to for a long time as "therapeutic orphans". It is a known fact that the paediatric population suffers from a lack of therapeutic trials. There are numerous reasons for this including ethical issues, possible litigation, possible adverse attention, methodological complications and economic reasons leading to failure in validation of such studies. Both children and young people are entitled to receive safe and effective medications. These should be dispensed and administered by professionals who are well-trained and can work with paediatrics (Stewart et al, 2007).

Pharmacokinetic and pharmacodynamic profiles differ between adults and paediatrics. These two profiles need close monitoring for their efficacy and adverse effects as they are continuously changing with age. Two examples of these changes which pharmacists should be aware of are found in protein binding and renal elimination. The knowledge of fluid requirements and

limitations for paediatrics in drug administration techniques and devices is critical (American Society of Hospital Pharmacists, 1994; Horace et al, 2015).

The development of pharmaceutical care has led to the evolution of the pharmacist's role in recent decades. Pharmaceutical care is defined by Fernandez-Llamazares (2012) as being the "active participation of the pharmacist in patient care, in collaboration with doctors and other healthcare professionals, the goal is to obtain results that will improve the quality of life of the patient". Veneables et al (2015) concluded that the knowledge on the risks of medicine handled by paediatric pharmacists, was superior to that compared to a healthcare professional team. This shows that healthcare professionals can make good use of the paediatric pharmacist's knowledge in prescribing medications to paediatrics.

Participation in the identification of polypharmacy through clinical pharmacy practice in the inpatient setting and participation in other activities such as medication reconciliation in the outpatient setting, providing a unique opportunity for pharmacists to advance health care for paediatric patients. The benefits of involving pharmacists as part of the healthcare team for paediatric patients is supported by strong evidence through various studies. Participation of clinical pharmacists who specialise in paediatric patients can combine forces in discharge counselling within the inpatient setting. This will reduce confusion with regards to drug administration, frequency, dose and also the appearance of side effects for parents or guardians at home (Horace et al, 2015; Venables et al, 2015).

Pharmacists are also important as they can detect any drug-drug interactions and provide beneficial recommendations for a change in therapy should problems occur, minimise medication errors and provide patients with monitoring for adverse drug events. Pharmacists should be involved in the promotion of patient safety as paediatric patients depend on adults for their health care (Horace et

al, 2015). As described by Abraham et al (2017) pharmacists are medication experts who are well positioned to reduce barriers by presenting correct medication education.

The increase in off-label prescribing in the community pharmacies and an absence in medical awareness and the growing number of paediatric medicines available over the counter (OTC), highlights the importance of the community pharmacists to guarantee appropriate paediatric medicine administration. Community pharmacists can provide education on polypharmacy to guardians and make crucial interventions with over-the-counter medicines. Important interventions with the management of polypharmacy can be done by pharmacists as they have the time and knowledge required to prevent any adverse events (Horace et al, 2015). An abundant amount of research proves that asthma care models can be successfully delivered by pharmacists through community pharmacy, hence improving asthma related outcomes (Stewart et al, 2007; Elaro et al, 2015).

Through a study carried out in several countries including Canada, Egypt and Madrid, pharmacists were capable of establishing their value as part of the health care team by decreasing the length of stay, undertaking medical interventions whilst improving the adherence for hospitalized paediatric patients (Horace et al, 2015). One way of minimising complications that could result from poor parental knowledge is to improve time management that would permit pharmacists to provide effective counselling to patients/parents. Shortage of pharmacists resulted in depriving patients from proper consultation. (Venables et al, 2015). A research carried out by Fernandez-Llamazares, (2012) showed that 93% of pharmacist's interventions on the patient's health had a positive impact. Hutchins et al (2017) study demonstrates that the rate of ECG monitoring in patients prescribed numerous QTc interval-prolonging medicines was improved by the intervention of pharmacists (Hutchins et al, 2017). Medication chart review by pharmacists is essential in determining medication related problems. It plays an important role in improving the child's drug therapy

(Sanghera et al, 2006). Clinical Pharmacists with adequate training specializing in paediatric patients, can prevent harmful mistakes made in medication administration particularly in paediatric prescribing (Wang et al, 2007).

Parents or caregivers should be educated by pharmacists on safe administration, storage conditions and disposal of medications. The pharmacist must also emphasize to caregivers as to why medication is to be administered according to the dose prescribed and must under no circumstance be administered to anyone unless prescribed. Public awareness on misuse of drugs such as Opioids must be made by educating parents and caregivers on prescription-drug abuse. Opioids are a class of drugs which are used in paediatrics. The safe administration of these medications is vital in both children and adolescents. Pharmacists, being medicinal experts are able to influence the public on how to use Opioids safely. Participation in pain management discussions, including non-opioid alternatives is recommended by the Paediatric Pharmacy Advocacy Group (PPAG) (Matson et al, 2019).

Most of the children's medications were adapted for adults and this shows the extreme demand for the management of medicines and pharmaceutical care in the paediatric population. The unlicensed or off-label use of medicines in children is common. This is because correct formulations with appropriate strengths are not available. This in turn leads to extemporaneous preparation of drugs i.e. division of tablets, liquid medicines and injections diluted. Due to this fact, the chances of miscalculation in doses increase and the beneficial effect of the medication on the patient decrease. Through these challenges, pharmacists can improve the quality of care for paediatric patients and are considered to be at the frontline of the primary healthcare team. For pharmacists to have job satisfaction, it is important they feel confident with knowledge in handling paediatric medication orders and answering questions with regards to drug information (Sanghera et al, 2006; Meyers et al, 2011; Elaro et al, 2015).

1.4 Lack of Medications Available for Paediatrics

The study carried out by Rieder (2019) highlights the importance of the fact that children are not to be considered as small adults and toddlers as large infants. This means that the effectiveness of a drug as well as its safety vary considerably, and therapy has to be individualized not only for paediatrics but as well in terms of the condition that is being treated and the drug being used (Reider, 2019).

The number of paediatric drugs is very limited. Currently, children medication data is extrapolated from research carried out in the adult medication field, disregarding the difference between children and adults (European Medicines Agency, 2001; Mukattash et al, 2011).

The (U.S. Food and Drug Administration 2011) also explains that paediatrics have long suffered from lack of access to medicines that are age appropriate mainly due to lack of money and ethical issues (Orubu et al, 2016).

There are several issues that cause difficulties with prescribing and supplying children's medicines. Some of which are prevalence of unlicensed medicines and medicines prescribed off-label, complications with drug administration, behaviour around medicine use, including influences by family, school and lifestyle, the adverse effects of medicines and various problems with adherence from specific patient groups (Venables et al, 2015).

The clinical requirements for paediatrics are not always covered by licensed indications which often lead to the use of medications outside the regulatory framework for medicines. This carries a great risk to the patient.[4]

4.Medicines use in children and young people: it is time for a reappraisal. The Pharmaceutical Journal [Internet]. 2020 [cited 2020 Jul 23]. Available from: https://www.pharmaceutical-journal.com/news-and-analysis/opinion/editorial/medicines-use-in-children-and-young-people-it-is-time-for-a-reappraisal/20207587.article?firstPass=false

Van der Vossen et al, (2019) also highlighting the fact that "despite the introduction of the Paediatric regulation there is still the extensive necessity for age-appropriate formulations in daily clinical practice." Age-appropriate formulations especially for neonates, infants and toddlers in daily clinical practise is necessary.

Healthcare professionals feel that there are many factors that cause obstacles with the administration of medicines to children (Venables et al, 2015). Venables et al (2015) illustrates in his research how certain characteristics of a tablet such as taste, texture and size are a common oral formulation-related problem in the intake of medicines. Studies show that taste is the most common problem. One way of improving drug acceptance in the form of a liquid is by improving the taste. This will lead to better adherence to the medication by infants and young children (Nahata, 1999).

Some additives present in ready prepared medicines such as preserving agents may be inadequate for paediatrics. Other preparations might have a marketing authorisation that does not have a clear age indication. Not all medications are child appropriate. In certain cases, for the tablet to be appropriate for the child it must be ground or diluted (Wimmer et al, 2015).

There are a number of acute and chronic diseases that infants and children can suffer from. Drug therapy plays a crucial role in the management of these diseases. More adult drugs are approved by the US Food and Drug Administration (FDA) in comparison to paediatrics. Most of these medicines are still frequently used in infants and children. Lack of suitable paediatric liquid dosage forms causes a disadvantage for use of these products in paediatrics. There is a lack of stability data to provide the correct liquid dosage form for paediatrics.[4]

4.Medicines use in children and young people: it is time for a reappraisal. The Pharmaceutical Journal [Internet]. 2020 [cited 2020 Jul 23]. Available from: https://www.pharmaceutical-journal.com/news-and-analysis/opinion/editorial/medicines-use-in-children-and-young-people-it-is-time-for-a-reappraisal/20207587.article?firstPass=false

A considerably high number of paediatric medications are not available in liquid dosage form resulting in dosing errors whilst preparation of medication is being controlled by the caregiver. Alternatively, preparation of a dosage form in extemporaneous liquid that can be prepared by Pharmacists is used (Nahata, 1999).

The European Medicines Agency, 2001 comment on the demand of developing new formulations that would allow exact dosing and improve patient compliance. For orally administered drugs, there are variations from one region to another with regards to tolerance of drug formulations, flavours and colours. Liquids, suspensions, chewable tablets and several other formulations might be essential for paediatric patients with different ages. These various formulations might also require different drug concentrations. Diverse delivery systems should also be developed. Appropriate drug concentrations for vaccination formulations should also be refined to assure accuracy and safety administration of the dose. It was also stated that: "International harmonization on the acceptability of formulation excipients and of validation procedures would help ensure that appropriate formulations are available for the paediatric population everywhere" (European Medicine Agency, 2001).

Professionals that are devoted to excellent medical care of children emphasized on the importance of having more valid medical treatments available. Supplying both clinical pharmacists as well as clinical pharmacologists with applicable research and educational skills could help in improving paediatric treatments (MacLeod, 2017).

1.4.2 Availability of Different Formulations for Paediatrics

The paediatric population presents scientific challenges with drug administration in which many of the innovative approaches focusing on the general adult population do not overcome. These include swallowing difficulty, mouthfeel and taste preferences. Preservative-free paediatric products are a significant advance in the industry, and this has led to the use of single-use oral

dosage form. Solid dosage forms that have been accepted by paediatrics in terms of oral administration include mini-tablets, granules, orally disintegrating tablets (ODTs) and pellets. Liquid formulation is commonly used in paediatrics and has been widely accepted. Unfortunately, stability and drug loading may be a problem for rendering its application in a wide range of APIs. An increasing interest has been gained by the mini-tablets due to two advantages - the ease of application and flexibility of dose. The use of mini tablets can also lead to high drug loading, enhanced stability and a reduction in the transportation cost (Lavan et al, 2019, Strickley, 2019). When a new chemical entity is in its phase two clinical trial, the development of paediatric formulations is usually conducted. Geriatric and paediatric formulations have similar challenges such as swallowing. The efficacy, ease of use, patient access and safety are all key considerations to be considered in the development of such formulations. Management of paediatric oral formulations is usually required, and sometimes certified guidelines are also given. In practice, the misuse of a drug product or non-authorized compounding is sometimes present (Strickley, 2019).

Mini tablets are presently being called granules. There are various studies showing the suitability of mini-tablets for different paediatric age-groups including that of infants and neonates. Children from 6 months up to 6 years show a higher acceptability of mini tablets when compared to liquid formulation. In case of neonates, syrup and mini-tablets have similar acceptability with mini-tablets having the added benefit of being easier to swallow. The age for which a child is allowed to take a mini-tablet of 2-mm diameter coated or uncoated has been determined to be that of 2-28 days. A placebo 4-mm diameter uncoated can be given to patients starting from the age of 1 year. Studies have shown that children as young as two have been able to swallow tablets up to 8mm in diameter whole (Mistry & Batchelor, 2016; Strickley, 2019; Lavan et al, 2019).

The popularity of dosage forms that are either retained or dispersed in the mouth for use in children is increasing. There are various forms of tablets including dispersible, soluble and effervescent

which form either a solution or suspension by being dissolved or dispersed in a liquid. The disadvantage of these dosage forms is that taste masking is still required since they are given as a fluid to the patient (Mistry & Batchelor, 2016).

Strickley (2019) describes that for paediatric oral formulations importance is to be given to age-appropriate considerations. Table 1.3 shows the paediatric age range, approximate mass, current dosage form, classification and proposed dosage forms.

Table 1.3: Age-appropriate Paediatric Oral Formulations: Current and Proposed

Age	Mass (kg)	Classification	Age-appropriate Dosage forms, current	Age-appropriate dosage forms, proposed
	< 3	Preterm infant	Nasogastric tube using solution or suspension	Nasogastric tube using tablets for oral suspension
0-28 d	3-5	Term new-born infants	Solution or suspension	Tablets for oral suspension
1 mo- 2y	5-10	Infants and toddlers	Solution, suspension, mini-tablets, ODT	Mini tablet(s)
2-6 y	10-25	Children (preschool)	Mini-tablets, ODT, sprinkle powder, oral powder, oral granules	
6-12 y	< 25	Children (school)	Chewable tablets, ODT	Chewable tablets, ODT, mini tablets
12-18 y	> 25	Adolescent	Small tablets, capsules	Small tablets, capsules, mini tablets
> 18	> 40	Adult	Tablets, capsules	Tablets, capsules, mini tablets

Reproduced from: Strickley R. Pediatric Oral Formulations: An Updated Review of Commercially Available Pediatric Oral Formulations Since 2007. Journal of Pharmaceutical Sciences. 2019;108(4):1335-1365.

Figure 1.3 is based on a review carried out by (Strickley 2019) between the years of 2007 to mid-2018 which established 16 different types of paediatric oral formulations. Seven out of these 16

were ready to use and 9 required manipulation. It was also observed that out of the total 51 number of products, 21were ready to use and 30 needed manipulation.

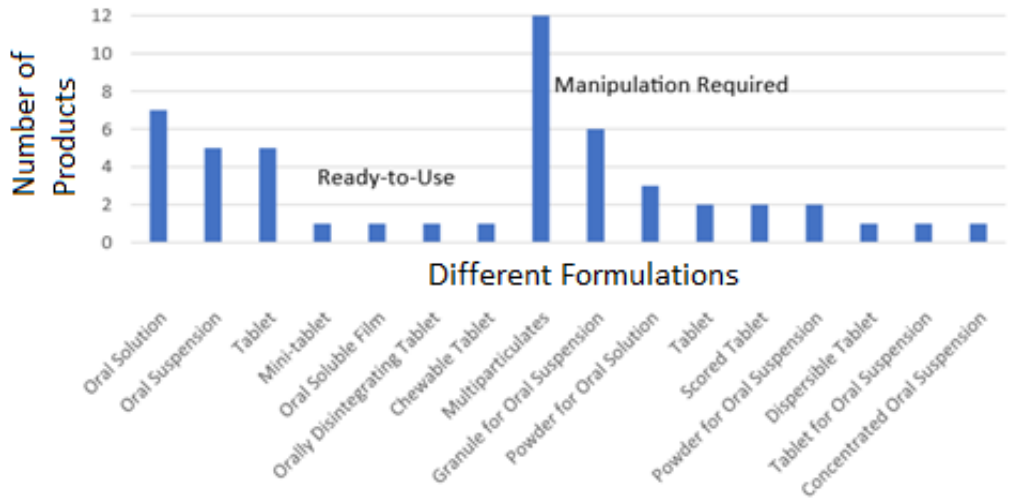

Figure 1.3: Occurrence of Oral Paediatric Formulations from 2007 to mid-2018 - *Reproduced from: Strickley R. Pediatric Oral Formulations: An Updated Review of Commercially Available Pediatric Oral Formulations Since 2007. Journal of Pharmaceutical Sciences. 2019;108(4):1335-1365.*

With chewable dosage forms, Mistry & Batchelor (2016) describe that most of the drugs found in this dosage form are usually hard to chew, leaving residue around the mouth and teeth. Chewable tablets may not be the safest solution for children under the age of three as their chewing skills may still be developing. One way of increasing paediatric acceptability is by presenting the drug in a more appealing dosage form such as gelatine gummy sweets.

1.5 Adverse Drug Reactions and Drug Related Problems in Paediatric Population

Wimmer et al (2015) defined drug safety as being the overall measures taken to monitor the safety of a medicinal product regularly and consistently with the desire of identifying adverse reactions when these products are used in accordance to their intended purpose, assess and understand these adverse reactions and to be capable of taking applicable measures to reduce risk. Understanding

the safety of a medicine entirely, constitutes a great contribution to the updating of the licensing status of medicinal products.

Medication safety was described as the overall measure to assure an enhanced medication process with the target in minimizing errors, hence avoiding risks to patients during their treatment. Adverse drug reactions (ADRs) were defined as being harmful and unintended reactions to a medicinal product which is licensed for the use in human beings. An adverse effect of an administered medicinal product can be anticipated or unanticipated. It can be due to an adverse drug reaction or can also occur due to a medication error (Wimmer et al, 2015; Renaudin et al, 2017) Adverse drug effects (ADEs) related to medication errors, are considered as being preventable. On the other hand, those not related to medication errors are considered to be non-preventable (Kaushal et al, 2001).

Medication errors and ADE studies are most of the time limited to adult patients. In paediatric patients, the epidemiology of medication errors and correlated injuries are less known. Early studies have shown that hospitalized infants and children are at a greater risk of error related ADEs. This is due to the broad range in age and size of this population, an increase in mistakes in drug dosing miscalculations, limited physiological reserve and lastly due to the lack of communication with caregivers (Wang et al, 2007).

The patient response to medication therapy varies widely and most of the time adverse events in children are unpredictable. There is the possibility that some patients when given standard doses might experience extensive adverse events in which case, they would require a reduction in dose (Reider, 2019).

Further issues with the paediatric population and medication is that a child may be under the care of different guardians, may be supplied by a different medical provider or various pharmacies. Interaction with medications taken for chronic diseases might occur due to over-the-counter medications taken by the paediatric patients (Horace et al, 2015). Excipients in formulations might have toxicity which vary across the paediatric age groups and between the paediatric and adult populations. An example is that of benzyl alcohol which is toxic in the preterm new-born (European Medicines Agency, 2001). Adherence to medicines is another problem encountered with the paediatric population and according to Venables et al, (2015) this problem is lower in adolescents and children than in adults. The rates of medication adherence varied between 11 and 93%. There is a great need to improve drug safety use of medicinal products that are intended for use in paediatrics and adolescents (Wimmer et al, 2015).

1.6 Communication between Pharmacists and Parents

In many cases, the parents/guardians of young patients have the essential role of consulting with healthcare workers, as infants, toddlers and young children are incapable of making health-related decisions. This highlights the importance of having an insight of a parent's perspective on primary care for improvement of the quality of paediatric care. Applying a two-way communication provides an enhanced and more timely diagnosis as transparent information is given by the parents. Engaging the patient or parent could improve adherence to therapy as the parent would understand and value the pharmacotherapy the patient requires. One way of increasing effectiveness of therapy is through transparent communication with the carer and having a patient-centred care (Verhelst et al, 2019).

The study carried out by Verhelst et al, (2019) was aimed by looking at the expectations of parents. Through this study it showed that most parents want reassurance and answers to their questions and feel they need to be comforted with regards to treatment.

Guardians should be informed on the health care of their children by pharmacists. Mukattash et al (2011) carried out a survey which revealed that the number of healthcare professionals available is inadequate to cater for the demand to provide information to guardians. In Northern Ireland most guardians refuse to administer certain medications or request a prescription having a licensed alternative.

It is recommended by the United States (US) Pharmacopeia that direct communication with children regarding their medication should be by health care professionals such as pharmacists. Pharmacists, being medication experts, have an important role in providing counselling to children with compliance to following their medication regimens. This can be done by having direct participation and communication about the effectiveness and safety of the medicines being administered (Abraham et al, 2017).

In a study carried out by Abraham et al (2017), pharmacy staff declared that most of the time paediatric patients appear to be uninterested in communicating with the pharmacy staff about their medications. Two factors that cause this situation are the child's age and the lack of privacy in the pharmacy. Older patients, between the age of 13-18 tend to be much more interested and less distracted than younger children. Patients younger than 12 years of age find it more difficult in understanding medication information. Pharmacy staff believe that adolescents have an adequate cognitive ability to understand, which with proper counselling, enables them to be responsible in taking their medications on their own (Abraham et al, 2017).

The degree of patient education, skills teaching, and counselling received by patients from pharmacists seem to be variable. For example, pharmacists do not always provide excellent asthma care to paediatric asthma patients or to their guardians (Elaro et al, 2015). One barrier in providing counselling to children regarding their medication by a pharmacist is time constraint especially due to their typical workload. Pharmacists believe that they would be more able to provide

counselling by spending more time with a child and their parent/guardian if their workload was less demanding (Abraham et al, 2017). Most pharmacists are not confident enough in communicating with paediatric patients about their medicines. Pharmacists acquiring experience with children will enhance the interaction between them (Condren et al, 2015).

Relations between a child and the pharmacist may benefit from engaging in an interactive game with him/her regarding their condition and medications required. Whilst using a pleasant and communicative tone and avoiding the use of medical jargon a pharmacist with a friendly and patient personality will often be successful in helping a child to understand and accept what he/she will be responsible for in the duration of treatment. Children are known to be receptive to counselling when greeted by a smiling and friendly faced pharmacist (Abraham et al, 2017).

1.7 Prescribing in Paediatrics

The definition of age-appropriate medicine may be described as medications which whilst delivering the intended dose, are safe and match the age or ability (Orubu et al, 2016). Healthcare professions face boundaries especially related to the adherence to medicines in children as they are a unique population (Abraham et al, 2017).

Children are admitted to hospital less frequently than adults yet there is great difficulty in selecting and ordering medications for paediatrics when compared to adults. Paediatrics have a high risk of ADRs and there are certain medications that cannot be used in specific paediatric populations, i.e.: a contraindication with the use of Ceftriaxone in neonates due to bilirubin's displacement. Children are at a great risk of medication errors and this risk is calculated to be three times more than in adults (Johnson et al, 2019).

Children are rarely involved in the premarketing clinical trials, resulting in medication being marketed without appropriate studies carried out. This was leading to an increased risk for adverse drug reactions. Prescribing medication in paediatrics is different from prescribing medication in adults. Calculations are required as nearly all drugs vary in doses according to changes that occur during the development of children, as in the weight and age of the child. Miscalculations in doses can lead to serious consequences especially in the case of children (Davis, 2010; Ferrajolo et al, 2014).

1.7.1 Unlicensed or Off-label use of Medicines in Paediatric Population

The word off-label use means that the medicine is administered in a way that is diverse to that represented in the licence, i.e. administering a medication which has a higher dose than that stated. Unlicensed use occurs when a medicine is licenced in countries other than Malta and must be imported. A medicine may have a licence but requires to be prepared and taken in an unlicensed formulation. This usually occurs with patients which have difficulty in swallowing and a specially prepared formulation is needed. Medications that do not have a licence at all are usually used to treat rare diseases (Aronson et al, 2017).

According to Weinberger and Hendeles (2018), the most common OTC medications consumed by both adults and children include decongestants, antihistamines, antitussives, intranasal corticosteroids and mucolytics. Most of the OTC medications are either recommended or prescribed by physicians. Whilst being familiar with the extensive marketing claims for these medications, few of the patients, parents and physicians are aware of the data linked to these agents and the pharmacodynamics and pharmacokinetics of these ubiquitous medicines (Weinberger and Hendeles, 2018).

Many prescribed medications are given to children yearly. The general concern of these medications is that they are given off-label. Allen et al (2018), stated that “the term off- label does

not imply an improper, illegal, contraindicated or investigational use." In practice, the term 'off-label' carries a negative connotation to it as it shows a certain ambiguity in the ratio of risk to benefit (Allen et al, 2018)

The first four medications listed Table 1.4 all have a high off-label use value and propose distinct future implications due to their variation in the risk to benefit profile and due to degrees of uncertainty. Example E is implying that it has a low frequency of use, but this should not be overlooked or disregarded. It is still unclear whether risk-benefit profiles require extra information for the optimization of safer use of medications (Czaja et al, 2017). Despite the availability of paediatric pharmacology there is still the need for paediatric formulations. This means that both off-label and unlicensed prescribing continue to be an important feature when talking about contemporary paediatric practice. There is also a lack in clinical trials that target the efficacy, safety and dosing parameters in paediatrics resulting in an increase of off labelling. The main issue with using children in clinical trials is that of an ethical consideration and most of the time children are excluded (Mukattash et al, 2011; Condren et al, 2015; Horace et al, 2015; Wimmer et al, 2015).

In his research, Mukattash et al (2011) showed that most of the General Practitioners (GPs), consultants and community pharmacists understood the term 'unlicensed' or 'off-label prescribing'. In a survey carried out in the UK it was found that in a community setting, the most common flaw of 'off-label prescription' was giving a lower dose than recommended, while the least frequently reported was prescribing to a younger age than recommended. There is limited guidance for pharmacists in the use of 'off-label' drugs in paediatrics. Balan et al (2017) raises the question of who is going to be held accountable for the risks that emerge from 'off-label' use and who is responsible for the authorization of such prescriptions. Both pros and cons of 'off-label' drugs have to be seriously analysed when alternative treatments which lack a license are needed (Wimmer et al, 2015).

Table 1.4: Potential Practice, Research, and Policy Implications of Examples of Medications being used Off-label in the Paediatric Population Based on Degree of Use, Benefit-Risk Balance, and Uncertainty of Evidence

Medication	Off-label Use	Benefits	Risks	Level of Certainty	Example Drug and Indications	Potential Implications
A	↑↑↑↑	↑	↓↓	↑	Azithromycin and acute otitis media	Generation of additional paediatric data may be necessary and sufficient
B	↑↑	↑	↑↑	↓	Antipsychotic and behaviour outside of autism spectrum in 2-5year olds	Policy changes directed toward risk mitigation may be necessary, decision support to clinicians around risks and generation of additional paediatric data
C	↑↑↑↑	↓	↓↓	↑↑↑	Albuterol and bronchiolitis	Efforts to stimulate practice change through education, dissemination, or policy change
D	↑↑↑	↑ ↑	↑	↑↑↑	Sertraline and paediatric major depressive disorder	Continue ongoing surveillance for new or long-term effects
E	↑	↑	↑	↑	Sildenafil and pulmonary arterial hypertension	Closer monitoring of these select cases by clinicians and encouragement to collect data

↑, high; ↓, low, number of arrows, degree of increased or decreased benefit, risk, and level of uncertainty. *Reproduced from: Czaja A, Fiks A, Wasserman R, Valuck R. Beyond the Label: Steering the Focus Toward Safe and Effective Prescribing. Pediatrics. 2017;139(5):e20163518.*

A study reported by Sanghera et al (2006) shows that the number of prescribed drugs that were unlicensed or used in an off-label manner in children was that of over two-thirds of 624 paediatrics which have been admitted to wards in five different European hospitals. Statistics from around 30 studies carried out by Mukattesh et al (2011) showed that 11-37% of community settings prescribed drugs to children, 16-62% of drugs were prescribed in paediatric wards. There was a

total of 80% of drugs prescribed in neonatal intensive care units in which their use was either 'unlicensed' or 'off-label'.

Healthcare professionals are increasing their concern with regards to the safety and efficacy of unlicensed or off-label medicines used in paediatrics, especially due to the scarcity of availability of this data in paediatrics which could lead to a higher risk of ADRs and treatment failure Mukattash et al, 2011).

1.7.2 Prescribing and Medication Errors in Paediatrics

Prescribing errors can be defined as being - a partial order leading to missing information such as frequency, strength and rate, prescribing to the wrong patient, prescribing a wrong dose or rate, poor handwriting from the prescriber or unclear order and can be crucial if there is an allergy or contra-indication present. A prescribing error takes place when there is an unpreceded fall in the effectiveness of a treatment or a rise in the risk of harming the patient. Prescribing errors can also occur if the patient's clinical condition or weight is not taken into consideration, if crucial pharmaceutical issues are not taken into consideration and if there is failure to communicate effectively providing the necessary information (Ghaleb et al, 2005; Cunningham, 2012; Fernández-Llamazares et al, 2012)

Medication errors occur due to a deviation from the medication process that is best for the patient, resulting in what may have been avoidable harm to the patient. Medication errors may occur at any step of the medication process and can be caused by all those involved - pharmacists, doctors and other healthcare professionals, patients themselves, relatives or third parties. Medication errors occur during the prescribing, transcribing, dispensing, administering, or monitoring of drug use. These errors can either be non-harmful or potentially harmful to the patient. Some medication errors can injure the patient and are referred to as potential ADEs. These potential ADEs may be prevented before reaching the patient. One of several factors which contribute to medication errors

is the human factor. Examples of such human factors include - burnout, fatigue, a false sense of security with technology and also poor team communication (Kaushal et al, 2001; Wong et al, 2004; Wang et al, 2007; Wimmer et al, 2015; Labib et al, 2018).

When compared to adult hospitalised patients, paediatric inpatients are at a three-time higher potential risk from medication errors. There are numerous explanations of how and why this is so. The fact that formulations are mainly adult oriented. The environment of a healthcare setting is more oriented for adults than children. Children are considered as vulnerable when it comes to communicating and expressing their feelings, especially at a very young age. Paediatrics have a smaller body surface area than adults and their enzyme system is still underdeveloped which in turn could lead to a three-time morbidity and also mortality rate when compared to adult patients (Cunningham, 2012; Condren et al, 2015).

In the UK hospitals it was observed that around one in eight medication orders has an error. These errors range from dosing errors to mistakes in either the preparation or administration. There is an increase in risk of errors in paediatrics as most drug doses are calculated based on the child's weight, age, body surface area and their clinical condition in which the risk of adverse events is increased to three times greater than for adults (Mukattash et al, 2019).[4]

From the study carried out by Mukattash et al (2011), 78.3% of healthcare professionals who took part of a survey claim that they encountered dosing errors when presented with a paediatric prescription. Errors are prone to happen at any phase during the drug process and can leave serious side effects. Medication errors occur at a similar rate in both the adult and paediatric population but can cause a three-times potential harm in paediatrics than in adults.

4.Medicines use in children and young people: it is time for a reappraisal. The Pharmaceutical Journal [Internet]. 2020 [cited 2020 Jul 23]. Available from: https://www.pharmaceutical-journal.com/news-and-analysis/opinion/editorial/medicines-use-in-children-and-young-people-it-is-time-for-a-reappraisal/20207587.article?firstPass=false

Several studies show that around one-third of ADE are correlated to medication errors, hence being preventable (Kaushal et al, 2001; Costello et al, 2007; Mukattash et al, 2011).

The most frequent prescription errors are dosing errors resulting in overdose, with potassium digoxin and insulin being the most involved drugs. The frequency for prescribing errors to occur with these drugs is not so much, however, their consequences are more serious clinically. Drugs having a narrow therapeutic index will have more serious repercussions when a dosing error occurs. Most orders containing medication errors occur in infants younger than two years of age in paediatric intensive care patients. The medication errors occur more with physicians who had the least amount of training (Cunningham, 2012; Fernández-Llamazares et al, 2012)

(Ghaleb et al, 2005). Table 1.5 represents a case from the United Kingdom and the US of dosing medication errors in children and the outcome of these errors.

In the healthcare system, patient health is the priority. Patients all over the world, every year, appear to be harmed by errors, and one third to one half of these errors can be avoided (Ghaleb et al, 2005). Society is becoming more aware of patient safety and prescribing errors are a definite area where very small and preventable errors can end up leading to serious harm to patients (Davis, 2010).

Table 1.5: Case Report of Dosing Medication Errors in Children

Patient Involved (Country)	Drug Involved	Nature of the error	Outcome
3-month-old baby (UK)	Sodium Nitroprusside	4 times overdose and given in wrong administration system	Death
9-year-old (UK)	Diamorphine	6 times overdose	Death
1-day-old infant (US)	Benzathine Benzylpenicillin	10 times overdose	Death
10-month-old baby (US)	Theophylline	10 times overdose	Vomiting, tachycardia and hypertension. Patient admitted to ICU for 3 days but no permanent harm
1-year-old male (US)	Ciclosporin	10 times overdose	Facial flushing and irritability
1-day-old baby (UK)	Digoxin	10 times overdose	Death
Neonate (UK)	Diamorphine	10 times overdose	Death
5-year-old girl (UK)	Tacrolimus	10 times overdose	Death
13-year-old (UK)	Epinephrine (Adrenaline)	10 times overdose	Allergic reaction (Rash and wheezing)
17-year-old (UK)	Intravenous fluids	10 times overdose	Death
1-day-old premature (UK)	Morphine	100 times overdose	Death
17-month-old infant (UK)	Benzylpenicillin	300 times overdose and injected the drug into spine	Death
5-year-old (UK)	Anaesthetic, Atropine, Epinephrine	Incorrect dose	Heart attack
9-year-old (UK)	Oral corticosteroid	Overdose	Died from chickenpox
4-year-old (UK)	Growth hormone test	Overdose	Death
3-year-old boy (UK)	Aciclovir	Overdose	No harm to patient
3-day-old triplet (UK)	Phenytoin	Overdose	Death

Reproduced from: Wong I, Ghaleb M, Franklin B, Barber N. Incidence and Nature of Dosing Errors in Paediatric Medications. Drug Safety. 2004;27(9):661-670.

1.7.3 Intervention of Pharmacists in Prescribing Errors

Medication errors are costly to different sectors including the healthcare system, patients, their family and clinicians and so the prevention of these errors has become a high priority worldwide. Pharmacists are facing challenges in recommending and enhancing drug use in children due to inadequate labelling and drug information for use in paediatrics. Moreover, this is also resulting in using drugs outside their approved terms of the product license (Balan et al, 2017). One of the earliest studies that looked at the intervention of pharmacists was conducted in the US in 1971. This determined the intervention of pharmacists in the monitoring of patient charts, providing admission drug histories. They could also contribute in discharge consultations and give information about drugs to medical and nursing staff. Through the involvement of pharmacists in these areas can lead to an enhanced paediatric medical care whilst providing beneficial service to both doctors and nurses working in the unit (Sanghera et al, 2006). Involving pharmacists in the review of medication orders results in a great reduction of potential harm from errors (Cunningham, 2012; Labib et al, 2018).

Mukattash et al, (2019) study concludes that there are extensive pharmacy related medication errors that occur when treating a child the majority of which occur when either a pharmacist is not able to identify a prescription error, gives incorrect drug administration instructions or also mislabels a medication. The role of pharmacist is also very important as there is evidence that they can reduce the rate of medication errors, especially in paediatrics for whom errors in this population can be fatal (Mukattash et al, 2019).

From A study carried out by Cunningham (2012), it showed with from 1300 interventions in just two months, trained clinical paediatric pharmacists can detect and prevent medication errors before reaching the patient. Approximately, one third of the pharmacists' interventions could have developed in an error or harm to the patient. Half of them could have also led to morbidity and mortality if these had not intervened. This highlights the significance of the role of the clinical

paediatric pharmacist which plays when combined with the inpatient paediatric team. Drug therapy recommendation is one of the most common types of intervention. Pharmacists recommending change in medication selection due to them being aware of the presentation of the patient, culture results, any allergies present, or any other factors which could be present led to this drug therapy intervention (Cunningham, 2012).

Clinical pharmacist's intervention could lead to a reduction in prescribing errors; hence an improved quality and safety care is provided (Fernández-Llamazares et al, 2012). It is important that for dosing errors to be intercepted by a pharmacist, patient weight should be included in prescriptions so as to check the dose of a paediatric prescription. Prescribing, dispensing and administration errors in paediatric prescriptions can be prevented by pharmacists (Condren et al, 2015). The integration of pharmacists in paediatric wards can result in a reduction of medication errors and play a vital role in the preparation and administration of medications. Harmful medication errors are most caused due to prescribing mistakes however, pharmacists intercept these mistakes before patient harm occurs. Ways of how medication errors can be reduced by interventions is crucial in paediatrics especially in neonatal intensive care units (NICU) as patients are more vulnerable and communication ability of small and critically ill children is decreased. Paediatrics need weight-based dosing and require dilution of stock medications by pharmacists. The most effective interventions of how the rates of ADEs in paediatrics can be reduced is by having clinical pharmacists present on ward rounds (Kaushal et al, 2001; Wang et al, 2007; Wimmer et al, 2015).

In the US there are over 70,000 pharmacies. This implies that pharmacists are among the most reachable health care professionals who can inhibit any medication errors and provide paediatric patients having both acute or chronic conditions with counselling (Abraham et al, 2017). Having a team approach can lead to prevention of medication errors. Clinical Pharmacists play a very

important role in preventing medication errors and any drug adverse effects, as well as providing an optimisation of drug therapy in the paediatric population (Cunningham, 2012).

1.8 Research for Medicines Used in Paediatrics

Paediatrics should have the same benefits as adults in terms of receiving both safe and effective medications. Safe and meaningful pharmacological research should be encouraged in paediatrics (Wenger et al, 2014; Pugi et al, 2015).

Most of the time children require less medications when compared to adults due to their lack of chronic conditions. Moreover, there are various barriers including both ethical and logistic barriers in learning the effects of medications in the paediatric population. There are other variable barriers to paediatric research including lack of appropriate infrastructure and capability for carrying out clinical trials and complications in trial design when carrying out research in paediatrics. Drug development in children has been overlooked for multiple years when compared to adult drug development. Pharmaceutical companies are not provided with enough incentives when considering the time needed for investment and resources in order to overcome these barriers presented in children's studies to bring appropriate drugs that have been tested for paediatrics on the market. There is also a lack of public awareness with regards to paediatric research resulting in lack of funding to carry out such studies (Wenger et al, 2014; Mukattash et al, 2019; Van der Vossen et al, 2019).[4]

This leads to fewer medications that hold a licence for use in paediatrics. The products that do not have the right marketing authorisation are referred to as 'unlicensed' medicines. When medications which are licensed are used or prescribed in a manner that does not reflect the recommendations listed on the marketing authorisation they are called off-label medications (Mukattash et al, 2019; Van der Vossen et al, 2019).[4]

4.Medicines use in children and young people: it is time for a reappraisal. The Pharmaceutical Journal [Internet]. 2020 [cited 2020 Jul 23]. Available from: https://www.pharmaceutical-journal.com/news-and-analysis/opinion/editorial/medicines-use-in-children-and-young-people-it-is-time-for-a-reappraisal/20207587.article?firstPass=false

Everybody has the right to have the medicines which meet their needs. There is evidence supporting the need for paediatric patients to be treated with age-appropriate medications. Medications should have a satisfying pharmaceutical quality with a quality assurance being legally enforceable with regards to both their development and use. All medicines should be administered at their indicated dose having an adequate risk-benefit profile. Access to appropriate medications that meet these criteria was largely denied to children in the past. Historically, medicines designed for adults used to be given to paediatrics without having been evaluated for use in this population. Most of the time the adaptation of medicines is carried out in an informal manner with no evidence, for example, cutting the tablet in half. During the decade between 2005-2015 overcoming hurdles in medicines provided to paediatrics have been given important attention and effort. In present time, we expect to have medicines that meet the children's needs (Turner et al, 2014; Mistry & Batchelor, 2016).

Children cannot be defined as being small adults, and this highlights the importance of carrying research in this population. Extracting results and information from adult studies rather than conducting studies in paediatrics lead to an increase in causing harm to children as their pharmacokinetics and pharmacodynamic profiles vary considerably when compared to adults. This could lead either to toxicity or, as well as underdosing the child (Caldwell and Spriggs, 2011). Caldwell and Spriggs, (2011) also explains that 80% of drugs that are marked as suitable for use in children do not have the correct paediatric dosing information. This continues to underline the importance of carrying out research in paediatrics in order to improve the health outcomes of children.

Paediatric patients present a barrier in the development of age-appropriate medications due to the lack of knowledge with regards to drug acceptability in this population. Two major jurisdictions in the European Union (EU) and US have been developed with both legislative and regulatory frameworks. These were developed in order to provide paediatrics with the medications they deserve. These frameworks were also important in establishing outlines on providing appropriate medicines to children (Turner et al, 2014; Mistry & Batchelor, 2016).

The EU Paediatric Regulation (EC)1 No 1901/2006 was adopted in December 2006 after the US Best Pharmaceuticals for Children Act was established. Various initiatives have been applied in order to improve the paediatrics drug formulation's availability since the introduction of the Paediatric Regulation (Van der Vossen et al, 2019).

1.8.1 Clinical Trials in Paediatrics

In the past, the results obtained from research that was conducted in adults used to be the determinants of decision making for the choice of treatment for acute or chronic health conditions in children, because of the absence of clinical trials that were needed for the evaluation of the effect of innovative medicines in children. (Ceci et al, 2015).

A spectrum of physiological conditions is created in the paediatric population due to the rapid development occurring from birth to adulthood. This development can be classified into various subgroups depending on the different levels of maturity namely, new-borns/neonates, infants, children and adolescents. In clinical trials, the ontogeny-driven effects are not well examined even though there are apparent differences in multiple paediatric subgroups. There is limited availability of participants accepting to take part in paediatric clinical trials, and this highlights the need for awareness of the importance of having an age-based striation based in the field. These are all ethical issues in which changes in current regulations created a paradigm shift in the public's point

of view. This shift is that to protect children through research instead of protecting them from research (Lavan et al, 2019).

Children can be enrolled in clinical trials depending on different conditions in which these conditions are explained by an ethical framework by the US' federal regulatory requirements for paediatric research. A direct clinical benefit is expected in order to place these number of risks in children. These risks are defined as being either "minimal risk" or "no more than a minor increase over minimal risk". For a protocol to be approved by the Institutional Review Board (IRB) it has to prove that it has a direct clinical benefit to paediatrics and the risk "a minor increase over minimal risk" is exceeded. In times where the research protocol is not approved by the IRB, the study involving an intervention or procedure can still be carried out as it is dependent on sound ethical principles. A review by the federal panel having applicable experts is needed for such studies to proceed. There should also be a determination by the secretary of the Department of Health and Human Services and/or the FDA that the study addresses a "serious problem affecting the health and welfare of children" and that it can "be conducted in accordance with sound ethical principles" (Synder & Nelson, 2018).

Assessments of the PK and PD in the drug development process are assessed through the safety and efficacy-oriented preclinical animal models. These are still needed to be established in paediatric research. In some cases, these traditional animal models have shown to be unsuitable for predicting adult PK/PD implying that suitable paediatric models would be even more difficult to create. Animal studies should also incorporate the differences in Administration, distribution, metabolism, excretion and toxicity (ADMET) properties as these would help in the determining the potential changes in age groups as well as potential implications on dosage adjustment to get a dynamic safe and efficacious dose range (Lavan et al, 2019).

The effects of excipients added in a formulation must also be considered in addition to the changes occurring in clinical responses to the API. Lavan et al, (2009) showed that some excipient levels which have been accepted to be used in adult formulations showed to be toxic in paediatrics at the same level of concentration. Benzyl alcohol is a commonly used preservative that showed to be the cause of gasping syndromes in neonates. The safety and toxicity of excipients for paediatrics (STEP) have created a database providing access to information on the use of excipients in children. This was created in response to toxicity issues resulting from the use of excipients in paediatric drug formulations (Lavan et al, 2019).

1.8.2 Promoting Paediatric Research

Further research in the understanding of the physiological conditions in paediatric patients having an effect on the clinical outcomes and toxicity is required in order to provide better paediatric medicines and meet the high demand in this population (Lavan et al, 2019).

For some time, the European Legislation included the need for the inclusion of paediatrics in drug development. However, these measures were not providing enough information that was required for the majority of medicines. Promotion of paediatric research activities in both industrial and academic settings as well as awareness have been raised through the work of both the WHO and international regulatory agencies. The EU paediatric regulation (REG 1901/2006/EU and Reg 1902/2006/EU) that was adopted on January 26, 2007 had a diverse implementation mechanism than that of the US legislation but both of them had a similar scope. Both legislations have a similar goal, of children's health by providing a new framework for a safe and efficacious use of drugs in paediatrics without subjecting paediatric population avoidable clinical trials (WHO, 2007; Breitkreutz, 2008; Turner et al, 2014; Lavan et al, 2019).

The first rule was developed by the FDA in 1994 which allowed the use of already existing data together with further PK, PD and safety studies. This was only possible if both children and adults

responded similarly to the drug. In 1997, the FDA modernisation Act introduced incentives in order to carry out studies of drugs in paediatrics for which patent protection or exclusivity were available. However, off-patent drugs were excluded (Ceci et al, 2015).

The present U.S. regulatory framework includes two important acts: The Best Pharmaceuticals for children Act (BPCA) and The Paediatric Research Equity Act (PREA) (Ceci et al, 2015).

- Drug companies are granted an extra six months of marketing exclusivity by the BPCA in order to carry out studies in paediatrics following an FDA written request. Once the product has received its exclusivity, it should provide a safety review containing adverse events that are reported during the year (WHO, 2007; Ceci et al, 2015).

- The PREA required that in certain circumstances drug companies should carry out studies of products in paediatrics. It is important that such studies are carried out with the equal drug having the same indication for which an approval for adults was granted (WHO, 2007; Ceci et al, 2015).

A document containing a summary of the results obtained by the Paediatric regulation was released by the European Commission (EC). This is the most recent document available in Europe and covers the period 2007-2012. Important information on Paediatric investigation plans (PIPs) and approved paediatric trials carried out in Europe are provided. This document shows that towards the end of the year 2012 the Agency acknowledged 600 PIPs out of which 453 were medicines which did not have an EU authorisation. The rest are associated with recent indications for products which are patent protected (Ceci et al, 2015).

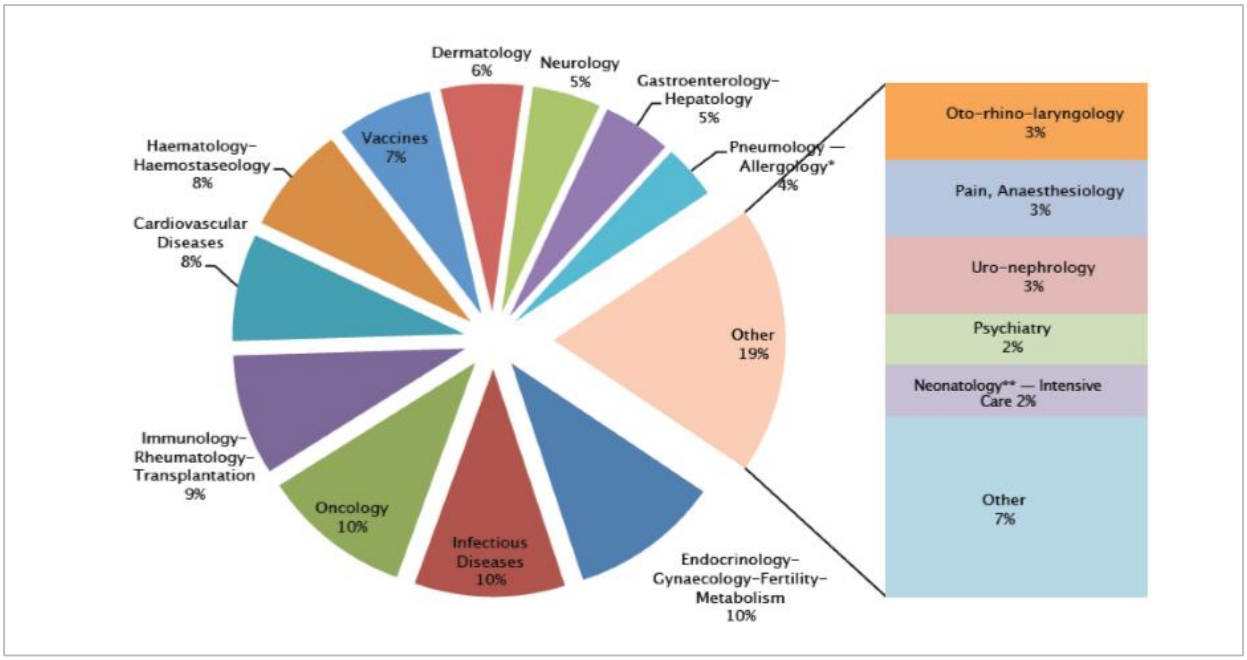

Figure 1.4: Therapeutic Areas Addressed by the Paediatric Investigation Plans (2007-2011). *Reproduced from: Bavdekar S. Pediatric clinical trials. Perspectives in Clinical Research. 2013;4(1):89.*

Research in children is fundamental as this will ensure the availability of better therapies for them. The rights of both children and their families have to be guaranteed by increasing the precautions to this population. Collaboration by Regulators, Parent groups, Practitioners, Ethics Committees, Academia, scientists and Pharmaceutical companies is vital to assure that promotion to ethical paediatric research occurs (Bavdekar, 2013).

1.9 Aims and Objectives

The aim of this study was to assess scientific evidence on safety and efficacy of pharmacist's recommended medications which can be used in paediatric patients and to develop proposals with regards to updating use of non-prescription medicines in paediatric patients.

Scenario analysis of products available on the market for paediatric patients was undertaken.

Chapter 2: Methodology

2.1.2 The Adopted Methodology

The method adopted for this study consists of five steps. A review of the OTC products available from a community pharmacy and on the Malta Medicines Authority was carried out. Evaluation of the safety of these products was carried out by analysing the side-effects, contra-indications and cautions of such products. The efficacy was evaluated by analysing the pharmacokinetic and pharmacodynamic relationship. Data sheets using excel containing information on the safety and efficacy data were created. Guidelines were developed on the correct dispensing of such medications.

Ethics Approval for this study was granted by the University Research Ethics Committee.

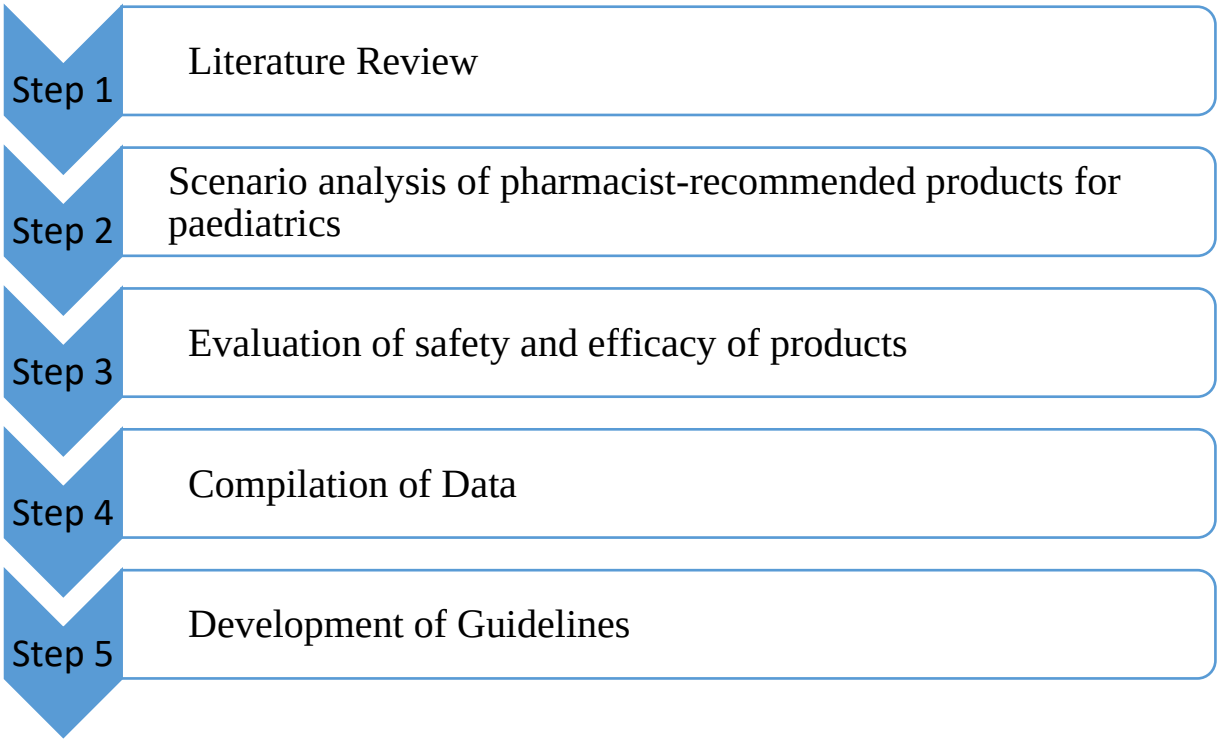

Figure 2.1: Methodology Adopted

2.1.4 Inclusion and Exclusion criteria

For the purpose of this study, the age range used to define paediatrics was from birth up to twelve years of age.

2.2 Collection of Data

A list of all paediatric OTC products available in community pharmacies was compiled. The SPC of each of these products was reviewed and products which had an indication for use for children 12 years or under were added to the list as seen in Appendix I. The list contained thirty-four OTC products. Further research showed that there are more products which can be used in paediatrics and which are available locally. SPCs of OTC products with a Marketing Authorisation in Malta were reviewed. The products added to the list were those that are either classified as paediatric products or products having an indication for children 12 years or younger on the SPC.

The list was divided in different sections depending on the product's main indication such as: analgesics, cough and cold preparations and antihistamines for systemic use, with each section having the number of products available for that particular use.

Products having the same active ingredient were not considered as one product. This was done in order to get the full list of the number of different products which can be dispensed in paediatrics. Various formulations of the same product which were also indicated for use in paediatrics were also added to the list.

2.2.1 Different Formulations Available

A table containing five different sections listing the most common formulations available was developed. The five sections are as follows:

1. Solid formulations (tablets, capsules)
2. Oral preparations (syrup, oral suspensions)
3. Sublingual and buccal administration (orodispersible tablets)

4. Topical preparations (creams, ointments)
5. Rectal Administration (suppositories, enemas)

2.2.2 Compilation of Safety Data

The safety of these products was assessed by evaluating three important parameters from the SPC. An excel sheet was developed for each of these three parameters.

1. Side-effects: The side-effects were divided into seven sections starting with common and very common, unknown, no known adverse effects, uncommon, rare and very rare side-effects. All side-effects listed on the SPC of each API were placed accordingly in the different sections mentioned above and the total number of each side-effect occurring was calculated.
2. Contra-indications
3. Caution for use: In the case of contra-indications and cautions for use, a single excel sheet was used for each. No sections were needed, and each contra-indication/caution was listed on the excel sheet.

2.2.3 Compilation of Efficacy Data

The efficacy of the products was evaluated by taking into consideration the pharmacodynamic and pharmacokinetic data available on the SPC. An Excel sheet containing various sections including the drug's onset of action, time to reach peak effects, Maximum concentration (C_{max}), activity decline, plasma half-life and the volume of distribution was created. The number of products having no pharmacokinetic or pharmacodynamic data available on the SPC was also noted.

2.3 Evaluation of the Compiled Data

The safety data was divided according to different body systems as found on the BNF such as the gastro-intestinal system, central nervous system and immune system. For each Excel sheet separate graphs and tables were compiled to provide better evaluation of the safety and efficacy of such

products. The Pharmacokinetic and Pharmacodynamic data was divided according to different ranges. For example, in the case of plasma half-life, the range is that of 1 hour up to 30 hours as can be seen in Appendix II. Then a table was created having three rows entitled: Data, Number of products and range.

2.4 Development of Guidelines

Guidelines were developed in order to aid pharmacists during the dispensing of non-prescription medications. These guidelines were presented in the form of a poster in which they highlighted 7 important steps including questions to ask on presenting complaints, understanding of the condition, identifying and recommending the best product, providing counselling to patient or guardian, ensuring adherence to medication, the use of pictograms and demonstration of any medical devices dispensed. These guidelines were disseminated to a panel consisting of 3 Pharmacists, 2 doctors one of which was a paediatrician, and 3 lay people for validation. The panel was asked on the clarity, specificity and comprehensiveness of these guidelines.

2.5 Publications

This study was published to two different FIP world congress, one in Abu Dhabi in 2019 and the other one in Seville, 2020.

Chapter 3: Results

3.1 Formulations Available for Paediatrics

From this study it was concluded that there is a total of one hundred and sixty-three products available for paediatrics which can be given as an OTC medication from pharmacists. This number adds up to one hundred and ninety-six when considering different formulations available. Through the evaluation of the SPCs of these products the following results have been concluded.

Table 3.1 represents the number of active ingredients, number of products and number of formulations available for that particular property. The most available product for paediatric use is cough and cold preparations with a number of 21 products (Table 3.1). There is a total number of 15 active ingredients and 9 different formulations which are licensed as cough and cold preparations. This is followed by analgesics with a total number of 16 products with 7 different formulations and only one active ingredient that is available as an analgesic. There is only one product as corticosteroid which can be safely used in paediatrics.

Table 3.1: Number of Products Available According to Their Property (N=196)

Property	Number of Active Ingredients Available	Number of products available	Number of formulations available
Analgesics	1	16	7
Antibiotics and chemotherapy for dermatological use	1	3	1
Antiemetic and anti-nauseates	1	1	2
Corticosteroids, Dermatological Preparations	1	1	1
Anti-diarrheals, intestinal anti-inflammatory/ Anti-infective agent	5	6	4
Antifungals for dermatological use	9	10	4
Antihistamines for systemic use	5	11	3
Anti-inflammatory and Antirheumatic Products	2	5	2
Antipruritics	4	4	2
Antiseptic and Disinfectants	7	7	4
Drugs for acid related disorders	4	6	4
Drugs for functional GI Disorders	4	5	3
Cough and Cold preparations	15	21	9
Ectoparasiticides	3	3	3
Drugs for Constipation	8	12	6

Table 3.1: Number of Products Available According to Their Property

Emollients and protectives	6	6	4
Nasal preparations	10	11	7
Other Dermatological preparations	3	3	3
Otologicals	4	4	2
Preparations for treatment of wounds	3	1	1
Stomatological Preparations	5	5	3
Throat preparations	7	8	2
Typical Products for joint and muscular Pain	8	8	5
Vasoprotectives	2	2	3

As can be seen in Table 3.2 below, the most available dosage form for paediatric is cream with a total number of 31 products. This is followed by tablets with a total number of 22 products available. There is only one product that exists as either chewable tablet, chewing gum, granules for oral, orodispersible tablets, pastille, rectal gel or surgical scrub.

Table 3.2: Number of Products Available According to the Dosage Form (N=196)

Dosage Form	Number of products
Cream	31
Tablet	22
Syrup	19
Oral suspension	15
Oral solution	13
Cutaneous solution	11
Ear, eye, nasal drops	11
Ear, eye, nasal solution	11
Lozenge	7
Ointment	6
Suppository	6
Gel	5
Powder for oral solution	5
Dermatological spray	3
Effervescent powder	3
Oromucosal spray	3
Bath additive	2
Capsule	2
Cutaneous powder	2
Drops	2
Effervescent tablet	2
Inhalation vapour	2
Nasal stick	2
Nasal spray	2
Tincture	2
Chewable tablet	1
Chewing gum	1

Granules for oral suspension	1
Orodispersible tablets	1
Pastille	1
Rectal gel	1
Surgical scrub	1

3.2.1 Number of Products Available According to Age

Table 3.3 represents the number of products that can be recommended by a pharmacist according to the child's age. The most products available are for children between 10 to 12 years with a total number of 136 out of 196 products can be recommended by a Pharmacist within this age range. This is followed by children with the age range between 6 and 10 years in which 132 products can be used within this range. There are only 20 products available for neonates. There are 4 products in which their use and the dose used depends on the weight of the child.

Table 3.3: Number of products available according the children's age (N=196)

Neonate	0 - < 1 month	20
Infant	1 month – 2 years	57
Children	2 years – 6 years	98
	6 years – 10 years	132
	10 years – 12 years	136
	According to Weight	4
	12 years and older	5

3.3 Safety and Efficacy of Products

The safety and efficacy of these products was established by evaluating the SPCs of these products. The following results were observed.

3.3.1 Pharmacokinetics vs Pharmacodynamics Relationship

Pharmacodynamics

In terms of Pharmacodynamics a total number of 10 products block the H-1 receptor of histamine which is followed by local anaesthetic with a total of 9 products. There is a total number of 12 products which do not have any pharmacodynamic data available on their SPC which highlights the importance of further studies and research with regards to these particular products.

Table 3.4: Pharmacodynamics of the Available Products (N=196)

No data	12
Blocking of the H-1 receptors of histamine	10
Local anaesthetic	9
Antiseptic	8
Specific action on alpha-1 adrenergic receptors	3
Expectorant	3
Antifungal	3

Pharmacokinetics

In terms of Pharmacokinetics data as can be seen in Table 3.5, the most common data available is excretion data (n=44) followed by total absorption data (n=43). There are 6 Active Ingredients which are excreted in breast milk. A total of 26 products are either rapidly, well or readily absorbed. The peak plasma concentrations vary between 0-48 hours after administration. A number of 13 products achieve a peak plasma concentration 0-2 hours after administration. The plasma half-life varies from 1 up to more than 20 hours in a drug. There is a total of 7 active ingredients who have their half-life that's between 1-4 hours and another 7 active ingredients that have their half-life between 4-8 hours.

There are 12 active ingredients where their mode of action is not dependent on absorption in systemic circulation.

Out of all the products, there were a total of 31 products which do not have any pharmacokinetic data available on the SPC. This continues to highlight the need for further research in medications especially when used in paediatrics in which they require closer monitoring to drugs being administered to them.

Table 3.5: Pharmacokinetics Data Available (N=196)

Excretion	44
Total absorption data	43
Peak Plasma Concentrations	33
No data	31
Distribution	22
Plasma half-life	18
Metabolism	17
Not dependent on absorption in systemic circulation	12
Absorption data only	9
Bioavailability	9
Clearance	4
Duration of Action	3
Linearity/Non-linearity	2
Onset of action	2
Elimination rate constant	2
Tmax	1

3.3.2 Safety

Side-effects

The most common side-effects observed from the total products are those affecting the Gastro-intestinal system with 27 products having a side-effect which can cause any GI discomfort. This is followed by the Integumentary system with a total of 19 products causing a very common side-effect affecting the Integumentary system. There is a total of 10 products in which they have no undesirable effects listed on their SPC. The least body system affected is the Respiratory system in which there is only 1 product that produces a very common side-effect affecting the respiratory system.

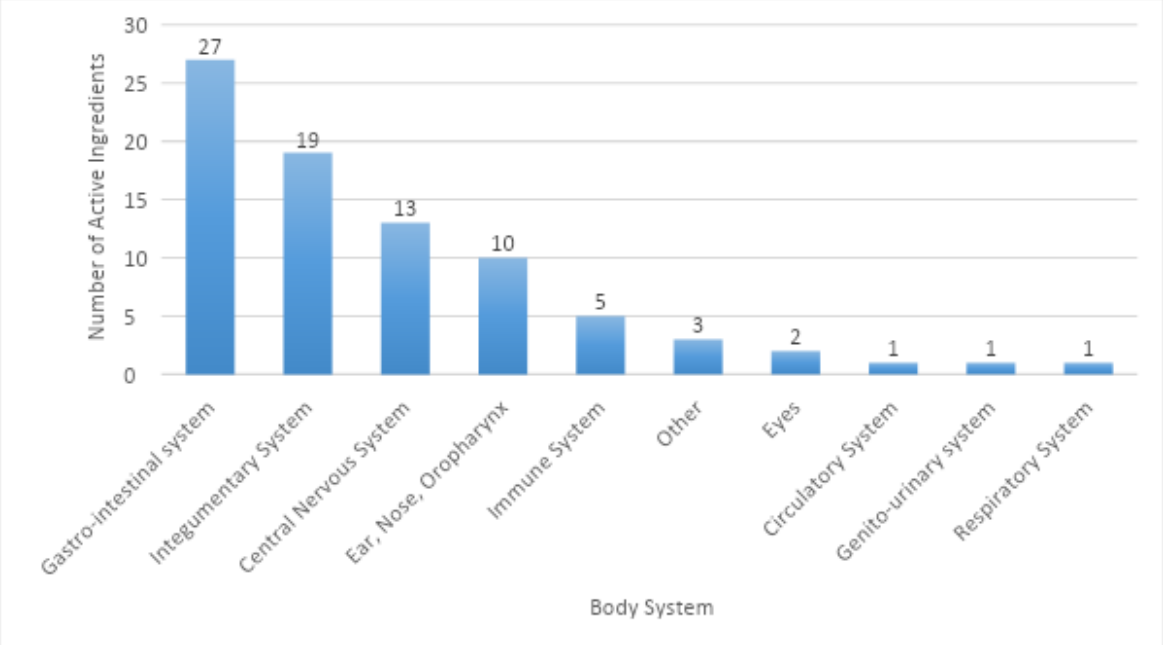

Figure 3.1: Body Systems are Mostly Affected with Very Common Side Effects

Cautions

There is a total of 29 products which should be used with caution in pregnancy and a total of 28 products that should be used with caution if there are any diseases affecting the Endocrine System (Figure 3.2). There are only 3 products that should be used with caution in case the patient experienced any hypersensitivity to the product. There is a product in which there were no cautions listed on its' SPC.

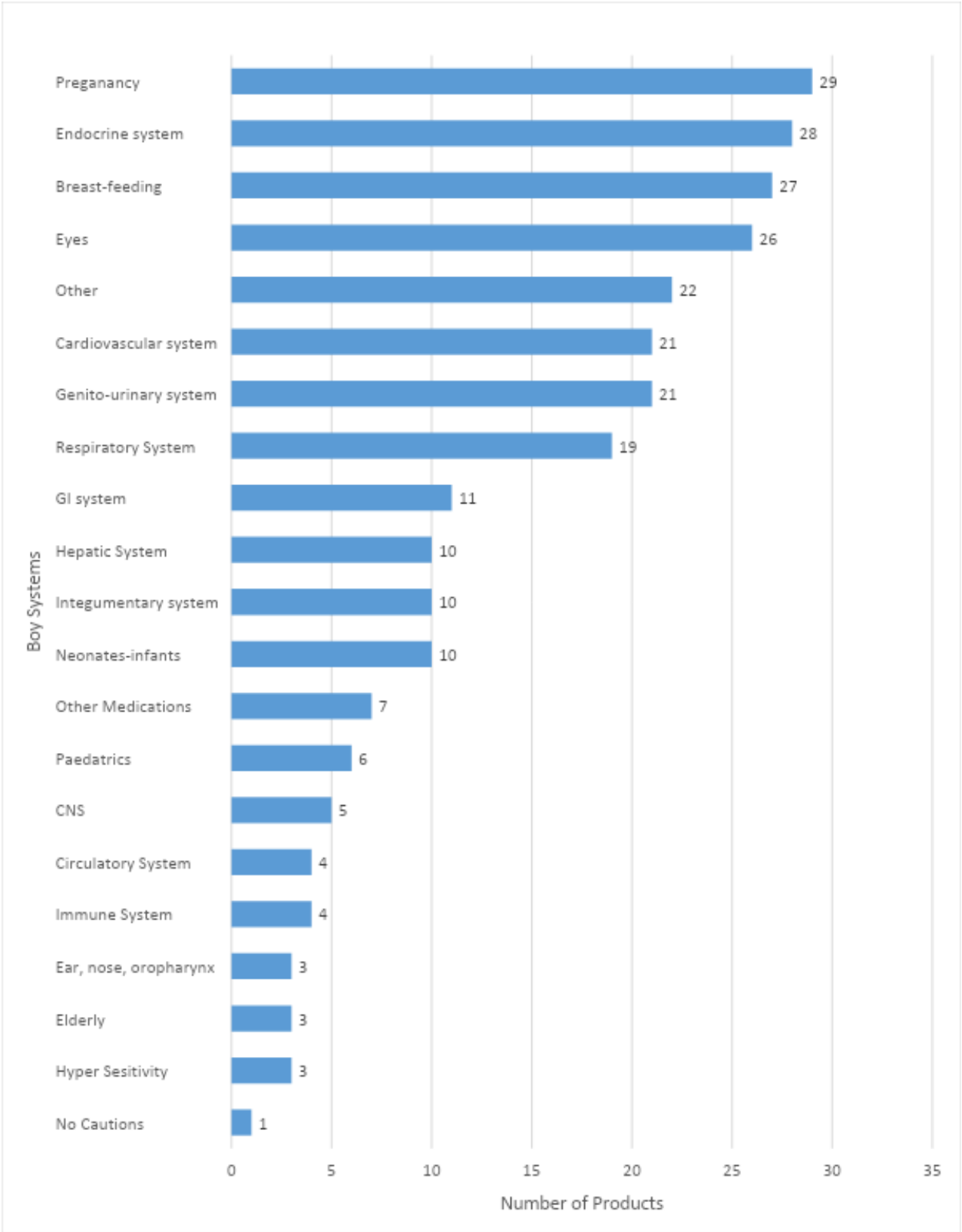

Figure 3.2: Number of Products That Must be Used with Caution in Particular Body Systems

Contra-indications

In terms of contra-indications, most of the products (n=95) are contra-indicated in case the patient has already experienced hypersensitivity to any of the active ingredients. This is followed by the respiratory system in which a total of 31 products are contra-indicated if there is a condition which affects the respiratory system (Figure 3.3). One of the products does not have any contra-indications available on the SPC. Another product lists that there are no contra-indications to the product.

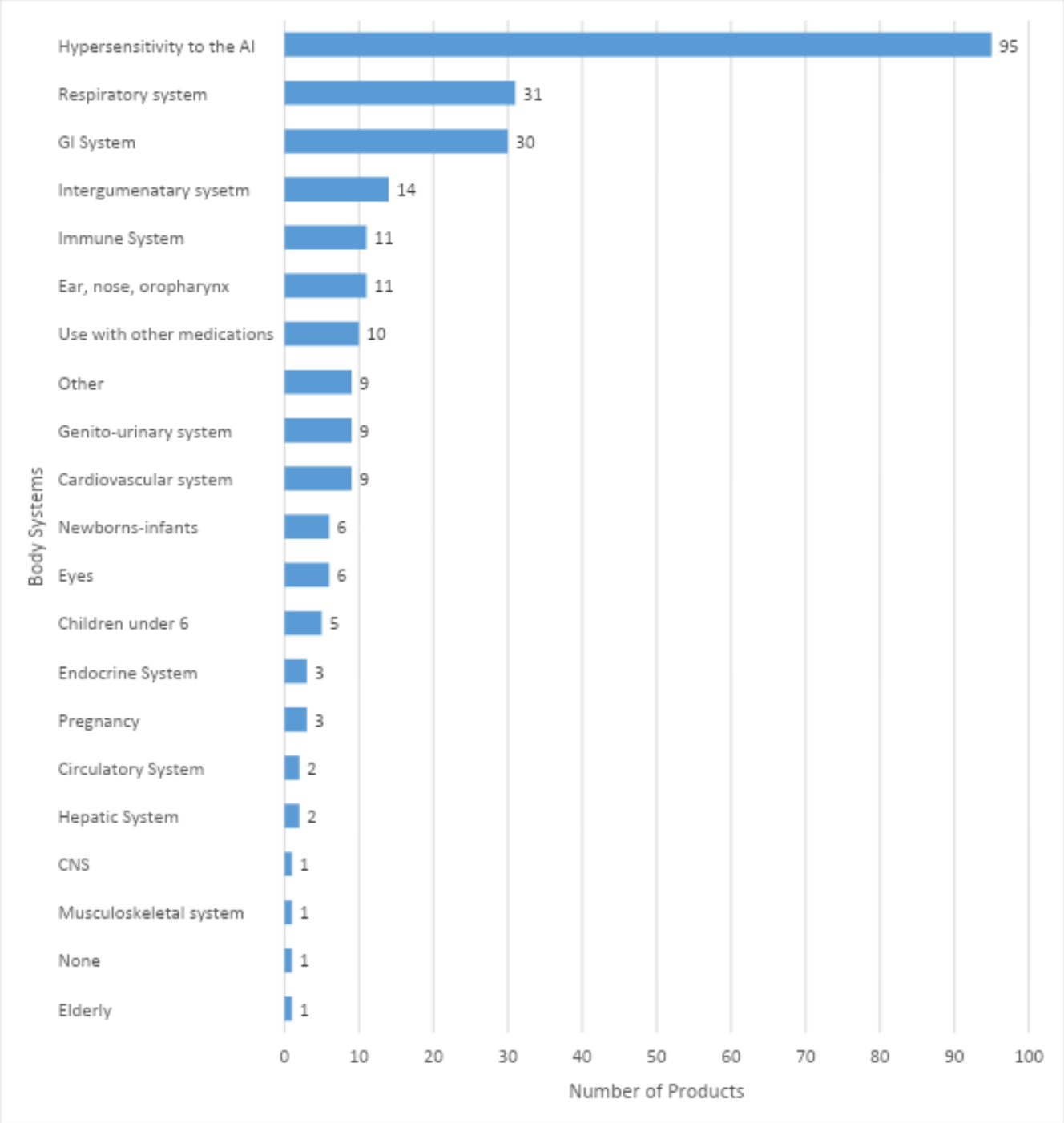

Figure 3.3: Number of Products having Contra-Indications to a Particular Body System

3.4 Development of guidelines

The poster with the proposed guidelines to aid pharmacists in dispensing non-prescription medications was disseminated to a panel for validation. The panel consisted of 8 persons in total in which 3 were Pharmacists, one general practitioner and one paediatrician and 3 lay persons. All the panel were females with age ranges from 27 to 37.

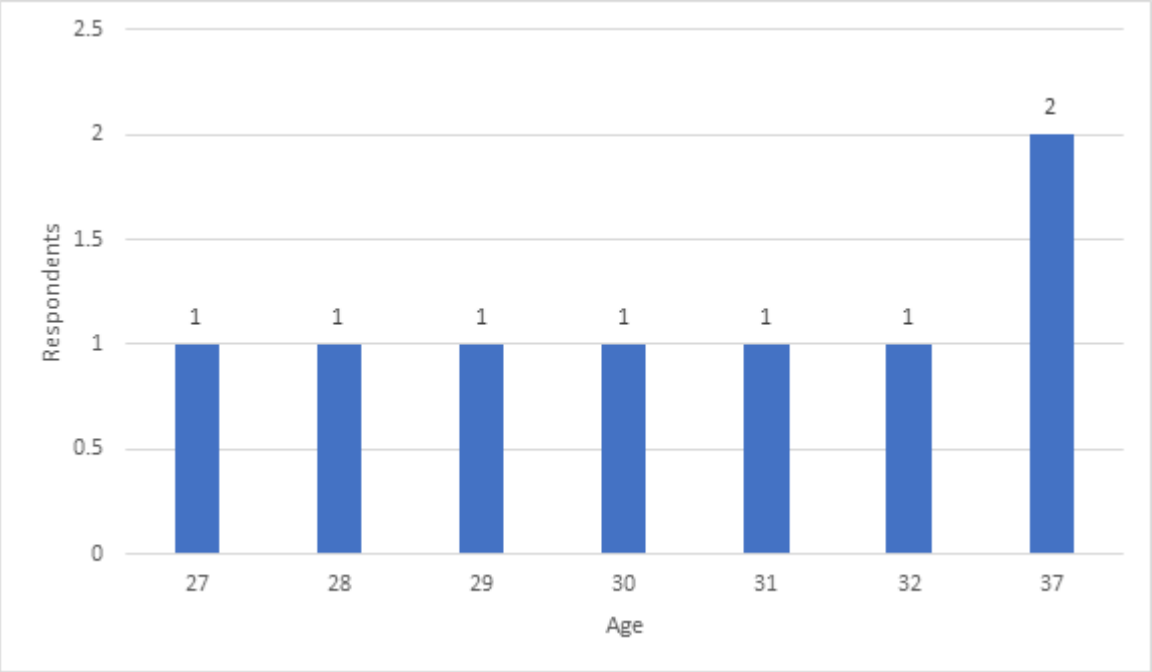

Figure 3.4: Age of questionnaire respondents

The guidelines were validated through a questionnaire which included the clarity, comprehensiveness and specificity of the poster containing the guidelines. It was observed that from the 3 questions asked, comprehensiveness was the one that got the highest score with 7 respondents choosing to score 5 which meant “the best” in the questionnaire. The question that got the lowest scores was specificity with only 4 respondents thinking it is very specific to paediatrics, 3 respondents gave it a score of 4 and one a score of 3.

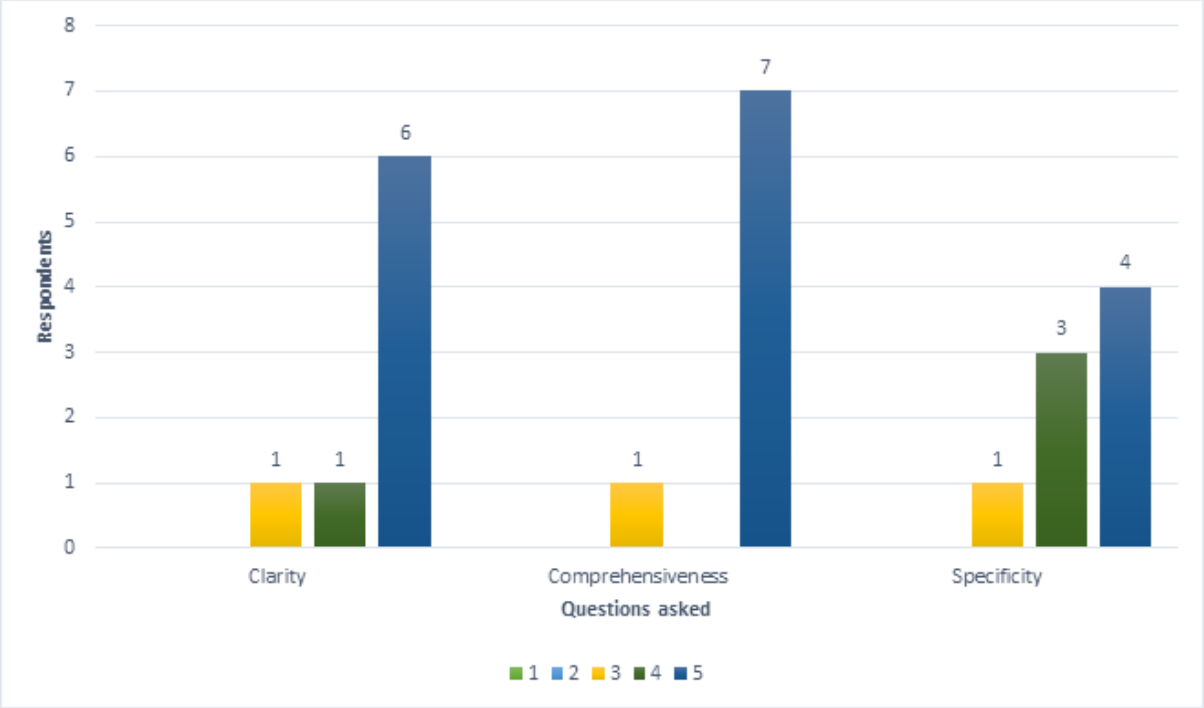

Figure 3.5: Answers of the 8 respondents

When asked on whether they would add or remove anything from the guidelines, 3 answered yes. The general feedback was that they would consider other siblings in the household to ensure that a product that could be used in a certain young patient might not necessarily mean that to the patient's sibling it can be used. Another respondent also highlighted the fact that something to add is whether the patient has had any previous illness and if so, what medication was administered. Another observation was that presenting individual points in bullet form would facilitate the task for the user.

Chapter 4: Discussion

This research concluded that the total number of OTC products that can be dispensed by a community pharmacist add up to 196 formulations. The total number of formulations that have a marketing authorisation in Malta and are available on the Maltese Medicines Authority website as OTC products add up to 7984 products. This shows the lack of medications available for paediatrics as OTC products in the local market. This huge difference in the availability of products could lead to pharmacists compounding drugs or even caregivers manipulating adult formulations before administration to paediatrics. The lack of paediatric products with respect to adult products could be caused by the fact that the occurrence of formulation problems occurs late in the trial protocol review process. This, in turn leads to delays, increasing costs and complications in the conduction of clinical trials and result interpretation of paediatrics. This shows the challenge the scientific community has in order to provide safe, effective age-appropriate medications. (Van der Vossen et al, 2019)

The results from this study shows that 15.82% of the 196 formulations available for paediatrics are creams. Cough and cold medications are the most available preparations which can be safely dispensed by a pharmacist as an OTC medication in Malta. The availability of these products is important as one of the most common illnesses experienced by paediatrics is common cold with many parents asking pharmacists for OTC cough and cold medications to treat these symptoms (Himmelstein et al, 2011). On the other hand, in the UK the most OTC products available are those used for gastrointestinal problems, with cough and cold products being the second most available OTC products (Connely D, 2018).

The most products available are for children between 10-12 years of age, whereas the least number of OTC products available are for infants from birth to 1 month with only 20 out of 196 products available for this age group. This is because neonates undergo maturational changes in physiology while also having immature organ function. These changes result in a lot of variability with regards to dosing in which a medicine indicated in a child of 3 years old is not possible to be used in a

new-born child as this could lead to serious toxicity. However, this lack of availability of products could still lead to unlicensed or off-label use of products in cases where effective treatment is required. This continues to highlight the importance of having the best pharmaceutical care in paediatrics by having enough studies carried out within this population in order to have more access to effective treatment in each case scenario (Allegaert & Sherwin, 2016)

The safety and efficacy of products was evaluated by considering the side-effects that each product has together with their pharmacokinetic and pharmacodynamic relationship.

Through this study one can evaluate that the most products having pharmacodynamic data available on their SPC are the ones that block the H-1 receptor of histamine with a total of 10 products. This figure indicates that nearly all antihistamines have pharmacodynamic data available on the SPC as there are a total of 11 products available as antihistamines for systemic use in paediatrics. This is not compatible with the result that shows that the most common formulations available are cough and cold preparations rather than antihistamines preparations. This could be due to the fact that there are some cough and cold medications that do not have their pharmacodynamic property properly listed on their SPC. Also, when comparing pharmacodynamic data this study took into consideration the active ingredient rather than the formulation. Therefore, it shows that there are only a few active ingredients available as cough and cold preparations having a lot of different formulations available. There is a total of 12 products which do not have any pharmacodynamic data listed on their SPC.

With regards to Pharmacokinetic data there are a total of 31 products which do not have any Pharmacokinetic data available on the SPC. This shows a total of 15.82% of the total products that do not have this valuable data.

This lack of data in both Pharmacodynamic and Pharmacokinetic could be since many pharmaceutical manufacturers do not invest in carrying out research in children due to both ethical and financial constraints that occur during trial design (Ivanovska et al, 2014).

However, the importance of both pharmacokinetic and pharmacodynamic data is crucial. It is a very necessary tool that needs to be implemented in both the discovery and the development of new drugs. Having both appropriate and successful clinical trials can be achieved by having effective preclinical data which can be model-based PK/PD analysis during the drug discovery phase in which it could lead to safer use of medicinal products for use in paediatrics (Tuntland et al, 2014).

From this study, one can notice the importance of including paediatrics in studies on new products for conditions in adults so as to have the safety and efficacy data available that is specific for paediatrics. This would reduce the use of off-label or unlicensed use of products while increasing the availability of paediatric products. The availability of safety data in paediatrics is truly essential in which lack of safety data in paediatrics could lead to under or over-dosing as well as increases the risk of complications such as drug interactions. In addition, it also highlights the importance of closer monitoring to drugs being administered to paediatrics with lack of pharmacokinetic data available.

It was also observed that off-label and unlicensed use of medicine is a common problem. Through the evaluation of the SPCs, the need for access to safety and efficacy for paediatrics is highlighted. Pharmacists should also increase their knowledge with regards to medicine use in paediatrics and decrease the use of off-label medicines in paediatrics. This data is useful to help pharmacists to critically evaluate the use of the products in patients particularly when looking at individualization of medication. The data is particularly relevant when comparing use of pharmaceutical products in paediatrics across the prescription and non-prescription classification.

The paediatric population presents scientific challenges with drug administration which are not tackled by many of the innovative approaches focusing on the general adult population. These include swallowing difficulty, mouthfeel and also taste preferences.

Guidelines were developed in order to continue to highlight the importance of this study by increasing knowledge to pharmacists on the importance of correct dispensing of non-prescription medications to paediatric patients. It was evaluated that most of the respondents found the guidelines quite clear, comprehensive and specific for paediatrics. These guidelines can be present in every pharmacy in the format of a poster so as they can be easily accessible during the dispensing time. It is very important that medications errors can be avoided, and adherence increased by providing the necessary counselling and guidance to a parent or child.

4.1 Strengths and Limitations

The major strength of this study was that an age range was set in the beginning of this study and different age groups were formed in order to be aware of the number of products available for each age group.

The only difficulty with this strength was the fact that different age ranges are explained by different articles and books and therefore, the BNF was used as a standard.

A limitation is that indications for use in paediatrics are continuously being updated due to more research being carried out by pharmaceutical companies which could result in an increase or decrease of paediatrics products available.

Another limitation was that the classification as a pharmacist-recommended product was based on the product registration status.

4.2 Further Research

This study can be carried on by evaluating each product indicating the age range used for the product and combining a list with each product having the side-effects, cautions and contra-indications listed which could improve further dispensing of medications in paediatrics. The development of pictograms which could be useful for paediatrics and their parents as well as the pharmacist when dispensing medications. Further studies to evaluate the rationale for active ingredients that are pharmacist recommended at different age groups would shed more light into accessibility aspects.

4.3 Conclusion

The study shows that there are one hundred and ninety-six available products for paediatrics. After evaluating the Summary of Product Characteristics, it highlights the need for availability to pharmacokinetic and pharmacodynamic data of these products. Another important observation is the importance of having more accessibility to essential medications for paediatrics. Through the evaluation of these products, guidelines are developed to support improvements in use of these medications which could help Pharmacists in dispensing medications safely for paediatric patients. Guidelines on safe use of medicines in paediatrics were developed in order to aid pharmacists during the dispensing of OTC products for paediatrics.

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List of Publications and Abstracts

The following abstract and poster were submitted for the FIP World Congress Abu Dhabi, 2019

Pharmacist's Recommended Medications for Paediatric Patients

Chiara Baldacchino, Maresca Attard Pizzuto, Lilian M. Azzopardi

Background Information: There is a differentiation between adults and children in various aspects of pharmacotherapy due to rapid development occurring from birth to adulthood.[1] There is lack of formulations suitable for paediatrics which often leads to the unlicensed use of adult medicines.[2]

Purpose: To develop guidelines to support improvements in use of paediatric medications.

Method: Scenario analysis of pharmacist-recommended products available on the local market for paediatric patients was carried out. The age range for paediatrics used in this study was that of neonates up to 12 years of age. The Scientific evidence of the safety and efficacy of these products is undertaken through the evaluation of the Summary of Product Characteristics.

Results: There is a total of 169 products available for paediatric use, which increased to 204 when taking into consideration same products in different formulations. The most formulations available for paediatric use are topical preparations (47%). The most available over-the-counter products for paediatric patients are cough and cold preparations (n=21) followed by analgesics (n=16).

Conclusion: After evaluating the summary of product characteristics, it highlights the need for access to safety and efficacy data for paediatrics.

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[1]Lavan M, Byrn S, Knipp G. Pediatric formulations: Knowledge gaps limiting the expedited preclinical to clinical translation in children. AAPS PharmSciTech. 2019;20(2): 73-79.

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L-Università ta' Malta | Faculty of Medicine & Surgery | Department of Pharmacy

PHARMACISTS RECOMMENDED MEDICINES FOR PAEDIATRIC PATIENTS

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INTRODUCTION

There are limitations in the availability of medications for use in paediatric patients. Children differ from adults in many aspects of pharmacotherapy and it is essential that paediatric medicines are formulated to best suit a child's age, size and treatment requirements, hence, different routes of administration, dosage forms and strengths may be required. Many existing formulations are not suitable for children, which often leads to the unlicensed use of adult medicines. [1]

AIMS

- To identify products available for paediatrics which are pharmacist recommended on the local market
- To assess scientific evidence on safety and efficacy of pharmacist's recommended medications which can be used in paediatric patients

METHOD

Data Collection

- Scenario analysis of pharmacist-recommended products available on the market for paediatric patients was undertaken

Data Analysis

- Scientific evidence of the **safety** of paediatric products is undertaken through assessment of the side-effect profile, contra-indications and cautions
- Scientific evidence of the **efficacy** of paediatric products is undertaken, through evaluation of the pharmacokinetic and pharmacodynamic relationship

Documentation

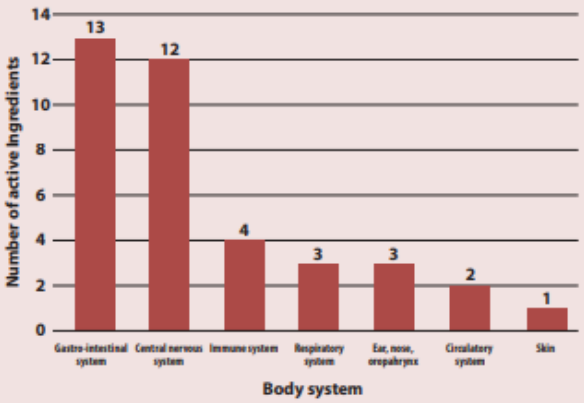
- Data is compiled on a documentation sheet using Excel and a statistical model to capture safety and efficacy of these products is developed using SPSS

RESULTS

So far, 34 products which can be used for paediatrics in Malta have been identified and evaluated. The most common pharmaceutical forms are syrups/solutions/suspensions (n=14) and gels/ointments/creams (n=11). Ten out of these 34 products have no pharmacokinetic (P.K.) or pharmacodynamic (P.D.) data available on the Summary of product characteristics (SPCs). The plasma half-life is the most common efficacy data available on SPCs (n=10) and varies between 1 hour up to 30 hours.

In terms of safety data, the most common side effects occurring from the 34 products are those affecting the gastro intestinal system (n=13) (figure 1). Nausea is the most common side-effect observed (n=4).

Fig 1: Comparison of the most common side-effects observed (N=34)



CONCLUSION

Availability of medications that may be recommended by pharmacists when responding to minor ailments in paediatric patients were identified. Recommendations on efficacy and safety aspects of the products will be evaluated and compared to medicinal products intended for the same use which are currently classified as prescription medicines.

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Pharmaceutical practice:
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Evaluating Available Pharmacist-recommended Medicines for Paediatric patients

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My preferred method of presentation is: Poster Presentation
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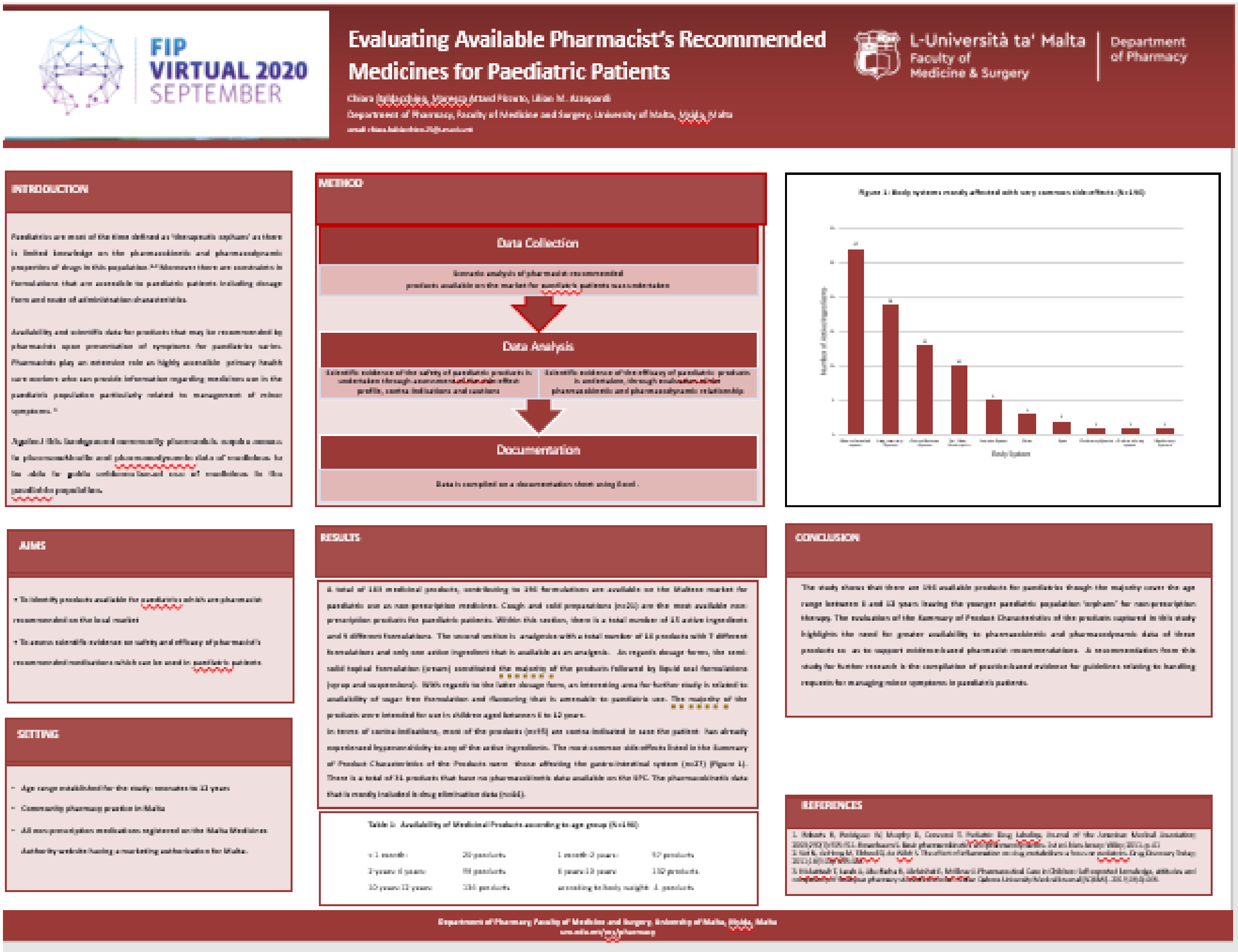
Background: Availability and scientific data for products that may be recommended by pharmacists upon presentation of symptoms for paediatric patients varies.
Purpose: To identify products, available for paediatrics, which are pharmacist-recommended, and to assess scientific evidence on safety and efficacy of these products.
Methods: Scenario analysis was carried out by reviewing all the SPCs of non-prescription medications available on the Malta Medicines Authority website having a marketing authorization for the market under study. The age range used for this study was that of neonates up to 12 years. The product's safety was assessed by reviewing pharmacodynamic and pharmacokinetic properties. Medicinal products available and their intended use, information on the safety and efficacy data for the products were identified.
Results: A total of 163 medicinal products, contributing to 196 formulations are available on the Maltese market for paediatric use as non-prescription medicines. Cough and cold preparations (n=21) are the most available non-prescription products for paediatric patients. The most common side-effects are those affecting the gastro-intestinal system (n=27). There is a total of 31 products that have no pharmacokinetic data available on the SPC. The pharmacokinetic data that is mostly included is drug elimination data (n=44).
Conclusion: This study identifies pharmacist-recommended products, available for paediatric use and the symptomatology they cover. Details on pharmacokinetic and pharmacodynamic data of these products are weak.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Evaluating Available Pharmacist's Recommended Medicines for Paediatric Patients
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Department of Pharmacy
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Appendix I: List of Over the counter products available or paediatrics

Analgesics

Trade Name	Active Ingredient	Dosage Form	Doses
Apotel	Paracetamol	Syrup	
Arfen	Paracetamol	Suppository	125mg, 250mg
Calpol 6 plus	Paracetamol	Oral suspension	
Calpol infant suspension	Paracetamol	Oral suspension	
Calpol sugar free	Paracetamol	Oral suspension	
Dolipraneorodoz	Paracetamol	Orodispersable tablets	
Enelfa	Paracetamol	Suppositories	125mg, 250mg
Panadol	Paracetamol	Tablet	
Panadol Actifast	Paracetamol	Effervescent tablet	
Panadol Advance	Paracetamol	Tablets	
Panadol baby	Paracetamol	Oral suspension	120mg/5ml
Paracetamol	Paracetamol	Tablets, suspension, effervescent, suppositories	250mg/5ml, 120mg/5ml, 500mg, 80mg
Paralink	Paracetamol	Oral solution	250mg/5ml, 120mg/5ml
Remedol	Paracetamol	Tablet, suppositories	500mg, 125mg, 250mg
Supofen	Paracetamol	Oral suspension	200mg/5ml
Tipol	Paracetamol	Suppository	125mg, 250mg, 500mg

Number of Products: 16

Number of Products in different formulations: 20

Antibiotics and chemotherapy for dermatological use

Trade Name	Active Ingredient	Dosage Form
Medovir Cream 5%	Aciclovir	Cream
Cold sore cream	Aciclovir	Cream
Cicloviral	Aciclovir	Cream

Number of Products: 3

Number of Products in different formulations: 3

Antiemetics and anti-nauseates

Trade Name	Active Ingredient	Dosage Form
Biodramina	Dimenhydrinate	Chewing gum, tablets

Number of Products: 1

Number of Products in different formulations: 1

Corticosteroids, Dermatological Preparations

Trade Name	Active Ingredient	Dosage Form
Cortopin	Hydrocortisone	Ointment

Number of Products: 1

Number of Products in different formulations: 1

Antidiarrheals, intestinal anti-inflammatory/ Anti-infective agent

Trade Name	Active Ingredient	Dosage Form
Biocarbon	Activated Charcoal	Tablet
Carbomix	Activated charcoal	Granules for oral suspension
Electrolade	Potassium Chloride, anhydrous dextrose, sodium chloride, sodium hydrogen carbonate	Powder for oral solution
Dioralyte	Potassium chloride, disodium hydrogen citrate, glucose, sodium chloride	Powder for oral solution
Dioralyte Relief	Potassium chloride, rice powder, sodium chloride, sodium citrate	Powder for oral solution
Bioflor	Sacchoromyces boulardii	Capsule, powder for oral suspension

Number of Products: 6

Number of Products in different formulations: 7

Antifungals for dermatological use

Trade Name	Active Ingredient	Dosage Form
Canesten	Clotrimazole	Dermatological spray, cream, solution
Mycoril	Clotrimazole	Cream, cutaneous solution
Pevisone	Econazole Nitrate, Triamcinolone Acetonide	Cream
Daktacort	Hydrocortisone + Miconazole nitrate	Cream
Canesten HC Cream	Hydrocortisone 1% w/w, Clotrimazole 1% w/w	Cream
Travogen cream	Isoconazole nitrate	Cream
Nizoral	Ketoconazole	Cream
Daktarin	Miconazole Nitrate	Cream, cutaneous powder
Bioselenium	Selenium sulfide	Cutaneous suspension
Mycota	Zinc	Cream, powder

Number of Products: 10

Number of Products in different formulations: 15

Antihistamines for systemic use

Trade Name	Active Ingredient	Dosage form
Rhinathiol Promethazine	Carbocisteine, Promethazine hydrochloride	Syrup
Benadryl Allergy Children	Cetrizine Dihydrochloride	Oral solution, tablet
Altacura allergy	Cetrizine Hydrochloride	Tablet
Histasin	Cetrizine Hydrochloride	Tablet
Zyrtec	Cetrizine Hydrochloride	Tablets, solution
Benylin Children's Night cough	Levomenthol	Syrup
Clarityn	Loratadine	Tablet, syrup
Horestyl	Loratadine	Syrup
Loratadine Galpharm	Loratadine	Tablet
Lorat	Loratadine	Tablet
Avomine	Promethazine Teoclate	Tablets

Number of products: 11

Number of Products in different formulations: 14

Anti-inflammatory and Anti-rheumatic Products

Trade Name	Active Ingredient	Dosage Form
Difflam spray	Benzydamine hydrochloride	Oromucosal spray
Esofen for children 6+	Ibuprofen	Oral suspension
Easofen for children	Ibuprofen	Oral suspension
Nurofen for children	Ibuprofen	Oral suspension
Ibuprofen oral suspension	Ibuprofen	Oral suspension

Number of Products: 5

Number of Products in different formulations: 5

Anti-pruritics

Trade Name	Active Ingredient	Dosage Form
Fenistil	Dimetindene Maleate	Gel
Histergan cream	Diphenhydramine hydrochloride	Cream
Anthisan	Mepyramine Maleate	Cream
Fenazil	Promethazine hydrochloride	Cream

Number of Products: 4

Number of Products in different formulations: 4

Antiseptic and Disinfectants

Trade Name	Active Ingredient	Dosage Form
Tea tree and witch hazel	Camphor, hamamelis virginiana, eucalyptus, zinc oxide, methyl salicylate, melaleuca oil	Cream
Care antiseptic first aid cream	Cetrimide	Cream
Savlon antiseptic cream	Chlorhexidine Gluconate, Cetrimide	Cream
Chloraprep with tint cutaneous solution	Chlorhexidine gluconate, isopropyl alcohol	Cutaneous solution
Germolene antiseptic cream	Phenol, chlorhexidine Digluconate	Cream
Betadine	Povidone-iodine	Surgical scrub
Friars balsam	Storax,Sumatra benzoin	Tincture

Number of Products: 7

Number of Products in different formulations: 7

Drugs for acid related disorders

Trade Name	Active Ingredient	Dosage Form
Setlers Antacid Chewable tablets	Calcium Carbonate	Chewable tablet
Gaviscon Original	Calcium carbonate, Sodium alginate, sodium hydrogen carbonate	Oral suspension

Philips milk of magnesia	Magnesium Hydroxide	Oral suspension
Magnesia San Pellegrino	Magnesium Hydroxide	Effervescent powder
Magnesium Hydroxide	Magnesium Hydroxide	Suspension
Gaviscon infant	Sodium alginate	Powder for oral suspension

Number of Products: 6

Number of Products in different formulations: 6

Drugs for functional GI Disorders

Trade Name	**Active Ingredient**	**Dosage Form**
Dentinox infant colic drops	Activated dimethicne	Drops
Actonorm gel	Activated Dimethicone, aluminium hydroxide, magnesium hydroxide	Oral suspension
Buscopan	Hyoscine butylbomide	Tablet
Kwells Kids	Hyoscine Hydrobromide	Tablet
Infacol NO SPC	Simethicone	Oral suspension

Number of Products: 5

Number of Products in different formulations: 5

Cough and Cold preparations

Trade Name	Active Ingredient	Dosage Form
Baby meltus cough linctus	Acetic acid	Oral solution
Abrolin	Ambroxol Hydrochloride	Oral solution
Muciclar	Ambroxol Hyrdochloride	Syrup, Capsule
Menthodex cough mixture	Ammonium chloride, tolu tincture, tussilago farfara, Marrubium vulgare, menthol, sodium citrate, squill tincture	Oral solution
Flecoxin	Bromhexine hydrochloride	Tablet
Bronchotussine syrup	Bromhexine hydrochloride	Syrup
Tiger Balm red ointment (NO SPC)	Camphor, Menthol, Cajuput oil, Clove oil	Ointment
Vicks Vapour rub	Camptor, Eucalyptus oil, turpentine, levomenthol	Ointment
Rhinathiol sugar free	Carbocisteine	Syrup
Fluifort	Carbocisteine	Syrup
Rhinathiol expectorant for children	Carbocisteine	Syrup
Benylin Children	Glycerol	Syrup
Benylin Children's chesty cough	Guaifenesin	Syrup
Numark chesty cough	Guaifenesin	Oral solution
Prospan	Hedera helix extract	Drops, cough syrup
Levotuss	Levodropropizine	Syrup

Covania	Liquorice liquid extract, Levomenthol, squill tincture	Oral solution
Olbas Pastilles	Peppermint oil, eucalyptus oil, clove oil, methyl salicylate, juniper berry oil, levomenthol	Pastille
Sopulmin Paediatric	Sobrerol	Suppositories
Friars balsam BP	Sumatra benzoin, storax	Tincture
Toularynx	Thymus vulgaris, ammonia extraction solvent, glycerol, ethanol	syrup

Number of Products: 21

Number of Products in different formulations: 23

Ectoparasiticides

Trade Name	**Active Ingredient**	**Dosage Form**
Eurax Cream 10%	Crotamiton	Cream
Lyclear Crème rinse	Permethrin	Cream
Para special lice solution	Piperonyl butoxide, Depallethrine	Cutaneous spray, solution

Number of Products: 3

Number of Products in different formulations: 4

Drugs for Constipation

Trade Name	Active Ingredients	Dosage Form
Dulcolax	Bisacodyl	Suppositories, tablets
Lax-tab	Bisacodyl	Tablet
Eucarbon	Charcoal, senna leaf, sulfur, rheum officinate	Tablet
Glycerol suppositories BP infants and children	Glycerol	suppositories
Bebegel	Glycerol	Rectal gel
Fybogel	Ispaghula Husk	Effervescent granules
Isbagel	Ispaghula Husk	Effervescent granules
Duphalac	Lactulose	Oral solution
Oilatum emollient	Liquid paraffin	Bath additive
Senokot	Sennoside B	Tablet
Senna	Sennoside	Tablet
Dulcolax Pico liquid	Sodium Picosulfate	Oral solution

Number of Products: 12

Number of Products in different formulations: 13

Ophtalmologicals

Trade Name	Active Ingredient	Dosage Form
Allergopos N	Antazoline phosphate, tetryzoline hydrochloride	Eye drops, solution
Azelastine-COMOD	Azelastine hydrochloride	Eye drops, solution
Opticrom Allergy eye drops	Cromoglicate sodium	Eye drops, solution
Catacrom	Cromoglicate sodium	Eye drops, solution

Number of Products: 4

Number of Products in different formulations: 8

Emollients and protectives

Trade Name	Active Ingredients	Dosage Forms
Sudocrem	Benzyl alcohol, benzyl benzoate, benzyl cinnamate, zinc oxide, lanolin	Cream
Calamine lotion	Calamine	Cutaneous suspension
Cetraben bath additive	Light liquid paraffin	Bath additive
Metanium Nappy rash Ointment (NO SPC)	Titanium dioxide, titanium peroxide, titanium salicylate	Ointment
Cetraben emollient cream	White soft paraffin, light liquid paraffin	Cream
E45	White soft paraffin, light liquid paraffin, lanolin	Cream

Number of Products: 6

Number of Products in different formulations: 6

Nasal Preparations

Trade Names	Active Ingredients	Dosage Form
Vicks inhaler	Camphor, Pine oil, Menthol	Nasal stick
Actifed Expectorant	Guaifenesin, Triprolidine hydrochloride, Pseudoephedrine hydrochloride	Oral solution
Covonia vapour drops	Menthol, Peppermint oil	Inhalation vapour, solution
Utabon Paediatric	Oxymetazoline	Nasal drops, solution
Olbas inhaler nasal stick	Peppermint oil, cajuput oil, eucalyptus, levomenthol	Nasal stick
Vibrocil	Phenylephrine, Dimetindene maleate	Nasal spray, solution
Medofed	Pseudoephedrine hydrochloride, triprolidine hydrochloride	Oral solution
Actifed syrup	Triprolidine hydrochloride, PSeduoephedrine hydrochloride	Syrup
Actifed DM cough linctus	Triprolidine hydrochloride, Pseudoephedrine hydrochloride, Dextromethophan hydrobromide	Oral solution
Otrivin child	Xylometazoline hydrochloride	Nasal drops, solution

Hysan Paediatric	Xylometazoline hydrochloride	Nasal drops, solution

Number of Products: 11

Number of Products in different formulations: 16

Other Dermatological preparations

Trade Name	**Active Ingredient**	**Dosage Form**
Aqueous cream BP	Cetostearyl alcohol, white soft paraffin, liquid paraffin, sodium lauryl sulfate	Cream
Duofilm	Lactic acid, salicylic acid	Cutaneous solution
Dentinox Cradle Cap treatment shampoo	Sodium Lauryl ether sulfo succinate	Cutaneous liquid

Number of Products: 3

Number of Products in different formulations: 3

Otologicals

Trade Name	**Active Ingredients**	**Dosage Form**
Earex (Just PIL no data)	Camphor oil, arachis oil, almond oil	Ear drops
Cerumol	Chlorobutanol, Arachis oil	Ear drops, solution
Molcer	Docusate Sodium	Ear drops, solution
Otipax	Phenazone, lidocaine hyrdochloride	Ear drops, solution

Number of Products: 4

Number of Products in different formulations: 7

Preparations for treatment of wounds

Trade Name	Active Ingredients	Dosage Form
Contractubex	Heparin sodium, extractum cepae, allantoin	Gel

Number of Products: 1

Number of Products in different formulations: 1

Stomatological Preparations

Trade Name	Active Ingredients	Dosage Form
Difflam spay	Benzydamine hydrochloride 0.15%	Ormucosal spray
Carbosan	Carenocolone sodium	Gel
Bonjela teething gel	Cetalonium chloride, lidocaine hyrochloride	Gel
Corsodyl dental gel	Chlorhexidine gluconate	Oromucosal gel
Clove oil dental solution	Clove oil	Dental solution

Number of Products: 5

Number of Products in different formulations: 5

Throat Preparations

Trade Name	Active Ingredients	Dosage Form
Trachilol lozenges	Alum, Lidocaine hydrochloride, propyl hydroxybenzoate	Lozenge
Strepsils Menthol and Eucalyptus	Amylmetacresol, Dichlorobenzyl alcohol, Levomenthol	Lozenge
Streprils	Amylmetacresol, Dichorobenzyl alcohol	Lozenge
Beechams max strength sore throat relief	Benzalkonium chloride, Hexylresorcinol	Lozenge
AAA sore throat spray	Benzocaine	Oromucosal spray
Tantum verde	Benzydamine hydrochloride	Lozenge
Trachisan Lozenges	Chlorhexidine gluconate, Tyrothricin, Lidocaine hydrochloride	Lozenge
Tyrozets	Tyrothricin, Benzocaine	Lozenge

Number of Products: 8

Number of Products in different formulations: 8

Typical Products for joint and muscular Pain

Trade Name	Active Ingredients	Dosage Form
Bell's Wintergeen	Cajuput oil, eucalyptus, methylsalicylate, menthol	Ointment
Radian B muscle rub	Camphor oil, methyl salicylate, menthol, Oleopresin Capsicum	Cream
Dubam Cream	Cineole, Methyl salicylate, menthol	Cream
Algesal	Diethylamine salicylate	Cream
Mentholatum deep heat spray	Ethyl salicylate, hydroxyethyl salicylate, methyl nicotinate, methyl salicylate	Cutaneous spray, solution
Eucalyptus oil	Eucalyptus oil	Cutaneous emulsion, inhalation vapor
Deep heat rub	Eucalyptus oil, Turpentine oil, Methyl salicylate, Levomenthol	Cream
Deep heat max strength	Methyl salicylate, menthol, levomenthol	Cream

Number of Products: 8

Number of Products in different formulations: 10

Vasoprotectives

Trade Name	Active Ingredients	Dosage Form
Proctosedyl	Cinchocaine hydrochloride, Hydrocortisone	Ointment, suppository
Hirudoid	Heparinoid	Cream

Number of Products: 2

Number of Products in different formulations: 2

Total number of Products: 163

Total number of products in different formulations: 196

Appendix II: Pharmacokinetic data

Absorption

Rapidly/well/Readily absorbed	26
Partly absorbed	3
Poorly/ Minimal absorption	12
Variable extent of absorption	1
Negligible systemic absorption	1

Peak plasma concentrations

0-2 hours after administration	13
2-4 hours after administration	8
4-10 hours after administration	3
24-48 hours after administration	1

Cmax

0-100 ng/ml	6
100-200 ng/ml	1

200-300 ng/ml	1

Plasma half-life

1 - 4 hours	7
4-8 hours	7
8-12 hours	3
12-16 hours	2
16-20 Ours	1
>20 hours	1

Tmax

2 hours	1

Duration of action

1-4 hours	1
4-8 hours	1
8-16 hours	1

Excretion

Urinary excretion	30
Faeces	6
Excreted in breast milk	4
Bile	3
Crosses placenta	1

Bioavailability

0-20%	6
20-40%	1
>40%	2

Appendix III: Guidelines Poster

Guidelines on safe use of medicines in paediatrics.

1. **Questions to ask parent/guardian:**
   a) Child's age
   b) Child's weight
   c) Child's allergies
   d) Child's medical condition
   e) Child's presenting complaint

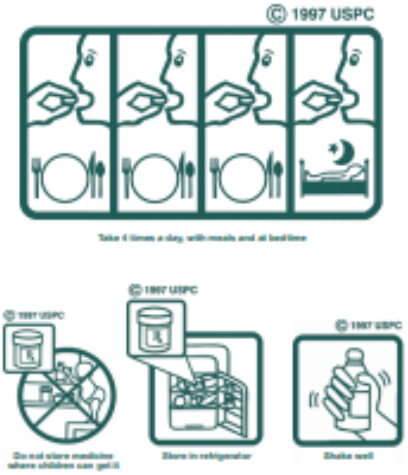
2. **Understand** the patient's condition and be able to see whether patient requires non-prescription product or whether referral to a physician is recommended.

3. **Identify** and **recommend** the non-prescription product appropriate for the specific patient needs, taking into consideration the indications and age indication of the product.

4. **Counselling** about the medications being dispensed including the indication for use, directions on how to administer, frequency, storage conditions, any drug interactions, common adverse events and when to seek medical advice in the event that symptoms do not subside.

5. Highlighting the importance of **adherence** to medication through the use of calendars or charts and marking once the medication is taken or rewarding the child once the medication is taken.

6. Use of **pictograms** to support use of medications especially when child is old enough to understand administration process.



7. **Demonstration** of use of medical devices required for drug administration such as the use of inhalers and spacer device and how to use syringes for liquid preparations.

Counselling to provide the necessary advice to the parent/guardian or child is very useful in avoiding a medication error such as overdosing or lack of adherence.

Reference: Benavides S, Huynh D, Morgan J, Briars L. Approach to the Pediatric Prescription in a Community Pharmacy. The journal of Pediatric Pharmacology and Therapeutics. 2011;16(4):298-307.